Cardiology in the Young

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Detection of occult thrombosis in individuals with Fontan circulation by cardiac MRI

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Abstract

Objective: Identifying thrombus formation in Fontan circulation has been highly variable, with reports between 17 and 33%. Initially, thrombus detection was mainly done through echocardiograms. Delayed-enhancement cardiac MRI is emerging as a more effective imaging technique for thrombus identification. This study aims to determine the prevalence of occult cardiac thrombosis in patients undergoing clinically indicated cardiac MRI. *Methods:* A retrospective chart review of children and adults in the Duke University Hospital Fontan registry who underwent delayed-enhancement cardiac MRI. Individuals were excluded if they never received a delayed-enhancement cardiac MRI or had insufficient data. Demographic characteristics, native heart anatomy, cardiac MRI measurements, and thromboembolic events were collected for all patients. *Results:* In total, 119 unique individuals met inclusion criteria with a total of 171 scans. The median age at Fontan procedure was 3 (interquartile range 1, 4) years. The majority of patients had dominant systemic right ventricle. Cardiac function was relatively unchanged from the first cardiac MRI to the third cardiac MRI. While 36.4% had a thrombotic event by history, only 0.5% (1 patient) had an intracardiac thrombus detected by delayed-enhancement cardiac MRI. *Conclusions:* Despite previous echocardiographic reports of high prevalence of occult thrombosis in patients with Fontan circulation, we found very low prevalence using delayed-enhancement cardiac MRI. As more individuals are reaching adulthood after requiring early Fontan procedures in childhood, further work is needed to develop thrombus-screening protocols as a part of anticoagulation management.

Fontan-associated thromboembolism contributes to morbidity and mortality in patients with Fontan circulation. Previous studies report the prevalence of intracardiac thrombosis between 17 and 33% with a mortality of 25% in patients with single ventricle physiology.[1–3] Thrombosis after Fontan procedures has been attributed to low-flow, hypercoagulable states, right-to-left shunting, blind cul-de-sacs, prosthetic materials, and atrial arrhythmias.[1,2,4–6] Over the years, identifying thrombus formation in single ventricle patients has been highly variable. Initially, transthoracic echocardiograms were the imaging technique of choice for thrombus identification and only later were found to be highly unpredictable and replaced by transesophageal echocardiograms.[1,5,7] More recent studies support delayed-enhancement cardiac MRI for thrombus identification.

Delayed-enhancement cardiac MRI with long inversion time has been shown to be superior to transthoracic echocardiograms and transesophageal echocardiograms for detection of intracardiac thrombus in adult studies.[8,9] Echocardiography has declining efficacy in detecting thrombosis as patients age due to diminishing acoustic windows.[9] Cardiac MRI assesses cardiac anatomy in multiple planes with high spatial resolution and, utilising gadolinium-contrast imaging, can identify thrombi.[9] The use of gadolinium-contrast imaging in multiplanar, high-resolution cardiac MRI is advantageous for identification of thrombi.[8]

Currently, limited research exists in utilising delayed-enhancement cardiac MRI for Fontan-associated thromboembolism detection. Due to the previous high variability of occult thrombi identification in individuals with Fontan circulation transthoracic echocardiograms and transesophageal echocardiograms, this study aims to determine the prevalence of occult cardiac thrombosis in patients undergoing clinically indicated cardiac MRI.

Materials and methods

We performed a retrospective chart review of individuals with Fontan circulation who underwent delayed-enhancement cardiac MRI imaging at Duke University Hospital from October 28, 2008, to February 29, 2020. All study procedures were approved by the Institutional Review Board at Duke University Hospital (Pro00104687).

Study data were collected and managed using REDCap electronic data capture tools at Duke University Hospital. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, provide an intuitive interface for validated data capture, audit trials for tracking data manipulation, and automate export procedures for seamless data downloads to common statistical packages and procedures for data integration and interoperability with external sources.[10,11]

Participants

Children and adults managed within the Duke University Hospital Fontan registry were eligible for study inclusion. Participants were included if they had a Fontan procedure at any age and at least one cardiac MRI documented within the electronic medical record. Individuals were excluded if cardiac MRI image sequences were missing or uninterpretable for primary end points.

