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Clinical Research

Clinical Importance of Fontan Circuit Thrombus in the Adult Population: Significant Association With Increased Risk of Cardiovascular Events

Gnalini Sathananthan, MD,[a] Niall Johal, BSc,[a] Tony Verma, MD,[a] Sherry Sandhu, BSc,[a] Shantabanu Chakrabarti, MD,[a] Mounir Riahi, MD,[a] Derek Human, MD,[a] Jonathon Leipsic, MD,[b] and Jasmine Grewal, MD[a]

[a] *University of British Columbia, Division of Cardiology, St Paul's Hospital, Vancouver, British Columbia, Canada*

[b] *University of British Columbia, Department of Radiology, St Paul's Hospital, Vancouver, British Columbia, Canada*

See editorial by Laflamme and Roche, pages 1631–1634 of this issue.

ABSTRACT

Background: The impact of Fontan circuit thrombus is poorly understood. The objectives of this study were to determine (1) the incidence of Fontan circuit thrombus and proportion of silent thrombus; (2) any association between Fontan circuit thrombus and markers of Fontan circulatory dysfunction; and (3) the association of Fontan circuit thrombus with adverse cardiac outcomes.

Methods: We conducted a retrospective review of adult patients who underwent the Fontan procedure (aged > 18 years) followed at St. Paul's Hospital who underwent cardiac computed tomography or magnetic resonance imaging assessment (n = 67). Fontan circulatory

RÉSUMÉ

Contexte : Les répercussions d'une thrombose du circuit de Fontan sont mal comprises. L'étude visait à déterminer : 1) l'incidence de la thrombose du circuit de Fontan et la proportion de thromboses silencieuses; 2) l'existence d'un lien entre la thrombose du circuit de Fontan et les marqueurs d'une dysfonction circulatoire du circuit de Fontan; et 3) le lien entre la thrombose du circuit de Fontan et les issues cardiovasculaires indésirables.

Méthodologie : Nous avons réalisé une revue rétrospective des cas des patients adultes (18 ans ou plus) qui ont subi une intervention de Fontan à l'hôpital St. Paul et fait l'objet d'un suivi comprenant un

The Fontan procedure was first described by Fontan and Baudet in 1971[1] for the surgical palliation of tricuspid atresia and is now the surgery of choice for patients with single ventricle physiology. The Fontan circulation enables passive flow from the systemic venous circulation to the pulmonary circulation, thereby enabling the single ventricle to function as the systemic ventricle. This procedure has revolutionized outcomes for neonates born with single ventricle physiology, with early mortality now reduced to less than 5%.[2] The Fontan procedure has evolved over time. The classic Fontan incorporated the right atrium into the subpulmonary circulation, while the more contemporary total cavopulmonary connection (TCPC) connects the systemic veins directly to the pulmonary arteries bypassing the heart entirely. Survival in a "modern" Fontan cohort is reported as 74% at 20 years.[3]

The Fontan circulation consists of a high-pressure venous circulation that results in progressive systemic venous congestion and relative deprivation of cardiac output. This, in addition to neuro-hormonal, inflammatory, and coagulation alterations, can result in varying degrees of Fontan circulatory dysfunction.[4] This can manifest in multiple ways, including clinical heart failure, decline in New York Heart Association class or exercise capacity, arrhythmias, protein-losing enteropathy, and noncardiac organ dysfunction including Fontan-associated liver disease and chronic kidney damage.

The reported incidence of clinical or silent thromboembolism (TE) in patients who underwent the Fontan procedure varies in the literature from 10% to 35%. Egbe et al.[5] reported a 25% cumulative incidence of clinical systemic and nonsystemic TE complications in 387 patients who underwent the Fontan procedure. Clinical systemic TE has been shown to be associated with increased mortality in the Fontan population.[5-10] The impact of thrombus in the Fontan circuit has not been well studied and is the focus of this study as another possible marker of Fontan circulatory dysfunction. The objectives of this study were to determine (1) the incidence of Fontan circuit thrombus and the proportion of silent thrombus; (2) if there is an association between Fontan circuit

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Corresponding author: Dr Jasmine Grewal, St Paul's Hospital, Rm 478-1081 Burrard St, Vancouver, British Columbia V6Z 1Y6, Canada. Tel.: +1-604-806-8785; fax: +1-604-806-8137.

E-mail: jasmine.grewal@vch.ca

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dysfunction markers included clinical heart failure, N-terminal pro-brain natriuretic peptide, ventricular dysfunction, atrioventricular valvular regurgitation, refractory arrhythmias, declining exercise capacity, and hepatic/renal dysfunction. Adverse cardiac outcomes were death, heart transplantation, or surgery for Fontan revision or atrioventricular valve replacement.

Results: Fontan circuit thrombus was present in 15 of 67 patients (22%): 41% (7/17) classic/modified Fontan and 16% (8/50) total cavopulmonary connection. Incidence was 36% among those suspected to have Fontan circuit thrombus; 14% in those with no clinical/echocardiographic suspicion; and clinically silent in 40% diagnosed with Fontan thrombus. The time from Fontan surgery to Fontan circuit thrombus diagnosis was 22 ± 6 years in the classic/modified group vs 14 ± 8 years in the total cavopulmonary connection group ($P = 0.03$. Fontan circuit thrombus was associated with adverse cardiac outcomes (27% [4/15] vs 8% [4/52], $P = 0.02$), but there was no difference in Fontan circulatory dysfunction markers.

