INTRACARDIAC THROMBUS FORMATION AFTER THE FONTAN OPERATION

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Objectives: Intracardiac thrombus formation is suspected to be a specific sequela after the Fontan operation and is difficult to determine by means of routine transthoracic echocardiography. The aim of our study was to evaluate the occurrence of intracardiac thrombi in the different types of Fontan modifications and to identify predisposing risk factors.

Methods: We evaluated 52 patients who had undergone a Fontan-type operation and were free of symptoms regarding thrombosis as determined by transesophageal echocardiography.

Results: In 17 (33%) patients thrombus formation could be found without clinical evidence of thromboembolic complications. Neither underlying morphologic disease nor age at operation, type of Fontan operation, sex, follow-up interval, arrhythmias, or laboratory or hemodynamic findings could be identified as predisposing risk factors.

Conclusion: In patients having had a Fontan operation with inadequate or without anticoagulation medication, we would recommend routine transesophageal echocardiography to exclude eventual thrombi. Because of the high incidence of thrombi, we suggest oral anticoagulation therapy in all patients. (J Thorac Cardiovasc Surg 2000;119:745-52)

Since 1968, the original Fontan operation has undergone several surgical modifications. It has been applied for palliation of a wide variety of complex cyanotic congenital heart defects with only one ventricle precluding biventricular repair.[1] Despite the significant progress in operative management, considerable late mortality and morbidity remain, mainly caused by atrial arrhythmias, liver dysfunction, protein-losing enteropathy, ventricular failure, thrombus formation, and thromboembolic events.[2-5]

The true incidence of cardiac thrombi and thromboembolic events is unknown. Moreover, no consensus is found in the literature regarding the tools for diagnosis of cardiac thrombi and the indication and optimal strategy preventing thromboembolism.[6]

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The aim of our study was to evaluate the occurrence of intracardiac thrombi and to identify predisposing risk factors to optimize diagnostic and therapeutic strategies for patients after the Fontan operation.

Because of the unexpected high occurrence of intracardiac thrombosis in this study, we decided to publish these preliminary data, which are in everyone's interest.

Patients and methods

Between 1978 and 1998, 227 patients with different types of univentricular hearts underwent a modified Fontan operation at our institution, and 169 of them were routinely followed up. Since January 1998, we initiated a study to evaluate the occurrence of intracardiac thrombi in all these patients visiting our outpatient clinic. Through June 1, 1999, the study included 52 patients consecutively visiting our outpatient clinic (24 female and 28 male patients), who were free of symptoms for thromboembolism or other clinical signs of hemodynamic deterioration and could be motivated to participate in the study. Informed consent was obtained for all participants.

Follow-up data were obtained by reviewing each patient's medical records. Besides a thorough physical examination, the medical examinations consisted of electrocardiography, 24-hour ambulatory electrocardiography, transthoracic and transesophageal echocardiography (TEE), cardiac catheterization, and laboratory testing.

The preoperative diagnosis included various forms of tricuspid atresia in 23 patients, double-inlet left ventricle in 21, mitral atresia in 4, and a complex type of a univentricular heart in 4 (Table I).