Date of birth, gender, dominant ventricle, baseline rhythm, age at each cardiac MRI, height, actual weight, and body mass index were extracted from the electronic medical record. For patients under 20 years old, body mass index percentiles were categorised as < 5%, 6–84%, > 85%, > 95%, and > 99%. Weight and body mass index were categorised, respectively, as underweight (< 5% or < 18.5), appropriate weight (5–85%, or 18.5–24.9), overweight (85–95% or 25–29.9), and obese (> 95% or > 30).

Native anatomy was defined as the initial anatomy prior to surgical intervention. Native anatomy was categorised by hypoplastic left heart syndrome, hypoplastic left ventricle, aortic atresia/aortic stenosis, tricuspid atresia, mitral atresia, pulmonary atresia, pulmonary atresia with intact ventricular septum, double-inlet left ventricle, double-outlet right ventricle, unbalanced atrioventricular septal defect, coarctation of the aorta, heterotaxy syndrome, or other. Type of Fontan was classified by atriopulmonary connection, lateral tunnel with and without fenestration, and extracardiac cardiac conduit with and without fenestration.

Data collection

MRI

Cardiac MRI imaging was reviewed for all participants. Delayed-enhancement cardiac MRI with long inversion time (600–800 msec) was used in each study to detect thrombi. Study images were reviewed for adequacy and agreement with the clinical report (Andrew W. McCrary).

MRI measurements

End-diastolic volume, end-systolic volume, and ejection fraction of the dominant ventricle were extracted from cardiac MRI reports.

Pulmonary valve stenosis was defined as present or not present. Aortic valve regurgitation was categorised into none, trivial/mild, mild to moderate, moderate, moderate to severe, and severe. Aortic arch obstruction was categorised into none, trivial/mild, mild to moderate, moderate, moderate to severe, and severe.

Historical thrombotic events and occult cardiac magnetic resonance thrombosis

Evidence of Fontan thrombus was defined as any thrombus present within Fontan circulation. Thrombotic events were initially classified into binary categories. Thrombotic events were then sub-classified as significant vascular thrombus (defined as a thrombus in the internal jugular vein or subclavian vein), deep vein thrombosis, pulmonary embolism, Fontan thrombus, other shunt thrombus, thrombus in a heart chamber, myocardial infarction, or cerebrovascular accident/transient ischaemic attack. Diagnosis of vascular thrombus and deep vein thrombosis was confirmed by ultrasound. Pulmonary embolism was defined by CT angiogram diagnosis. Historical cardiac thromboses were diagnosed by echocardiography (transthoracic and transesophageal). Cerebrovascular accident/transient ischaemic attack was diagnosed by the neurology service with medical record documentation and corresponding imaging as appropriate.

Results

Participants

A total of 119 unique individuals met inclusion criteria with a total of 171 scans. The majority of participants were male, with appropriate weight at their first and second cardiac MRI, and overweight at their third cardiac MRI (Table 1). The median age at Fontan procedure was 3 (interquartile range 1, 4) years. The median age at the first cardiac MRI was 16 (interquartile range 12, 23; n = 119) years, second cardiac MRI was 19 (interquartile range 13, 30; n = 36) years, and third cardiac MRI was 22 (interquartile range 15, 32; n = 16) years. The majority of patients had native hypoplastic left heart anatomy, and a dominant right ventricle (Fig. 1). Fenestrated extracardiac conduit was the most common type of Fontan intervention.

Cardiac function

Ejection fraction, end-diastolic volume index, and end-systolic volume index were assessed for patients who received up to three cardiac MRIs (Table 1).