Conclusion: Given the incidence of Fontan circuit thrombus and association with adverse cardiac outcomes, routine surveillance of the Fontan circuit should strongly be considered. The identification of thrombus should lead to anticoagulation implementation/optimization, along with screening/intervention for reversible Fontan circulatory issues in an attempt to prevent adverse cardiac outcomes.

examen par tomodensitométrie cardiaque ou par imagerie par résonance magnétique (n = 67). Les marqueurs de la dysfonction circulatoire du circuit de Fontan comprenaient l'insuffisance cardiaque clinique, le propeptide natriurétique de type B N-terminal, la dysfonction ventriculaire, la régurgitation valvulaire auriculoventriculaire, l'arythmie réfractaire, le déclin de la capacité à l'effort et la dysfonction hépatique/rénale. Les issues cardiovasculaires indésirables étaient le décès, la greffe cardiaque ou une intervention chirurgicale visant à corriger le circuit de Fontan ou à remplacer la valve auriculoventriculaire.

Résultats : Une thrombose du circuit de Fontan était présente chez 15 (22 %) des 67 patients : 7 (41 %) des 17 patients ayant un circuit de Fontan classique/modifié et 8 (16 %) des 50 patients ayant une connexion cavopulmonaire totale. L'incidence s'établissait à 36 % chez les patients chez qui une thrombose du circuit de Fontan était soupçonnée et à 14 % chez ceux chez qui on ne soupçonnait aucune anomalie clinique/échographique; la thrombose était silencieuse chez 40 % des patients ayant reçu un diagnostic de thrombose du circuit de Fontan. L'intervalle entre l'intervention de Fontan et le diagnostic de thrombose du circuit de Fontan était de 22 ± 6 ans chez les patients ayant un circuit de Fontan classique/modifié et de 14 ± 8 ans chez les patients ayant une connexion cavopulmonaire totale ($p = 0,03$). La thrombose du circuit de Fontan a été associée à des issues cardiovasculaires indésirables (27 % [4/15] vs 8 % [4/52], $p = 0,02$), mais il n'y avait pas de différence entre les marqueurs de dysfonction circulatoire du circuit de Fontan.

Conclusion : Compte tenu de l'incidence de la thrombose du circuit de Fontan et du lien établi avec les issues cardiovasculaires indésirables, nous recommandons vivement une surveillance de routine du circuit de Fontan. Si une thrombose est détectée, il convient d'instaurer une anticoagulothérapie ou d'optimiser le traitement anticoagulant déjà prescrit et de procéder à un dépistage ou, s'il y a lieu, à une intervention à l'égard des problèmes circulatoires réversibles du circuit de Fontan afin de prévenir les issues cardiovasculaires indésirables.

thrombus and other known markers of Fontan circulatory dysfunction; and (3) if there is an association of Fontan circuit thrombus with adverse cardiac outcomes.

Methods

Study population

This is a retrospective study of adult patients (aged > 18 years) who have undergone a Fontan operation and are being actively followed in the Pacific Adult Congenital Heart Clinic at St. Paul's Hospital. Patients were included if they underwent Fontan circuit evaluation with cardiac computed tomography (CT) or magnetic resonance imaging (MRI). The institutional ethics review board approved the study.

All patients underwent annual clinical review, including a complete history, physical examination, and assessment of New York Heart Association functional class. The following data were also obtained from the patient records: underlying cardiac diagnoses, age at and type of Fontan procedure, other cardiac interventions, current cardiac medications, and history of all cardiac events that had occurred up until the time of last follow-up. Standard investigations including electrocardiogram, cardiopulmonary stress testing, and echocardiogram were obtained from the most recent clinical follow-up. The blood work was obtained within 6 to 12 months of the CT/MRI.

Fontan type was defined as follows: (1) Classic Fontan refers to an anastomosis between the right atrial appendage and either the main or right pulmonary artery; (2) TCPC refers to both the lateral tunnel and extracardiac Fontan; and (3) modified Fontan refers to any Fontan surgery that does not fit the description of a classic, lateral tunnel, or extracardiac Fontan.

Thromboembolism

Fontan circuit thrombus is being studied as a marker of Fontan circulatory dysfunction and defined as thrombus in the proximal inferior vena cava, Fontan conduit or tunnel, or right atrium in the setting of the classic atriopulmonary Fontan or modified Fontan. Pulmonary artery thrombus was defined as thrombus in the branch pulmonary arteries or emboli distal to the main branch pulmonary arteries. Peripheral TE was defined as transient ischaemic attacks confirmed by a neurologist, cerebrovascular accidents (CVAs) confirmed by CT, or other peripheral embolism.