Table I. *Patients, diagnosis, and thrombus*

Patient No.	*Sex*	*Diagnosis*	*Operation before Fontan*	*Age at Fontan operation*	*Fontan modification*	*Age at TEE*	*Thrombus*
1	F	MA, CA, MGA, levocardia	PAB	7.1	Modified RA-RV	16.0	Thrombus
2	F	DILV, MGA, PS	PAB	9.5	RA-PA	18.2	Thrombus
3	F	TA IIc, MGA	PAB	6.3	RA-PA	14.9	
4	M	DILV, PS, MGA		11.7	RA-PA	25.6	
5	F	DILV, PS, MGA		5.8	RA-PA	16.5	Thrombus
6	F	DILV, PA, hypoplastic LPA	2 × shunt	6.8	RA-PA	14.0	Thrombus
7	F	TA IIc, CoA	CoA resection, PAB	9.9	RA-PA	19.0	
8	M	DILV, L-MGA, PA	Shunt	1.8	RA-PA	12.2	Thrombus
9	M	DILV, MGA, PS	Shunt	23.1	RA-PA	40.8	
10	M	DILV, L-MGA	PAB	8.0	RA-PA	22.5	
11	M	DILV, L-MGA	PAB	6.7	RA-PA	14.5	
12	M	DILV, PS, straddling AV valve	2 × shunt	18.9	RA-PA	28.9	
13	F	TA IIb, PS		13.9	RA-PA	22.4	Thrombus
14	F	DORV; left AV valve atresia, PS, LPSVC, hemiazygos continuity	Valvotomy PV	5.5	RA-PA	17.4	
15	F	DILV, left AV valve atresia, L-MGA, PS	Shunt	10.3	RA-PA	23.9	Thrombus
16	F	DILV, MGA, CA, azygos continuity, subvalvular AS	PAB	14.3	RA-PA	24.2	
17	M	DILV, PS	Shunt	13.2	RA-PA	20.3	
18	M	MA, LV hypoplasia, VSD	PAB, ASE	4.9	RA-PA	15.4	
19	F	TA IIc	2× shunt	8.2	RA-PA, DKS	14.7	Thrombus
20	M	Tricuspid stenosis, PS, VSD, ASD	VSD closure	6.5	RA-RV	18.4	
21	M	DILV	2 × PAB	19.4	RA-RV	26.9	Thrombus
22	M	TA Ib	Valvotomy PV, shunt	5.3	RA-RV	21.6	
23	M	TA Ib	VSD enlargement	2.1	RA-RV	13.9	
24	M	TA, PS, ASD		6.7	RA-RV	19.3	Thrombus
25	M	Hypoplastic RV, TV, VSD, PS	Shunt	9.7	RA-RV	21.8	
26	F	TA Ib, PS	Shunt	4.2	RA-RV	18.1	Thrombus
27	F	TA Ib, PS		3.6	RA-RV	17.3	
28	M	TA Ib, PS		16.4	RA-RV	20.7	Thrombus
29	M	TA Ib, restrictive VSD, RVOT obstruction	RVOT patch, VSD enlargement	1.0	RA-RV	11.1	
30	F	TA Ic	PAB	5.9	RA-RV	19.6	Thrombus

Preceding the definitive Fontan operation, 41 patients had undergone different forms of palliation. The Fontan procedure was performed as a direct atrial-pulmonary anastomosis in 23 patients, an atrial–right ventricle connection (Fontan-Björk modification) in 19 patients, and a total intracardiac cavapulmonary connection (TCPC) in 10 patients. Included are two patients who had conversion to a TCPC 8 years after a primary Fontan-Björk connection.

The laboratory protocol included measurements of hematologic parameters (red blood cell count and hematocrit level), serum protein, albumin, and renal and liver function parameters (serum alkaline phosphatase, gamma-glutamyl transferase, alanine transaminase, aspartate transaminase, and total bilirubin), as well as the coagulation status (prothrombin time, international normalized ratio [INR], fibrinogen, antithrombin III, activated partial thromboplastin time, protein C, and protein S). All laboratory tests were done at the same time as TEE evaluation.

The transthoracic echocardiography, including cross-sectional view, pulse wave and continuous wave Doppler scanning, and color flow mapping, was evaluated by two experienced investigators with a Vingmed ultrasonographic system (GE Vingmed Ultrasound AS; Strandpromenaden, Horten, Norway) by using a 5.0-, 3.5-, or 2.5-MHz phased-array transducer. The TEE study was performed after achievement of local anesthesia in 27 patients and after achievement of general anesthesia and intubation in the remaining 25 patients. A Vingmed 7.5-MHz mechanical multiplane pediatric probe was used for all examinations with local anesthesia, and a Vingmed 5-MHz mechanical multiplane adult probe was used for those with general anesthesia. All examinations were done by the same physician, and all tapes were reviewed independently by another experienced investigator blinded for the initial outcome.

A thrombus was defined as any localized echogenic mass within the lumen of the left or right atrium or any other