Historical thrombotic events and occult cardiac magnetic resonance thrombosis

There was a high prevalence (n = 44; 37%) of history of thrombotic events with nine individuals (7.5%) experiencing more than one type of thrombotic event (Table 2). Cerebrovascular accident/transient ischaemic attack was the most prevalent event (39%), followed by thrombus in a heart chamber (36%). Five of the 17 (29%) cerebrovascular accident/transient ischaemic attacks were noted within one year of cardiac surgery. Thrombotic complications by history were found to be highest in atriopulmonary connection Fontan (12, 27%), lateral tunnel-fenestrated Fontan (12, 27%), and extracardiac conduit Fontan (11, 25%), followed by extracardiac conduit-fenestrated Fontan (8, 16%) and lateral tunnel non-fenestrated Fontan (1, 2%). However, at the time of delayed-enhancement cardiac MRI (171 Studies), only one study demonstrated a cardiac thrombus; in this case, within the Fontan circuit (0.5% of all studies) (Fig. 2).

Discussion

Overall, despite previous echocardiographic reports of high prevalence of occult thrombosis in patients with Fontan circulation, we found very low prevalence using delayed-enhancement cardiac MRI. By history, most thromboembolic events after Fontan procedures were attributed to cerebrovascular accident/transient ischaemic attack rather than a Fontan-associated thrombus. Fontan circulation anatomical characteristics place patients at risk for developing thrombi due to prosthetic materials, blind pouches, low-flow states, and hypercoagulable states.[1,12] Despite these risk factors, occurrence

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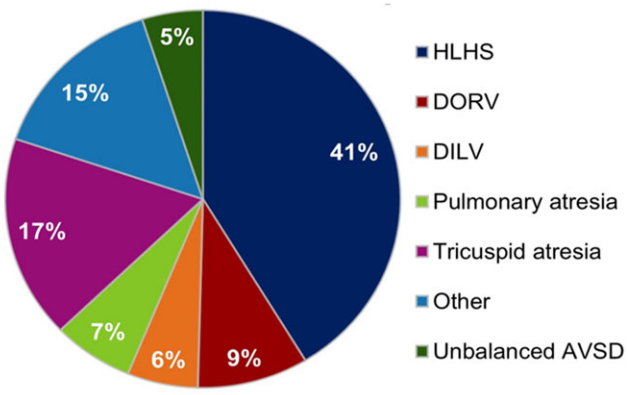
Table 1. Study population demographics

Demographic	N (%)
Age at Fontan (years)	
• 1–5	102 (86)
• 6–10	7 (6)
• 11–15	8 (7)
• 16–20	0 (0)
• 21–25	2 (2)
Type of Fontan	
• Atriopulmonary connection	16 (13)
• Lateral tunnel-fenestrated	29 (24)
• Lateral Tunnel	9 (8)
• Extracardiac conduit-fenestrated	33 (28)
• Extracardiac conduit	32 (27)
Sex	
• Male	68 (57)
Dominant Ventricle	
• Left	55 (46)
• Right	62 (52)
• Balanced	2 (2)
First CMR (n = 119)	
Age (years)	
• 1–5	8 (7)
• 6–10	24 (20)
• 11–15	28 (23)
• 16–20	19 (16)
• 21+	42 (35)
BMI	
• Underweight	11 (10)
• Appropriate Weight	72 (65)
• Overweight	17 (15)
• Obese	11 (10)
Cardiac Function	
EF	51% (47, 61)
EDV (ml/m^2)	79 (61, 102)
ESV (ml/m^2)	35 (25, 50)
Second CMR (n = 36)	
Age	
• 1–5	0 (0)
• 6–10	3 (8)
• 11–15	10 (25)
• 16–20	9 (23)
• 21+	18 (45)
BMI	
• Underweight	1 (5)
• Appropriate Weight	13 (65)
• Overweight	6 (30)
• Obese	0 (0)
Cardiac Function	
EF	56% (47, 60)
EDV (ml/m^2)	79 (63, 98)
ESV (ml/m^2)	33 (25, 47)
Third MRI (n = 16)	
Age (years)	
• 1–5	0 (0)
• 6–10	1 (5)
• 11–15	4 (24)
• 16–20	1 (5)
• 21+	11 (65)
BMI	
• Underweight	0 (0)
• Appropriate Weight	4 (33)
• Overweight	6 (50)
• Obese	2 (17)
Cardiac Function	
EF[1]	54 (49, 59)
EDV (ml/m^2)	81 (68, 93)
ESV (ml/m^2)	36 (30, 42)