Markers of Fontan circulatory dysfunction

Markers of circulatory dysfunction were assessed and included clinical and biochemical heart failure (N-terminal

pro-brain natriuretic peptide [NT-proBNP]), systemic ventricular dysfunction, systemic atrioventricular valvular regurgitation (SAVVR), refractory arrhythmias, protein-losing enteropathy, declining exercise capacity, and extracardiac organ dysfunction, namely, hepatic and renal.

Clinical heart failure was defined as a hospital admission for inpatient treatment of heart failure or at least 2 of the following items in an outpatient setting: increasing dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, increasing peripheral edema, ascites, radiologic signs of heart failure, or new/escalating diuretic therapy. Refractory arrhythmias defined as $\geq$ 1 inpatient hospital visits/admissions in a given year for arrhythmias refractory to pharmacologic management or electrophysiologic ablation. Protein-losing enteropathy was defined as requiring the following 3 criteria: hypoalbuminemia (<30 g/L) for > 3 months in the absence of significant liver or renal disease, accompanying ascites, pleural effusion, edema, diarrhea, or abdominal pain for > 3 months and positive stool alpha 1 anti-trypsin.[11]

Extracardiac dysfunction was assessed and included the presence of liver or kidney dysfunction. The following parameters were noted for the assessment of liver dysfunction: (1) imaging or biopsy confirmation of liver cirrhosis and (2) VAST (Varices, Ascites, Splenomegaly, Thrombocytopenia) score > 2. The VAST score is calculated by the sum of clinical findings, namely, varices, ascites, splenomegaly, and thrombocytopenia defined as platelets < 150.[12] Varices, ascites, and splenomegaly were assessed clinically or based on imaging; (3) liver enzyme levels; (4) direct bilirubin; and (5) albumin. Kidney dysfunction defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or urine albumin creatinine ratio > 3 mg/mmol.

The adverse composite cardiac outcome was defined as death, heart transplantation, or surgery for Fontan conversion or systemic atrioventricular valve replacement.

Transthoracic echocardiogram

All echocardiograms were reviewed by an experienced echocardiographer (JG, MK), blinded to both dual-energy cardiac CT/cardiac MRI and clinical data. Ventricular function was assessed qualitatively and graded as normal, mild dysfunction, moderate dysfunction, or severe dysfunction. Severity of SAVVR was graded qualitatively following the American Society of Echocardiography guidelines for native valve regurgitation and reported as mild, moderate, moderate to severe, or severe.

Dual-energy cardiac CT

All studies were acquired with a multidetector CT scanner (Discovery HD 750, Gemstone Spectral Imaging, GE Healthcare, Chicago, IL). Standard contrast injection protocol was used with a body mass index–determined contrast volume ranging from 80 to 125 mL of ioversol 320 (Optiray 320 syringe, Tyco Healthcare, St. Louis, MO) injected into the upper left or right limb. Contrast was injected at a flow rate of 3 mL/second. A 180-second scan delay was used to optimize homogeneous opacification of the upper and lower limb of the Fontan circuit, the cardiac structures, and the central pulmonary vascular bed. The following imaging protocol was used: dual-energy scanning with rapid switching between 140 and 80 kVp, tube current of 600 mAs, rotation time 0.5 seconds, table feed/rotation 0.984 mm, and section collimation 1.25 mm. Images were then reconstructed at low monochromatic energy levels of 40 and 50 kEV to increase the attenuation of the vascular bed. Delayed phase imaging using dual-energy CT helps increase the signal in the Fontan circuit and reconstruction using low monochromatic reconstruction increases the attenuation in the Fontan circuit to improve conspicuity of thrombus.[13,14]

Cardiac MRI

Cardiac MRI examinations were performed on a 1.5 T MR platform (GE HD Signa, Waukesha, WI). Imaging protocol included axial double inversion recovery, sagittal oblique, right ventricular and left ventricular outflow tract steady-state free precession, phase-contrast imaging of the Fontan circuit, and time resolved post-gadolinium magnetic resonance angiography. By using time-resolved magnetic resonance angiography, the gadolinium is followed and imaged as it opacifies both the upper and lower limbs of the Fontan circuit over time through temporal sampling.

Statistical analysis

Descriptive statistics for categorical variables were reported as frequency and percentage, and continuous variables were reported as mean $\pm$ standard deviation. Survival and freedom from adverse cardiac outcome not subjected to competing risks were examined using Kaplan–Meier analysis. The adverse composite cardiac outcome for Kaplan–Meier analysis was defined as death, heart transplantation or surgery for Fontan conversion, or systemic atrioventricular valve replacement. Categorical data were analysed using the Fisher exact test. Continuous data were analysed using paired t test. A P value of less than 0.05 was considered statistically significant. All data were analysed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

Results

At the time of this retrospective study, our clinic was following 140 patients who had underwent Fontan palliation, of whom 70 had Fontan circuit evaluation with cardiac CT or MRI. Three patients were excluded because the results of the imaging were inconclusive for the presence or absence of thrombus, and ultimately 67 (48%) met criteria and were included in this study (Table 1). Fifty-two patients (78%) underwent a cardiac CT, and 15 patients (22%) underwent a cardiac MRI. No patients had both tests. The indication for imaging was as follows: (1) rule out Fontan circuit or pulmonary artery thrombus in 25 (37%); (2) routine imaging in 33 (49%); (3) rule out collaterals/fenestration in 5 (7%); (4) assess lung nodules in 1 (1%); (5) preablation assessment in 1 (1%); (6) Blalock–Taussig shunt assessment in 1 (1%); and (7) chest pain evaluation in 1 (1%). At our centre, cardiac CT or MRI is performed every 3 to 5 years as a part of routine imaging in Fontan patients for complete assessment of Fontan circuit patency. This is in line with the 49% who underwent routine imaging in this study.

