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Editorial

Fontan Circuit Thrombus in Adults: Often Silent, Rarely Innocent

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See article by Sathananthan et al., pages 1807–1814 of this issue.

A Fontan circulation is a surgically modified vasculature with pathways created to separate oxygenated and deoxygenated blood and to permit function with only a single ventricular pump. In effect, systemic venous blood reaches the lungs passively. Achieving a Fontan circulation can require several surgeries or interventional procedures and has become the usual approach for diagnoses such as tricuspid atresia, hypoplastic left heart syndrome, double inlet left ventricle, or an unbalanced atrioventricular septal defect. The ability to pursue a Fontan strategy (in any of its many iterations or refinements) has undoubtedly transformed outcomes for infants born with a single ventricle physiology. Era-related 20-year survival rates might be as high as 90% for children who received surgery in the 2000s.[1] To uphold the legacy of this success, attention must now turn to promoting health and mitigating complications in the still-growing population of adult survivors. Growth in the number of adults living with congenital heart disease is set to continue until approximately 2050[2] and estimates from New Zealand have predicted that the adult Fontan population will double in size over the next 20 years.[3] Although most adult Fontan patients have yet to enter their 40s, their risk of death is among the highest for any form of adult congenital heart disease and many patients experience substantial morbidity.[4,5] Problems relate not only, or even primarily, to cardiac residua, but rather to the chronic effects of the Fontan circulation on all body systems (Fig. 1).

The emerging cohort of adult Fontan patients has much to teach us about life with this extraordinary physiology and there remain far more puzzles than answers. However, over the past decade, like the number of patients, the body of research has begun to grow, and we have learned which questions are the most pressing. The hematologic and hemodynamic abnormalities that result in an increasing risk of thromboembolism in the decades after Fontan creation[6] certainly demand attention because they contribute to at least 8% of Fontan deaths in adults.[7] In this issue of the *Canadian Journal of Cardiology*, Sathananthan et al. focus on this important complication.[8] They report their sizeable, single-centre, retrospective experience of adult Fontan patients who underwent cross-sectional imaging.[8] Their data adds epidemiologic and phenotypic detail and the authors make the case for better recognition of Fontan thrombus as a manifestation of wider Fontan failure. It is an argument that carries weight.

Thrombus in Fontan patients can be located in either the venous Fontan circuit and pulmonary arteries, or in the systemic arterial circulation, where it can cause stroke or peripheral embolism.[9] Although Sathananthan et al. report that systemic arterial thrombus occurred in 10 patients, their study focused on thrombus in the venous Fontan circulation and its relation to clinical outcomes.[8] Of the 67 Fontan patients who underwent cardiac magnetic resonance (CMR) or computed tomography (CT) imaging, 22% (15 patients) were diagnosed with Fontan circuit thrombosis. A significant proportion of patients with thrombus were already prescribed warfarin (40%) or aspirin (27%) at the time of diagnosis. As previously reported,[10,11] thrombosis was more frequent in older-style Fontan circuits than in more contemporary cavopulmonary pathways.[8] In this study, more patients with Fontan thrombus than without experienced the composite outcome of death, heart transplantation, or cardiac surgery (27% vs 8%) and thrombus was also linked, although less closely related to, softer indices of ill health.[8] Previous studies have associated clinically apparent thromboembolic events to an increased risk of heart failure hospitalization and death or shown that a proportion of Fontan deaths are caused by thrombus.[7,10] However, this is the first study, to our knowledge, to attempt to estimate the overall prevalence of Fontan circuit thrombosis (clinically apparent and silent) and then investigate its significance.[8]

No Evidence of Thrombus? Until Proven Otherwise…

The study from Sathananthan et al. contains important and new information about clinically silent Fontan thrombus (ie, thrombus present without clinical symptoms or signs and