Table I. *Continued*

Patient No.	*Sex*	*Diagnosis*	*Operation before Fontan*	*Age at Fontan operation*	*Fontan modification*	*Age at TEE*	*Thrombus*
31	M	TA Ib, PS	3 × shunt	7.2	RA-RV	24.4	
32	F	TA Ib, PS	Shunt	15.6	RA-RV	32.4	Thrombus
33	F	TA Ic	PAB	13.7	RA-RV	22.3	
34	M	TA Ib, PS		3.2	RA-RV	16.8	Thrombus
35	F	TA Ib, PS		6.0	RA-RV	21.5	
36	M	TA Ic	PAB, ASE	5.7	RA-RV	14.7	
37	M	DILV, PS	3 × shunt, PCPC	9.5	TCPC fenestrated	10.2	
38	F	DILV	3 × shunt, PCPC	16.9	TCPC fenestrated	24.1	
39	F	TA Ib, PS	2 × shunt, Fontan	15.0	TCPC fenestrated	25.1	
40	M	DILV, single AV valve, MGA	PAPVC	1.0	TCPC fenestrated	1.7	
41	F	TA Ib, PS	Shunt, Fontan	19.7	TCPC fenestrated, MVR	38.1	
42	F	DILV, MGA, restrictive VSD	ASE, PAB, PCPC, VSD enlargement	4.8	TCPC, DKS	6.7	
43	M	DILV, subaortic RVOT, MGA	2 × PAB, VSD enlargement	6.6	TCPC, nonfenstrated DKS	10.5	Thrombus
44	M	DORV, hypoplastic AV valve + LV, PS		6.0	RA-PA	15.9	
45	M	DILV, MGA, PS	Shunt	4.4	RA-PA	13.5	Thrombus
46	F	MV, hypoplastic LV, MGA, PS	ASE	3.2	RA-PA	15.0	
47	M	DILV, MGA, PS	PAB, CoA resection, PCPC	18.1	TCPC fenestrated	22.4	
48	F	TA Ib, PS	PAB, PCPC	4.4	RA-PA	13.4	
49	M	DORV, hypoplastic AV valve + LV, PS	Shunt	5.5	TCPC fenstrated	6.4	
50	M	TA Ib, PS		23.6	RA-PA	36.0	
51	F	TA Ib, PS	Shunt	10.6	RA-RV	21.1	
52	M	DILV, PA, dextrocardia	2 × shunt	8.1	RA-PA	21.7	

MV, Mitral valve atresia; *CA,* common atrium; *MGA,* malposition of the great arteries (L-MGA, levo-malposition); *DILV,* double-inlet left ventricle; *PS,* valvular and/or subvalvular pulmonary stenosis; *TA,* triscupid atresia (classification: Edwards and Burchell, 1949); *PA,* pulmonary atresia; *LPA,* left pulmonary artery; *CoA,* coarctation of the aorta; *DORV,* double-outlet right ventricle; *LPSVC,* left persistent, superior vena cava; *AV,* atrioventricular; *AS,* aortic stenosis; *TV,* tricuspid valve; *RVOT,* right ventricular outflow tract; *LV,* hypoplastic left ventricle; *PAB,* pulmonary artery banding; *PV,* pulmonary valve; *ASE,* atrial septectomy (Blalock-Hanlon septectomy); *VSD,* ventricular septal defect; *PCPC,* partial cavopulmonary connection; *PAPVC,* partial anomalous pulmonary venous connection; *RA-RV,* right atrium–right ventricle; *RA-PA,* right atrium–pulmonary artery; *DKS,* Damus-Kaye-Stansel; *TCPC,* total cavopulmonary connection; *MVR,* mitral valve replacement.

intracardiac or extracardiac location with a visible basis to a heart structure. The mass had to be seen in at least two different orthogonal planes. Furthermore, ventricular and atrioventricular valve function, eventual right-to-left shunt at the atrial level, and spontaneous echocardiographic contrast, which is regarded as a marker for stagnant blood flow, were documented. The ventricular function was classified as good, fair, or poor, and aortic and atrioventricular valve regurgitation was classified as absent, mild, moderate, or severe.

Cardiac catheterization was performed in 43 patients. The exclusion criterion for catheterization was newly diagnosed thrombus formation. A minimum of a 3-month interval of oral anticoagulation therapy was regarded to be sufficient to avoid potential complications provoked by a thrombus during atrial catheterization. The study included measurement of pressures and oxygen saturations within the superior and inferior caval veins, the right and left atria, the pulmonary artery system on the ventricular level, and the aorta. Cardiac output was calculated by the Fick method with measured oxygen consumption values. Biplane angiocardiograms of the systemic veins, the right atrium, the pulmonary artery, the ventricle, and the aorta were obtained.

Analysis of data. For statistical analysis, the measured values are reported as means ± SD, median, and range when appropriate. Patients were grouped by the presence or absence of an atrial thrombus. Data was compared by computer-assisted analysis (StatView; Abacus Concepts, Inc, Berkeley, Calif) by using the Mann-Whitney *U* test or contingency tables (the Fisher exact *P* test).