Table 1. Patient characteristics

Characteristic	Study cohort n = 67
Age, y	30.8 ± 9.3
Male	39 (58%)
Ventricle type	
Left	49 (73%)
Right	16 (24%)
Indeterminate	2 (3%)
Fontan type	
Atriopulmonary	11 (16%)
Lateral tunnel (TCPC)	24 (36%)
Extracardiac conduit (TCPC)	26 (39%)
Modified Fontan	6 (9%)
Systemic ventricle	
Normal	37 (55%)
Mildly depressed function	20 (30%)
Moderately/severely depressed function	10 (15%)
Systemic AV valve regurgitation	
Moderate	8 (12%)
Severe	3 (4%)
Medications	
ACE inhibitor	25 (37%)
β-Blocker	26 (39%)
Aspirin	26 (39%)
Warfarin	37 (55%)
Diuretic	13 (19%)

ACE, angiotensin-converting enzyme; AV, aortic valve; TCPC, total cavopulmonary connection.

Fontan circuit thrombus and other thromboembolic complications

Fontan circuit thrombus was present in 15 (22%) of the patients studied (Table 2). Of the patients referred for Fontan circuit thrombus evaluation, 9 of 25 (36%) had a positive scan (Fig. 1). The indication for imaging in the remaining 6 patients with Fontan circuit thrombus was routine surveillance, meaning that 40% (6/15) of diagnosed Fontan circuit thrombus was clinically silent. The incidence of Fontan circuit thrombus in patients with no clinical or echocardiographic suspicion of such was 14% (6/42). Twelve (80%) were detected on cardiac CT, and 3 (20%) were detected on cardiac MRI. Fontan thrombus was suspected by transthoracic echocardiogram in 3 of the 15 patients (20%). Fontan circuit thrombus was present in 41% (7/17) of patients with a classic or modified Fontan compared with 16% (8/50) of patients with TCPC. The time from Fontan surgery to diagnosis of Fontan circuit thrombus was 22 ± 6 years in the classic/modified group vs 14 ± 8 years in the TCPC Fontan group ($P = 0.03$).

Six patients (40%) who developed Fontan circuit thrombus were taking warfarin at the time of diagnosis: (1) Two patients had documented therapeutic international normalized ratios (INRs) immediately before the event (INR 2-3); (2) 3 patients had subtherapeutic INRs leading up to the event; and (3) 1 patient had been taking Coumadin but had discontinued it in the prior week for an upcoming procedure. Four patients (27%) who developed Fontan circuit thrombus were taking aspirin (81 mg daily) at the time of diagnosis. None of the patients were taking a combination of antiplatelets and anticoagulation. All patients were placed on anticoagulation after the diagnosis of thrombus if they had not been on it previously (Fig. 1).

Pulmonary artery thrombus was present in 6 patients (9%). All 6 patients with pulmonary artery thrombus also had Fontan circuit thrombus. Peripheral TE was present in 10 patients (15%). Only 1 patient with peripheral TE also had Fontan circuit thrombus. This patient had an embolic middle cerebral artery territory CVA a few months before the detection of thrombus. The patient did not have a fenestration or known arrhythmias. Among the 10 patients with peripheral TE, there were 3 transient ischaemic attacks; 1 left middle cerebral artery territory CVA postcardiac catheterization; 3 left

Table 2. Fontan circuit thrombus characteristics and treatment

	Sex	Age	Fontan type	Thrombus details	PE	Coumadin at time of diagnosis	Treatment postdiagnosis
1	M	29	Lateral tunnel	Extensive mural Fontan thrombus extending to intrahepatic IVC	No	No	IV heparin/Coumadin
2	M	35	Extracardiac	Mural Fontan thrombus	No	Yes	Coumadin
3	M	22	Extracardiac	Mural Fontan thrombus	No	No	LMWH/Coumadin
4	F	28	Extracardiac	Mural Fontan thrombus	No	Yes	Coumadin
5	M	20	Extracardiac	Mural Fontan thrombus	No	No	Coumadin
6	F	20	Lateral tunnel	Distal/mid conduit and within the SVC-MPA conduit	Yes	Yes	Thrombolysis/Coumadin
7	M	24	Lateral tunnel	Gore-Tex (WL Gore & Associates, Flagstaff, AZ) graft between hepatic and azygous veins	No	Yes	Coumadin
8	M	19	Extracardiac	Extensive mural Fontan thrombus	Yes	No	Thrombolysis and surgery
9	M	19	Classic	RA thrombus	No	Yes	Coumadin
10	M	26	Modified	RA thrombus	No	No	Thrombolysis
11	F	46	Classic	Large RA thrombus	Yes	No	IV heparin/Coumadin
12	M	33	Classic	RA thrombus	Yes	No	LMWH/Rivaroxaban
13	M	29	Modified	Mural Fontan thrombus in IVC tunnel within atrium	No	Yes	Coumadin
14	F	36	Classic	RA thrombus	Yes	No	Thrombolysis
15	M	24	Modified	Extensive thrombus in right atrium and anterior aspect of RVOT, extending into MPA	Yes	No	IV heparin