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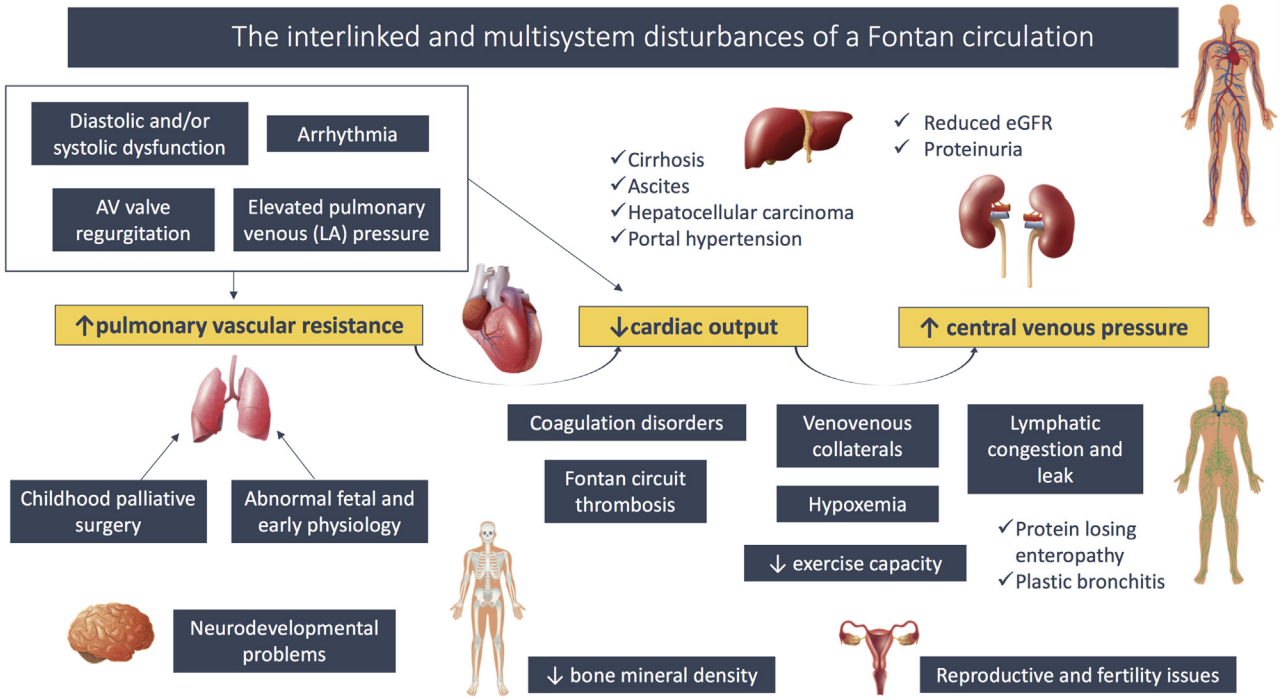
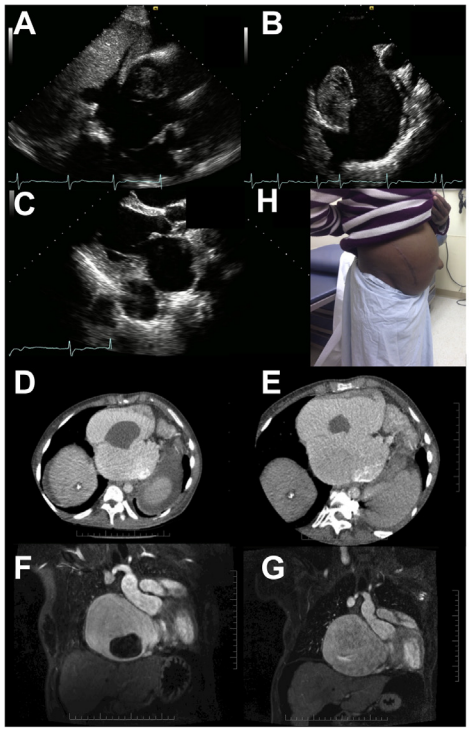


Figure 1. Schematic representation of the chronic multisystemic effect of a Fontan circulation. The **yellow boxes** represent underlying mechanistic drivers and the **grey boxes**, clinical consequences. AV, atrioventricular; eGFR, estimated glomerular filtration rate; LA, left atrium.