Results

The age of the patients at the definitive Fontan procedure varied between 1.0 and 24.1 years (mean, 9.3 ± 5.6 years; median, 7.2 years). The patients' ages at investigation ranged between 1.7 and 40.8 years (mean, 19.3 ± 7.4 years; median, 18.7 years). The mean interval between Fontan operation and our study ranged from 0.7 to 18.4 years (mean, 9.9 ± 4.5 years; median, 10.0 years).

According to the functional status for congenital heart disease,[7] 27 patients were in class I, 17 in class II, 6 in class III, and 2 in class IV. No significant differ-

Table II. *Patients*

	No thrombus	*Thrombus formation*	P *values*
No. of patients (n = 52)	35	17	
Sex (F/M)	14/21	10/7	.2
Age at Fontan operation (y)	9.7 ± 5.9	8.6 ± 5.0	.5
TEE follow-up (y)	19.6 ± 8.3	18.6 ± 5.5	.6
Diagnostic group (DILV/TA/MA/others)	13/15/3/4	8/8/1/0	.5
Operation group (RA-PA/RA-RV/TCPC)	16/10/9	8/8/1	.14
PLE	5	0	.15
Recurrent effussions (no PLE)	2	2	.6
History of stroke	3	0	.5
Arrythmias	17	9	.99

DILV, Double-inlet left ventricle; *TA,* triscupid atresia; *MA,* mitral atresia; *RA-PA,* right atrium–pulmonary artery anastomosis; *RA-RV,* right atrium–right ventricle anastomosis; *TCPC,* total cavopulmonary anastomosis; *PLE,* protein-losing enteropathy.

Table III. *Laboratory findings*

	No thrombus	*Thrombus formation*	P *values*
No. of patients (n = 52)	35	17	
Hematocrit level (V/V)	0.47 ± 0.05	0.46 ± 0.05	.7
Albumin (%)	54.4 ± 6.4	55.6 ± 3.8	.5
PTT (%)	83.0 ± 22.6	76.0 ± 16.3	.3
Antithrombin III (%)	90.2 ± 11.1	91.4 ± 11.7	.7
Protein C (%)	85.7 ± 25.5	91.7 ± 22.2	.5
Protein S (%)	91.6 ± 7.6	90.9 ± 11.6	.8

V/V, Volume fraction (volume red cells/volume whole blood); *PTT,* partial thromboplastin time.

ences could be shown between the functional status of the patients with or without intracardiac thrombus formation (11 in class I and 6 in class II).

Five (12%) patients had refractory protein-losing enteropathy, and another 4 patients had a history of recurrent effusions or ascites but normal serum albumin and α_1-antitrypsin levels.

These findings and others, such as sex, type of underlying heart disease, age at first Fontan operation, type of Fontan modification, follow-up interval, presence of cyanosis, or cardiac index, were not significantly different between the patients with or without intracardiac thrombi (Table II).

Anticongestive medication (angiotensin-converting enzyme inhibitors, glycosides, and diuretics) was given to 38 patients, 26 of whom were additionally receiving antiarrhythmic therapy. Fourteen patients did not take any antiarrhythmic or anticongestive medication. Before the investigation, 7 patients were receiving anticoagulation therapy because of an unfavorable hemodynamic condition. In 2 of them, a thrombus formation could be detected by TEE despite prophylactic anticoagulation with phenprocoumon (INR 2.0-2.5) for 0.8 to 1.8 years before thrombus detection.

The standard electrocardiographic recordings showed sinus rhythm in 30 patients, intermittent atrial tachycardia in 18 patients, and permanent atrial arrhythmia in another 3 patients. One had an atrioventricular universal pacemaker implanted. A history of significant atrial arrhythmia, documented by 24-hour ambulatory monitoring, was present in 26 patients during the last 12 months. In 9 of these 26 patients a thrombus formation could be detected, but no statistically significant difference between patients with or without arrhythmias could be found.

Laboratory findings of all patients are listed in Table III, and catheterization data were available in 43 patients (Table IV). There was no statistically significant difference in pressure and calculated parameters between the patients with or without intracardiac thrombus.