IV, intravenous; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; MPA, main pulmonary artery; PE, pulmonary embolism; RA, right atrium; RVOT, right ventricular outflow tract.

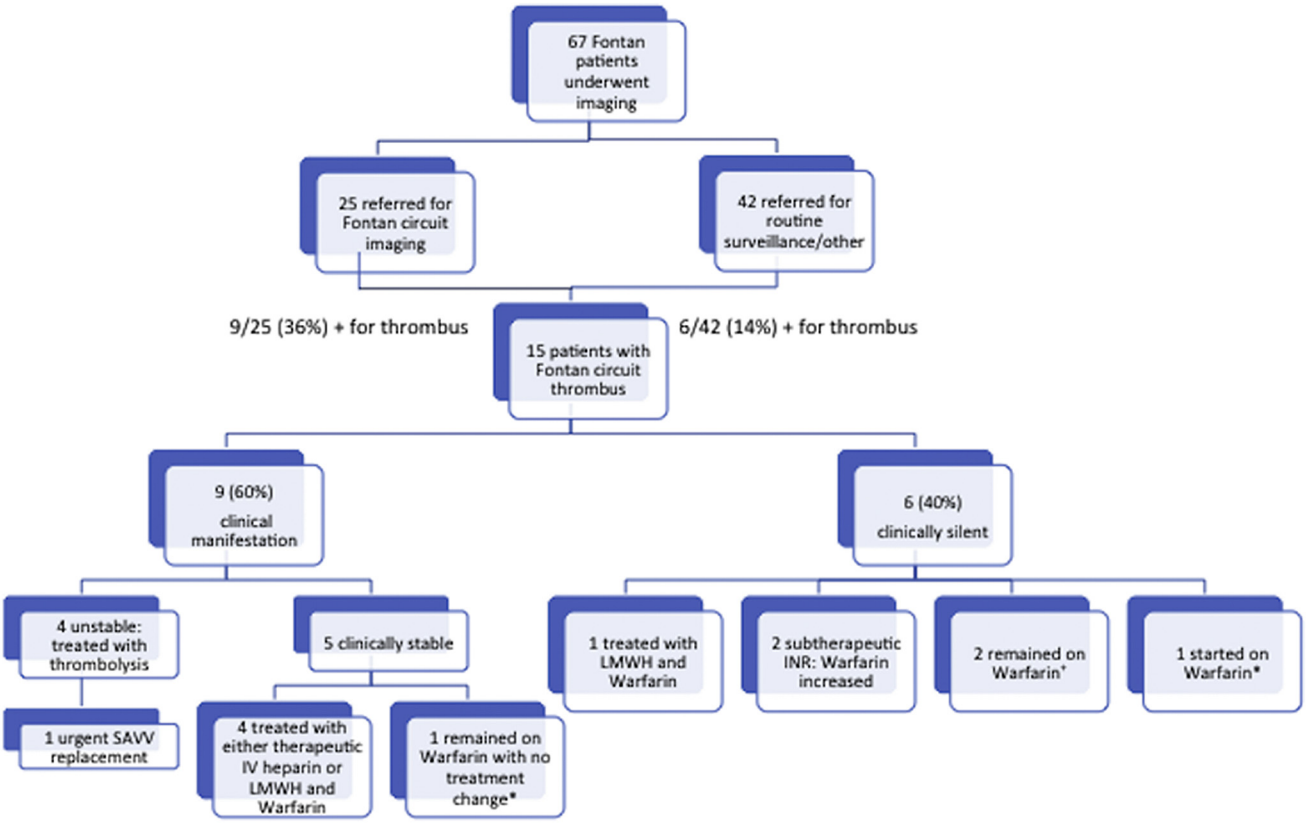

Figure 1. Presentation of Fontan circuit thrombus. *Low burden mural thrombus. [+]One patient underwent Fontan revision not longer after diagnosis of thrombus, and 1 patient had low-burden mural thrombus. IV, intravenous; LMWH, low-molecular weight heparin; SAVV, systemic atrioventricular valvular regurgitation.

embolic middle cerebral artery territory CVA; 1 embolic cerebellar CVA; 1 brainstem CVA; and 1 embolic CVA associated with a right to left shunt.