CMR = cardiac magnetic resonance; BMI = body mass index; EF = ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume.



HLHS – hypoplastic left heart syndrome; DORV – double outlet right ventricle; DILV – double inlet left ventricle; AVSD – atrioventricular septal defect

Figure 1. Native cardiac anatomy. HLHS = hypoplastic left heart syndrome; DORV = double-outlet right ventricle; DILV = double-inlet left ventricle; AVSD = antrioventricular septal defect.

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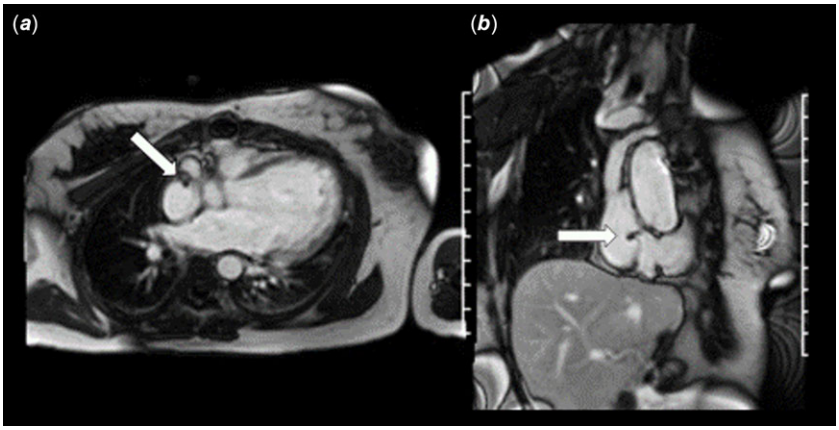

Figure 2. Cardiac MRI of Fonton thrombus. Single-shot delayed-enhancement images (TI = 600msec) of patient with Fonton thrombus. White arrow indicates area of absence of contrast uptake, in this case, thrombus.

Table 2. Historical thrombotic events type

Thrombotic event	N (%)
Significant vascular thrombus	6 (14)
DVT	3 (7)
PE	7 (16)
Fontan Thrombus	1 (2.3)
Other Shunt Thrombus	2 (5)
Thrombus in Heart Chamber	16 (36)
Myocardial Infarction	2 (5)
CVA/TIA	17 (39)

DVT = deep vein thrombosis; PE = pulmonary embolism; CVA = cardiovascular accident; TIA = transient ischaemic attack.

of Fontan-associated thromboembolism was found to be lower than expected using delayed-enhancement cardiac MRI.

Delayed-enhancement cardiac MRI-cardiac magnetic resonance and thrombus detection

Only 0.5% of patients in our study were found to have a thrombus in the Fontan circuit detected by delayed-enhancement cardiac MRI as compared to previously reported 7–33% detected by echocardiography.[2] Cardiac MRI provides a more detailed assessment of cardiac anatomy in multiple planes with high special resolution.[9] Gadolinium-contrast cardiac MRI images display low-signal intensity avascular thrombus surrounded by high-signal intensity contrast-filled blood pool and myocardium.[9] This allows for a more precise identification of thrombus as compared to echocardiographic imaging.