not seen on echocardiography).[8] In their study, 40% of the thrombus detected on cross-sectional imaging was clinically silent and 14% of patients with no pretest suspicion were nevertheless diagnosed with Fontan thrombus when they underwent CMR or CT imaging.[8] In previous reports, the incidence of silent thrombus has varied from 9% to 33% with differences in study methodology and thrombus definition likely to explain the wide range.[12-15] Advantages of the study by Sathananthan et al. are that all patients underwent cross-sectional imaging, that images were acquired using techniques reliable for detection of thrombus in slow flowing circulations, and that images were reviewed by experts in congenital heart disease.[8] In this cohort, only 20% of the patients diagnosed with thrombus had concerning echocardiograms[8] and we agree that definitively establishing the presence or absence of thrombus in Fontan patients using either transthoracic or transesophageal echocardiography is difficult. In clinical practice, we sometimes fail to clear Fontan patients for direct current cardioversion because transesophageal echocardiography returns a high suspicion of thrombus, only to find contemporaneous cross-sectional imaging conclusively excludes it. Because of the challenges of echocardiography and the lack of symptoms is sometimes false reassurance, Sathananthan et al. suggest we need to consider increased use of routine advanced imaging in Fontan patients.[8] Their argument is stronger because they also show associations between thrombus and adverse clinical events.[8] As a separate issue, which would necessitate longer discussion, the substantial risk of silent thrombus should be considered when debating whether Fontan patients benefit from routine anticoagulation.

Routine Advanced Imaging: Who, When, and How?

If routine cross-sectional imaging is of interest in the early detection and treatment of Fontan circuit thrombosis, questions about access, imaging modality, and frequency remain. In their practice, and in line with American Heart Association/American College of Cardiology guidelines,[16] Sathananthan et al. perform cross-sectional imaging in Fontan patients at 3- to 5-year intervals.[8] At the current time, it is unlikely that most Canadian adult Fontan patients attain this standard of care. Advanced imaging in this population requires institutional availability and a high level of training and expertise. In their methods section, Sathananthan et al. rightly emphasize technical aspects such as location of contrast injection and timing of image acquisition.[8] The hazard of over-calling Fontan thrombus or pulmonary embolism due to slow contrast mixing and incomplete opacification is well described.[17,18] In their informative article about the role of CMR and CT imaging in Fontan patients, Yeong et al. explain that adequate imaging requires more time in the scanner and more contrast than is usual for general cardiac studies.[17] Time factors are important for work flow and because the kidney is also affected by chronic exposure to Fontan physiology, additional consideration must be given to the risks of contrast.[19] Most patients in the study by Sathananthan et al. underwent CT (78%) imaging instead of CMR (22%),[8] and, although not discussed by the authors, this probably reflects another barrier to routine cross-sectional imaging in this population. Degrading artifacts caused by vascular coils, fenestration closure devices, and epicardial or transvenous pacemaker systems are limiting factors in the use



A 32-year-old with modified Bjork Fontan for tricuspid atresia was followed by a local, non-ACHD cardiologist after graduation from pediatric care. Less well for 12 months, she was referred to our team in 2012. At her first ACHD clinic visit, a large right atrial (RA) thrombus was diagnosed on transthoracic echocardiography (**A & B**). The coronary sinus was severely dilated and contained "smoke" (**C**). On warfarin for chronic, rate-controlled atrial fibrillation, INR at presentation was 1.7. An urgent multidisciplinary team meeting was convened.

We discussed the following: 1) Thrombolysis, 2) Surgical thrombectomy +/- Fontan conversion 3) Urgent assessment for heart transplant or 4) Intensification of oral anticoagulation management. We opted to start iv heparin before transitioning to oral anticoagulation monitored carefully by the thrombosis team. Further investigation showed Fontan pressures of 21mmHg and left ventricle ejection fraction of 35%. The thrombus largely resolved (**D**:CT at presentation versus **E**:CT 3 weeks later, and **F**:CMR at presentation showing a 5.1 x 6.9 cm RA thrombus versus **G**:CMR 1-year later showing thrombus regression with persistence of a chronic mural layer).

In the months after presentation, she developed worsening ascites (**H**) and fatigue. We considered Fontan conversion, but instead, 7 months after initial presentation, she was listed for heart transplant. With further clinical decline she was admitted for intravenous diuretics and inotropes. Waiting the entire time as an inpatient, she was successfully transplanted 7 months later, 14 months after initial presentation with thrombus. The ascites was drained at transplant and did not reaccumulate. She remains well 4.5 years later.