Association of Fontan circuit thrombus with markers of Fontan circulatory dysfunction

Patients with vs without Fontan circuit thrombus were similar in age (33.7 ± 8.6 years vs 29.9 ± 9.3 years, $P = 0.16$). Patients with and without Fontan circuit thrombus had no statistically significant differences in clinical heart failure, NT-proBNP, refractory arrhythmias, ventricular dysfunction, and significant atrioventricular regurgitation, although the rates were higher in the thrombus group (Table 3). Exercise capacity was similar between the 2 groups. Among the 7 patients with a classic/modified type Fontan who developed thrombus, 5 had clinical heart failure, and it was temporally related to Fontan thrombus in 2 patients (Fig. 2). Among the 8 patients with TCPC type Fontan who developed thrombus, 1 had clinical heart failure, and it was temporally related to the Fontan thrombus in this case (Fig. 2).

Urine albumin to creatinine ratio was similar between the 2 groups, as were liver enzymes, VAST score, and protein-losing enteropathy. There was a lower eGFR among those with thrombus ($P = 0.02$), although the value still remained within the normal range.

Table 3. Fontan circulatory dysfunction in patients with Fontan circuit thrombus

Characteristic	Yes N = 15	No N = 52	*P* value
Heart failure			
Clinical heart failure	5 (33%)	8 (15%)	0.17
NT-proBNP	516 ± 633	283 ± 448	0.23
VO2max, mL/kg/min	22 ± 5	22 ± 7	0.85
Moderate/severe ventricular dysfunction	3 (20%)	7 (14%)	0.34
Moderate/severe AV valve regurgitation	4 (27%)	7 (13%)	0.24
Refractory arrhythmia	2 (13%)	4 (8%)	0.57
Atrial fibrillation/flutter	9 (60%)	20 (38%)	0.13
Protein-losing enteropathy	0 (0%)	2 (4%)	0.42
Liver disease/dysfunction			
VAST > 2	3 (20%)	13 (25%)	0.59
Platelets	161 ± 53	169 ± 62	0.78
AST	30 ± 7	31 ± 18	0.85
ALT	30 ± 13	34 ± 32	0.69
Direct bilirubin	31 ± 19	22 ± 21	0.22
Albumin	44 ± 6	44 ± 5	0.69
Kidney disease/dysfunction			
Urea	11 ± 20	5 ± 3	0.05
eGFR, mL/min/1.73 m^2	94 ± 19	106 ± 16	0.02
eGFR < 60 mL/min/1.73 m^2	1 (7%)	2 (4%)	0.56
uACR, mg/mmol	2.9 ± 2.3	3.9 ± 5.1	0.44
uACR > 3 mg/mmol	4 (27%)	11 (21%)	0.61

ALT, alanine transaminase; AST, aspartate aminotransaminase; eGFR, estimated glomerular filtration rate; uACR, urine albumin creatinine ratio; VAST, Varices, Ascites, Splenomegaly, Thrombocytopenia.

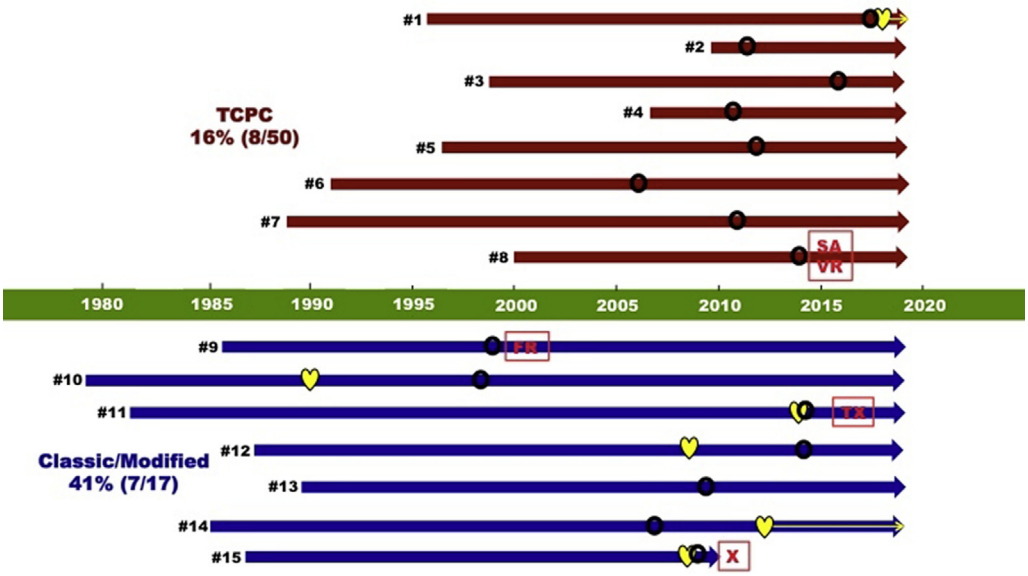

Figure 2. Fontan circuit thrombus and adverse cardiac outcomes. **Red bars** represent patients with a TCPC Fontan, and **blue bars** represent patients with a classic/modified Fontan. Onset of the **arrow** is date of Fontan completion. **Black circle** = diagnosis of Fontan circuit thrombus; **yellow heart** = clinical heart failure. FR, Fontan revision; SAVR, systemic atrioventricular valve replacement; TCPC, total cavopulmonary connection; TX, heart transplant; X, death.