TEE identified thrombus formation in 17 (33%) of 52 patients. All thrombi were detected within the right atrium, and only one was additionally found in the left atrium close to the mitral valve. In 5 cases the thrombus was localized at the superior part of the posterior wall of the right atrium close to the superior caval vein. Thrombi were located at the inferior part of the posterior wall in 4 cases, and 4 thrombi were covering the complete posterior wall. Another 3 thrombi were adherent to the lateral part and a fourth to the anterior wall.

Table IV. *Hemodynamic data*

	No thrombus	*Thrombus formation*	P *values*
No. of patients (n = 43)	31	12	
RA mean pressure (mm Hg)	12.8 ± 3.5	11.8 ± 2.8	.4
PA-LA gradient (mm Hg)	4.1 ± 2.3	3.9 ± 2.4	.8
PA mean pressure (mm Hg)	11.9 ± 3.8	11.9 ± 4.8	.98
LV end-diastolic pressure (mm Hg)	8.4 ± 4.0	7.6 ± 2.4	.5
Arterial So_2 (%)	92.8 ± 4.2	93.9 ± 3.7	.5
Q_p ($L \cdot min^{-1} \cdot m^{-2}$ BSA)	2.6 ± 0.6	3.1 ± 1.3	.06
Q_s ($L \cdot min^{-1} \cdot m^{-2}$ BSA)	2.8 ± 0.9	2.9 ± 0.8	.7
R_p ($U \times m^2$ BSA)	1.8 ± 1.2	1.4 ± 0.9	.2
R_S ($U \times m^2$ BSA)	23.6 ± 9.8	22.9 ± 9.8	.8
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$ BSA)	2.4 ± 0.6	2.4 ± 0.6	.8

RA, Right atrium; *PA,* pulmonary artery; *LA,* left atrium; *LV,* left ventricle; SO_2, oxygen saturation; Q_p, pulmonary flow; *BSA,* body surface area; Q_s, systemic flow; R_p, pulmonary resistance; *U,* Wood units; R_S, systemic resistance.

Table V. *Echocardiographic findings*

	No thrombus	*Thrombus formation*	P *values*
No. of patients (n = 52)	35	17	
Spontaneous contrast	23	11	.99
SV function (normal/fair/reduced/poor)	17/6/6/6	9/3/4/1	.7
AV valve regurgitation (no/mild/moderate/severe)	7/23/4/0	5/12/0/1	.4

SV, Single ventricle; *AV,* atrioventricular.

Table VI. *Reports with TEE to assess occurrence rate of intracardiac thrombi in patients after Fontan operations*

Authors	*No. of patients*	*No. of patients with thrombus*	*95% CI*
Stümper and colleagues, 1991[16]	18	3 (17%)	3.6–41.4
Fyfe and colleagues, 1991[17]	30	6 (20%)	7.7–38.6
Feltes and colleagues 1994,[18]	9	4 (44%)	13.7–78.8
Shirai and colleagues, 1998[19]	16	3 (19%)	4.1–45.7
Presented study	52	17 (33%)	20.3–41.1

CI, Confidence interval.

By using TEE, spontaneous contrast in the right atrium or within the Fontan connection was documented in 34 (65%) patients. The occurrence of spontaneous microcavitations in the atrium did not differ significantly between patients with or without thrombus formation. Furthermore, no significant difference was found between the two groups regarding atrioventricular function and ventricular function (Table V).

A thrombus formation within the right atrium could be suspected by use of transthoracic echocardiography before TEE in only 1 patient. The remaining 16 cases could be visualized only by means of TEE.

Discussion

Thrombi are an important complication after a Fontan operation. The true incidence of central venous intracardiac thrombosis and subclinical occurrence of arterial embolization is certainly unknown and often underestimated in patients having undergone a Fontan operation. In a study of cerebrovascular accidents after a Fontan operation, du Plessis and coworkers[8] described a stroke incidence of 2.6% among 645 patients over a 15-year period.

In our series of 52 patients after Fontan-type operations, we found a high occurrence rate (33%) of intracardiac thrombi. In all but one patient transthoracic echocardiography before TEE was unable to identify a thrombus. All thrombi were detected within the right atrium, and only one was additionally found in the left atrium close to the mitral valve. Location of intracardiac thrombi may also occur in the systemic ventricle, rudimentary ventricle, pulmonary artery, or pulmonary artery stump after its distal ligation,[9-12] but not in our study so far.