Earlier studies focused on using transthoracic echocardiograms and transesophageal echocardiograms for thrombus identification in Fontan circulation. In 1991, a case study reported transesophageal echocardiogram's success in identifying thrombi formation as compared to transthoracic echocardiograms.[13] Transesophageal echocardiogram was able to provide a unique view of the caval-pulmonary connection and adjacent structures after a Fontan operation. This case series mainly focused on patients who already experienced thromboembolic complications after Fontan procedures and not as a screening technique. Echocardiography allows for significant interobserver variability and up to 46% are inconclusive for thrombus identification.[14,15] While discussing the role of MRI and CT in Fontan circulation, a review article argued that echocardiography may not be as helpful as patients age due to image degradation from declining acoustic windows.[9] Elevated body mass index, chest wall deformities, and prior surgical procedures diminish the quality of echocardiography.[9]

Early studies utilising cardiac MRI for thrombus detection focused on identification of left ventricular thrombi in patients with left ventricular systolic dysfunction.[16] In 2006, a retrospective chart review examined patients with evidence of ischaemic heart disease and who had surgical or pathological confirmation of presence or absence of a thrombus.[16] In 160 patients who had transthoracic echocardiograms, transesophageal echocardiograms, and cardiac MRI completed prior to surgical intervention, contrast-enhanced MRI was found to have the highest sensitivity and specificity for thrombus detection (88 ± 9% and 99 ± 2%, respectively) compared to transthoracic echocardiograms (23 ± 12% and 96% ± 3.6%, respectively) and transesophageal echocardiograms (40 ± 14% and 96 ± 3.6%, respectively).[16] In 2008, a retrospective cohort study compared left ventricular thrombus identification between delayed-enhancement cardiac MRI versus cine-cardiac MRI.[8] They found delayed-enhancement cardiac MRI was a better reference standard for thrombus identification than cine-cardiac MRI, as delayed-enhancement cardiac MRI detected thrombi in 100% of patients who had thrombi verified by pathology ($p < 0.005$).[8] Delayed-enhancement cardiac MRI was also found to provide further information on myocardial scarring as compared to cine-cardiac MRI.[8] Although these studies were not focused on patients with Fontan circulation, identification of thrombi was more sensitive and specific with cardiac MRI, as compared to other imaging modalities.

Fontan-associated thrombi

In our study population, only one patient was identified with a Fontan-associated thrombus. She was born with tricuspid stenosis and pulmonary atresia with an intact ventricular septum. After initial palliation at birth with a central aortopulmonary shunt, she then had a classic right-sided Blalock-Taussig-Thomas shunt at 18 months old. Following immigration to the United States, she underwent a fenestrated lateral tunnel Fontan, hemi-Fontan, and takedown of a classic Blalock-Taussig-Thomas shunt at age 23 years old. Prior to Fontan, she had oxygen saturations between 80 and 85% and was anticoagulated with aspirin alone. At discharge from the Fontan and hemi-Fontan, her oxygen

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saturation had improved to 90–95%. At 32 years old, she presented with chest pain and elevated troponins with subsequent electrocardiographic changes concerning non-ST segment myocardial infarction. She had an initial transthoracic echocardiogram that did not identify a thrombus. Due to concern for a paradoxical embolic myocardial ischaemic event, cardiac MRI was performed in anticipation of interventional catheterisation. The cardiac MRI revealed a small thrombus in the Fontan circuit and right atrial appendage, and catheterisation confirmed thrombus burden. Due to the thrombus burden and systemic complications, the decision was made to close the Fontan fenestration.

Thromboembolic events

Thromboembolic complications are a well-recognized source of morbidity and mortality in patients with Fontan circulation. Cerebrovascular accidents/transient ischaemic attacks were found to be the most common thromboembolic events in our population and occurred remotely from the time of the cardiac MRI scan. A retrospective review of the incidence, outcomes, and risk factors for stroke after Fontan procedures identified individuals with pulmonary artery banding had an increased risk for stroke as compared to other intervention procedures.[17] In our study, only one patient underwent pulmonary artery banding during their second intervention and did not experience a thromboembolic complication.