Among the 15 patients with Fontan circuit thrombus, 4 (27%) had hemodynamic or respiratory instability that led to thrombolysis. Of these 4 patients, 1 had a classic Fontan, 1 had a modified Fontan, 1 had a lateral tunnel, and 1 had an extracardiac Fontan (Fig. 1).

Association of Fontan circuit thrombus with adverse cardiac outcomes

Thrombus was associated with increased rates of adverse outcomes defined as death, heart transplantation, or surgery (for Fontan revision or atrioventricular valve replacement) compared with those without thrombus (27% [4/15] vs 8% [4/52], $P = 0.02$). Freedom from adverse outcomes was greater among the group with no Fontan circuit thrombus, with early cardiac outcomes seen in the thrombus group (Fig. 3).

Among the 7 patients with classic/modified Fontan circuit thrombus, 3 had adverse cardiac outcomes, all of which occurred in close proximity to the diagnosis of Fontan circuit thrombus: (1) patient 9 underwent a Fontan revision due to recurrent arrhythmias; (2) patient 11 underwent a cardiac transplant within 2 years of the diagnosis of thrombus during which time clinical heart failure had developed; and (3) patient 15 had a cardiac arrest at the time of diagnosis of Fontan thrombus. This patient also had severe ventricular systolic dysfunction and SAVVR. He sustained significant hypoxic brain injury and had withdrawal of treatment after lengthy discussions.

Among the 8 patients with TCPC Fontan circuit thrombus, 6 had isolated low burden thrombus with no associated cardiac events. One patient had a diagnosis of Fontan circuit thrombus diagnosed in close proximity to an adverse cardiac outcome: patient 8 with severe SAVVR decompensated despite thrombolysis and developed cardiogenic shock requiring emergent systemic atrioventricular valve replacement. Patient 1 presented with worsening heart failure secondary to severe ventricular systolic dysfunction and severe SAVVR, and was found to have a large burden of thrombus but did not go on to have a defined adverse cardiac event.

Discussion

In this contemporary cohort of adult patients who underwent the Fontan, the overall incidence of Fontan circuit thrombus was 22%: the incidence was 36% among those with

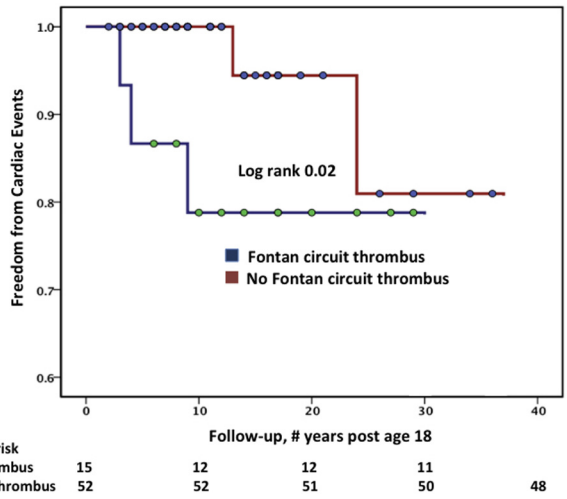

Figure 3. Kaplan–Meier graph demonstrating freedom from adverse cardiac outcomes of death, heart transplantation, or surgery for Fontan revision or atrioventricular valve replacement after age 18 years. The **blue line** demonstrates patients with Fontan circuit thrombus, and the **red line** represents those without.

suspected Fontan circuit thrombus and 40% of diagnosed Fontan circuit thrombus was clinically silent. The incidence of Fontan circuit thrombus in patients with no clinical or echocardiographic suspicion of such was 14%. There was no significant relationship found between Fontan circuit thrombus and markers of Fontan circulatory dysfunction, perhaps because the study lacked invasive haemodynamic data and due to limited study size. However, 27% of patients with Fontan circuit thrombus did present with acute circulatory dysfunction requiring thrombolytic therapy. Fontan circuit thrombus was associated with significantly increased adverse cardiac-outcome incidence, including death, heart transplantation or surgery for Fontan revision, and atrioventricular valve replacement.

The findings in this study are applicable to the broader Fontan population, given that 49% of our cohort underwent imaging as a part of routine surveillance and 13% underwent imaging for a number of other indications. A smaller proportion (37% of the patients) were referred specifically because of concern with the Fontan circulation. The rate of Fontan circuit thrombus was higher in the classic/modified Fontan compared with TCPC, as has been reported.[9] The classic and modified Fontan were both early approaches to patients with single ventricle physiology, and these patients consequently have longer follow-up time, which may explain the increased thrombus seen. In our study, the average follow-up time was 22 years and 14 years for classic/modified and TCPC, respectively. One of the many reasons for moving away from the classic/modified Fontan to a TCPC was to reduce the incidence of thrombus, so it could be argued that a 16% incidence in the TCPC group is somewhat high at short- to medium-term follow-up. The Fontan circuit thrombus seen in these groups is different with the TCPC tending to have a low burden mural thrombus in the majority of the patients. The longer-term impact of this will need to be the focus of future study.