The symptoms of thrombus formation include venous obstruction, progressive cyanosis, paradoxic emboli to the cerebral or peripheral circulation (if right-to-left atrial shunt is present), or atrial tachyarrhythmia.[13-15] One of our patients had a history of pulmonary embolization, and 3 others had a history of systemic or cerebrovascular embolization. The source of thromboembolism remained unknown, but cardiac anatomy was not investigated by TEE at that time. None of our patients had acute clinical signs of thromboembolic events at the time of investigation, which was mandatory for inclusion into the study. In a retrospective study, Rosenthal and coworkers[9] reported that approximately 43% of the patients with thrombi were asymptomatic. However, 21% of the patients in whom a thrombus formation was previously demonstrated died of a thromboembolic event.

Predisposing risk factors for the development of thrombi and subsequent embolization are a slow and nonpulsatile flow through the caval veins; a poorly contracting, enlarged, and thickened atrium with or without arrhythmias; a small transpulmonary gradient that decreases flow within the tunnel; a low cardiac output with or without atrioventricular valve regurgitation; or an obstructed conduit or a complex baffling because of unusual venous return.[16]

The overall reported incidence of intracardiac thrombus formation after the Fontan operation identified by TEE ranges has been shown to be between 6% and 44%,[17-21] but the number of the investigated patients was small and selected for various problems (n = 9-30 patients, Table VI). Despite this, TEE is rarely used for postoperative follow-up.

Our study confirms the high occurrence of intracardiac thrombi (33% in 52 patients), but we were unable to define specific previous surgical management as a risk factor for thrombosis.[9,11] The frequency of thrombosis was similar after total cavopulmonary, atriopulmonary, or atral–right ventricular connections. However, we mainly studied older patients with a long follow-up period (>10 years). The number of patients with TCPC was too small in comparison with those with the classic atriopulmonary or atrial–right ventricular connection to predict the occurrence rate of thrombosis in patients with that type of modification, which is more commonly used today.

There is a substantial incidence of early and late arrhythmias after the various modifications of the Fontan procedure.[22,23] Parallel to previous TEE studies,[18,19] we could not show any consistency between thrombus formation and arrhythmias or the type of Fontan modification.

Abnormalities of the clotting system, mainly protein C or protein S deficiency, reduced concentration of antithrombin III, and elevated activity of the von Willebrand factor may additionally be involved in prothrombotic reactions in patients having undergone a Fontan operation,[3,15,20] although it failed in this study to be a prognostic risk factor. This was because the number of patients with clotting abnormalities was not significantly different in the groups with and without intracardiac thrombi.

Specific hemodynamic data, such as blood flow, saturation, atrial pressure, and pulmonary resistance or obstructions, did not differ significantly in patients with or without thrombus formation.

In a literature review of children having undergone a Fontan-type operation, Michelson and coworkers[24] found 26 publications dealing with 486 patients. Only 3 of the included publications reported the use of antithrombotic therapy.

Today the role of long-term anticoagulation with warfarin remains controversial. No consensus is found in the literature or routine clinical practice about the optimal type or duration of anticoagulation.[6] Predominantly, patients with low cardiac output, with or without residual right-to-left shunting, are thought to benefit from anticoagulation.

At most cardiac centers, a wide variety of prophylactic anticoagulation regimens exists, ranging from no antiplatelet therapy in asymptomatic patients up to a life-long regimen of anticoagulation therapy with warfarin in all patients having undergone a Fontan operation.[9,11,15,25] Virtually no information regarding the safety and efficacy or the duration of prophylactic oral anticoagulation therapy exists. Because randomized, controlled, prospective trials are not available, statistically based guidelines for the management of children and adolescents after Fontan-like operations do not exist.[6]

The use of anticoagulant therapy has always been weighed against the risk of hemorrhagic complications. Rosenthal and coworkers[9] estimated an approximately constant hazard rate of 3.9 bleeding events per 100 patient-years. Apart from the therapeutic aspects, a "good Fontan adolescent" will struggle against any medication that distances him or her further from normality to maintain his or her self-esteem and will tend to neglect his or her medical history and current problems.[2]

At our institution, we keep the INR target levels in patients after a modified Fontan operation between 3.0 and 4.5**.** The recommendations for an appropriate INR for children may be lower than that found in adults,[24,26,27] but the optimal INR to prevent thrombus formation in children having undergone a Fontan operation remains unclear, and recommendations are usually defined according to the experience with patients after prosthetic valve operations.