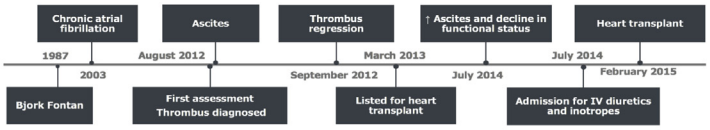


Figure 2. A clinical vignette detailing the complex care pathway of an adult Fontan patient after incidental diagnosis of a large right atrial thrombus. ACHD, adult congenital heart disease; CMR, cardiac magnetic resonance; CT, computed tomography; INR, international normalized ratio; iv, intravenous.

of CMR in Fontan patients.[17,18] If regular cross-sectional imaging becomes standard of care, we will certainly expose the adult Fontan population to more ionizing radiation. Taking all of this and cost into account, perhaps the results of Sathananthan et al. would better be considered an argument for an individualized imaging plan for every Fontan patient with attention given to baseline risk factors such as age and type of Fontan circuit, as well as to the risks and benefits of the various imaging techniques at our disposal.

An Incidental Finding That Opens Pandora's Box

Fontan circuit thrombosis presents in many different ways, from an incidental finding to acute major cardiovascular collapse. Sathananthan et al. describe 4 patients who presented with hemodynamic or respiratory instability for whom thrombolysis was the initial management strategy.[8] Decision-making in patients with an acute clinical presentation is certainly challenging, because all options seem high-risk and the literature contains only case reports.[20-23] With its focus on prevalence and late implications, a weakness of the study by Sathananthan et al. is the lack of information about the management of Fontan thrombus or about the success of chosen management strategies.[8] Successful thrombolysis, either with systemic infusion or catheter-directed local thrombolysis and surgical embolectomy,[20-26] has been reported but at this point it is impossible to know whether similar results can be obtained from supportive management and closely monitored oral anticoagulation. There is no straightforward decision pathway and multidisciplinary team discussion is mandated. Although initial treatment might appear simpler when chronic thrombus is discovered incidentally, this scenario should nevertheless impose a deep-thinking process. The occurrence of thrombus should prompt us to question the state of our patient's Fontan circulation: could there be asymptomatic, untreated underlying atrial arrhythmia? Should we measure the patient's Fontan pressures? Can the patient's hemodynamics be improved? And should that be attempted, if to do so requires surgery? What will be gained? And what could be risked? In the slow, insidious, but frequently relentless progression of Fontan failure (Fig. 1), detection of circuit thrombosis should trigger further investigation and intensify management discussion. In our practice, it triggers referral to the adult congenital heart disease (ACHD) heart failure clinic for consideration of all options including discussion of where the patient might be on the path toward consideration for heart transplantation (Fig. 2).

Facing the Emerging Challenges Alongside Our Patients

The population of adult Fontan patients in Canada continues to increase, and we need collective strategies and planning to face the challenges of late complications. National and provincial discussion about care delivery are necessary to unify and optimize management. The benefits of a structured multidisciplinary team approach with coordinated care pathways for the follow-up of children with a Fontan circulation were evaluated in a recent publication.[27] After implementation of the program, there was an increase in appropriate testing and several undiagnosed pathologies were identified

and treated in a timely manner.[27] Dedicated ACHD Fontan clinics are certainly something to consider. In a country such as Canada, patients might live at great distances from institutions with access to the technology and level of expertise required. Perhaps yearly review in a smaller, local ACHD centre with 3- to 5-year review in a central hub multidisciplinary Fontan clinic could be a model to consider. It is even more problematic that many adult Fontan survivors receive no care at all from ACHD specialists. In 2009, Marelli's group reported that fewer than 80% of Quebec's complex ACHD patients were seen by specialists after their 18th birthday[28] and our own estimates in Toronto suggest loss to follow-up numbers of similar scale. However, most of these adults maintain contact with their primary care physician,[28] which affords an opportunity for reconnection with specialist teams, if that physician was aware of the need. Studies like that from Sathananthan et al. enhance our understanding of Fontan failure. As we learn more about the needs of this new population, it becomes increasingly urgent we act to optimize and standardize adult Fontan follow-up, to reconnect with lost to follow-up patients, and to facilitate access to expert care, regardless of postal code.

Disclosures

The authors have no conflicts of interest to disclose.

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