The results of this study would support the routine use of multi-modality imaging of the Fontan circuit, because 40% of diagnosed Fontan circuit thrombus was clinically silent, and the incidence of Fontan circuit thrombus in patients with no clinical or echocardiographic suspicion of such was 14%. Dual-energy cardiac CT with delayed-phase imaging to ensure opacification of the entire Fontan circuit is the most frequently used modality at our centre and thus in our study. Cardiac CT is the preferred modality when it comes to the detection of thrombus because of superior spatial and temporal resolution. Fontan thrombus was suspected by transthoracic echocardiogram in only 15% of those with Fontan circuit thrombus in our study, highlighting the limitations when this imaging tool is used alone for the assessment of Fontan circuit patency. Often, only the most proximal and distal aspects of the TCPC Fontan circuit are well visualised, missing the remainder of the circuit and any low-burden thrombus. In the case of the classic Fontan, the right atrium can be very large so that the entire structure is difficult to interrogate for thrombus by echocardiography alone.

Fontan circuit thrombus formation can result in ventilation perfusion mismatch, elevation of pulmonary vascular resistance, or significant obstruction of the circuit itself, all of which can significantly impede the Fontan circulation. There is no consensus around the optimal strategy to prevent TE in the Fontan population. Previous work has shown that prophylaxis with antiplatelet or anticoagulation therapy is associated with a lower incidence of thromboembolic events in patients post—Fontan palliation.[15-17] These studies often referred to systemic thromboembolic events that were most commonly the result of atrial arrhythmias. Our study focuses on Fontan circuit thrombus diagnosed by cross-sectional imaging, which likely has different mechanisms than systemic TE. Many of the study patients developed Fontan circuit thrombus on antiplatelet therapy, whereas some also developed thrombus on warfarin, but in most cases were not in the therapeutic range. The results of this study do not justify routine prophylactic anticoagulation but would support routine surveillance with multimodality imaging to help identify patients with clinically silent Fontan circuit thrombus. These patients would likely benefit from anticoagulation to prevent disruption of the Fontan circulation integrity.

Our data would suggest that Fontan circuit thrombus is more likely to occur in the context of other markers of circulatory dysfunction. Fontan circuit thrombus was associated with higher rates of significant ventricular dysfunction, significant valvular regurgitation, heart failure, and arrhythmias, although this did not reach statistical significance likely because of the small sample size. NT-proBNP was also higher in the thrombus group, although this was also not statistically significant. Elevated BNP has been shown to be an independent predictor of Fontan failure and mortality.[18] Certainly many of the patients with a classic/modified Fontan circuit thrombus had associated heart failure, whereas this was not the case in the TCPC thrombus group. Moreover, the TCPC circuit thrombus was mural and mostly lower burden. Longer follow-up in the TCPC group will be beneficial to better understand this relationship. It is intuitive that abnormal upstream hemodynamics as a result of ventricular dysfunction, valvular regurgitation, or arrhythmias would lead to an increase in Fontan circuit congestion, stasis, and thrombus formation. If routine surveillance for Fontan circuit thrombus with cross-sectional imaging is prohibitive because of availability or financial constraints, it should be seriously considered in select patients with markers of circulatory dysfunction as described.

In addition to long-term relative deprivation of cardiac output, neuro-hormonal, and inflammatory changes, Fontan circulatory dysfunction is thought to predispose patients who have undergone the Fontan to extracardiac organ damage.[12,19-21] We did not find a relationship between Fontan circuit thrombus and extracardiac organ dysfunction, with the exception that eGFR was reduced but still within normal limits in the thrombus group. These results likely reflect the multifactorial nature of organ dysfunction in this complex population and that we do not have accurate ways of detecting subclinical organ dysfunction at this time.

Clinical thromboembolic events have been shown to be associated with adverse events in the Fontan population.[5,17] Our data uniquely show that Fontan circuit thrombus diagnosed on cross-sectional imaging is also associated with an increased rate of adverse cardiac events in the form of death, heart transplantation, Fontan conversion, or atrioventricular valve replacement. In all of these cases, there were other markers of Fontan circulatory dysfunction present, and

Fontan circuit thrombus was a part of the overall presentation. Regardless, Fontan circuit thrombus is a predictor of adverse outcomes, thus supporting routine imaging surveillance and identification/intervention of any reversible Fontan circulatory issues in the setting of Fontan circuit thrombus.

Conclusion

In this study of patients with cross-sectional imaging of the Fontan circuit, an important incidence of Fontan-circuit thrombus was documented and found to be associated with adverse cardiac outcomes. Although it is unclear to what extent Fontan circuit thrombus is the direct cause of worse outcomes vs a marker of circulatory dysfunction leading to worse outcomes, routine surveillance of the Fontan circuit with cross-sectional imaging should strongly be considered so that anticoagulation can be started or improved, and screening/intervention for other reversible Fontan circulatory issues can be implemented to optimize the Fontan circulation. Future studies with longer follow-up should be performed to confirm the lower incidence of TCPC Fontan circuit thrombus.

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Disclosures

The authors have no conflicts of interest to disclose.

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