Of the 7 patients who were receiving oral anticoagulation therapy, 2 were shown to have an intracardiac thrombus formation. At the time of our study, one of these patients had an INR of 2.5, and the other had an INR of 2.0. Both were symptom-free. An additional anticoagulation disorder could not be diagnosed in these patients.

Jahangiri and colleagues[11] described one patient with left-sided hemiparesis after administration of warfarin (INR 2.8), and a similar case was reported by Danielson in his comment. The incidence of venous thrombosis despite prophylactic oral anticoagulation with warfarin, as published by Jonas[10] in 1995, was 7.4%.

Conclusion

Intracardiac thrombi and consecutive thromboembolism can cause significant morbidity and mortality after a modified Fontan operation. This study found a high occurrence of intracardiac thrombi in asymptomatic patients. Although thrombus detection by transthoracic techniques is insufficient, TEE has proven to be the method of choice because it provides an excellent view of the atrial structures and central venous connections.

The incidence of thrombosis despite oral anticoagulation remains unknown. We were unable to define anatomic, laboratory, or hemodynamic risk factors. Thrombus formation seems to be unpredictable in the postoperative course. The preliminary data of this study may justify the recommendation of oral anticoagulation prophylaxis in patients having undergone a Fontan operation. The outcome of clinical studies with a controlled, prospective, randomized design should allow us to conclude whether life-long prophylaxis is indicated and to determine the optimal INR target level. For all patients without anticoagulation medication or inadequate INRs, we would suggest a TEE screening for thrombosis.

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Commentary

The article by Balling and associates addresses the very important issue of intracardiac thrombus formation and its possible prevention by routine anticoagulation in patients after the Fontan procedure. Thromboembolic stroke in a child is a devastating complication that often has lifelong consequences for the child and family. Furthermore, evidence is steadily accumulating that there is indeed a procoagulant state with Fontan physiology. For example, recent work by Jahangiri and associates, both in London and in Boston, has demonstrated a decreased level of protein C and protein S, as well as an increase in some procoagulant factors.

Balling and associates reviewed the case histories of 52 patients late after a Fontan procedure. All patients had undergone transesophageal echocardiographic (TEE) studies as part of a program intended to identify the incidence of thrombus in these patients, although it appears that much of the non-TEE patient-related data were not collected prospectively, but through a retrospective chart review. They identified a remarkably high incidence of intra-atrial thrombi (almost all in the right atrium), although not inconsistent with previous reports. They conclude that routine TEE is probably justified for patients after the Fontan procedure and that routine anticoagulation is probably advisable.

Before accepting the recommendations of Balling and associates, it is important to recognize some significant limitations of their report. As noted above, this is effectively a retrospective review of a selected group of patients who agreed to the TEE procedure. Most patients had undergone their Fontan operation many years before, and therefore only 9 of the 52 had had lateral tunnel–type Fontan procedures. Most had had the old-style right atrium–pulmonary artery anastomosis. Only 7 had a fenestration. Interestingly, none of the patients with a fenestration had detectable thrombus.

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None of the patients had had a recent thromboembolic event that was symptomatic, and of the 3 patients who had had cerebrovascular events in the past, none had identifiable thrombus by TEE.

With respect to the recommendation regarding anticoagulation, it is important to note that thrombi developed in 7 of these patients despite warfarin sodium (Coumadin) anticoagulation, although the authors would argue that some of these patients at least did not have adequate anticoagulation. The risks of anticoagulation need to be balanced against the morbidity of asymptomatic thrombi detected by routine screening. The risks of routine screening also need to be carefully considered when one notes that nearly 50% of this population required general anesthesia to undergo the TEE procedure.

The technique of TEE is probably quite sensitive to detect intra-atrial thrombi, but the authors have not addressed the specificity of the method. They are now embarking on a study in which magnetic resonance imaging will be used to exclude false positive results, but until the results of that investigation and others are available, it is hard to support the aggressive recommendation for routine TEE and routine anticoagulation in this difficult patient population. Nevertheless, a provocative report such as this article by Balling and associates does highlight the importance once again of urgently completing at least one (and ideally more than one) carefully organized prospective randomized study to address the issue of warfarin sodium versus aspirin versus no anticoagulation in patients after the Fontan procedure. It is important that such studies have sensitive and specific methods for intracardiac thrombus formation, as well as careful prospective assessment for symptoms and signs of thromboembolic events.

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