In our study population, thromboembolic complication was associated with atriopulmonary connection, lateral tunnel-fenestrated, and extracardiac conduit equally. Early studies report no significant difference between type of Fontan procedure and thromboembolic events.[18] The two types of thrombus formation associated with Fontan are a venous thrombus due to the slow-flow state in an enlarged right atrium, or a systemic embolus, which can form in native intracardiac chambers.[18] Each can lead to thromboembolic complications such as pulmonary emboli or cerebrovascular accident/transient ischaemic attack, respectively. In our study population of older patients after Fontan procedures, thrombosis risk, regardless of type of Fontan, may increase with age. In our patient with Fontan-associated thromboembolism, her fenestration was closed because of multiple thromboembolic complications.

Recent studies focus on thrombus prophylaxis in patients with Fontan circulation. In a retrospective evaluation of aspirin initiation on post-operation day one and the development of thrombi in patients with Fontan circulation, a high inherent risk of thrombosis and thromboembolic complications was appreciated in all types of Fontan procedures, supporting the necessity of prophylaxis.[19] In 2002, a meta-analysis assessed major causes of morbidity and mortality after a Fontan operation. Twenty-three per cent of patients experienced a thromboembolic complication within two years of the procedure, with systemic venous atrium and pulmonary venous chambers being the most common locations of primary thrombi.[20] Although thrombi were identified, there was insufficient evidence to make clear recommendations about optimal anticoagulant prophylaxis at the time of this study.

Finding optimal strategies for thromboembolic complications in Fontan patients continues to be refined. The UNIVERSE study aimed to provide dosing, safety, and efficacy information on the use of rivaroxaban compared to aspirin for thromboprophylaxis in the paediatric population.[3] Patients who received rivaroxaban for thromboprophylaxis experienced similar safety profile and fewer thrombotic events compared to patients who received aspirin, although results were not statistically significant.[6] In 2023, a meta-analysis examined the efficacy and safety of aspirin, warfarin, and non-vitamin K oral anticoagulants for thromboprophylaxis in patients with Fontan circulation. Aspirin, warfarin, and non-vitamin K antagonist oral anticoagulants were all associated with lower risks for thromboembolic events (incidence risk ratio (IRR) 0.24; IRR 0.23; and IRR 0.11, respectively). Although non-vitamin K antagonist oral anticoagulants have only been examined in a limited number of patients and heterogeneity of studies, they have favourable safety and efficacy in patients with Fontan circulation.[21] Further research is required to identify the best strategy to prevent thromboembolic complications in patients with Fontan circulation.

We note several limitations. Our retrospective cohort was recruited by convenience sampling and may not be representative of the general population. Additionally, our cohort did not classify whether patients were on anticoagulation at the time of MRI, which would impact the overall risk for thrombosis. Furthermore, our cohort did not specifically receive transesophageal echocardiograms or transthoracic echocardiograms prior to delayed-enhancement cardiac MRI. Continually, we were limited by the high percentage of unknown baseline rhythm as atrial arrhythmias are a known risk factor for thrombus formation in Fontan circulation. Lastly, our sample includes only individuals able to complete a cardiac MRI and may exclude other important single ventricle groups at risk for thrombosis (those individuals with extensive metal artefact, intolerance of exam, test accessibility, and preclusive renal function for gadolinium).

Despite previous echocardiographic reports of high prevalence of occult thrombosis in patients with Fontan circulation, we found very low prevalence using delayed-enhancement cardiac MRI. As more individuals are reaching adulthood after requiring early Fontan procedures in childhood, screening for thrombi needs accuracy. With results from the UNIVERSE study and the added benefits of volumetric and functional assessment, interval delayed-enhancement cardiac MRI should be incorporated as part of routine longitudinal surveillance of individuals with Fontan circulation.

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Author contribution. SFC and MC contributed equally to this manuscript.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by institutional committees (Duke University Hospital Institutional Review Board).

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