REVIEW ARTICLE

Thromboembolism and anticoagulation after Fontan surgery

Sangeetha Viswanathan
Department of Paediatric Cardiology, SRM Institute of Medical Sciences, Chennai, Tamil Nadu, India

ABSTRACT

This review attempts to answer the common questions faced by a clinician regarding thromboembolism and thromboprophylaxis in patients following Fontan surgery. The review is in an easy to understand question and answer format and discusses the currently available literature on the subject in an attempt to arrive at practical clinically relevant solutions. Patients who have undergone the Fontan operation are at a high risk for thromboembolism. Based on available evidence, there is a strong rationale for thromboprophylaxis. However, it is not clear as to which agent should be administered to prevent thromboembolic events. While the available evidence suggests that antiplatelet agents alone may be as good as oral anticoagulants, there is a need for a large multicenter randomized control trial comparing these two common strategies to deliver a clear verdict.

Keywords: Anticoagulation, Fontan, thromboembolism

INTRODUCTION

This review attempts to address the controversial subject of the occurrence of thromboembolic events (TEs) and its prevention through a series of clinically relevant questions. While the answers to many questions are not entirely clear, the available evidence that has been presented may enable the clinician to make a better-informed decision.

WHAT IS THE INCIDENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH FONTAN CIRCULATION, THAT IS, HOW BIG IS THE PROBLEM?

The Fontan operation is currently reported to have a 10-year survival of up to 94% with a trend to improving survival across surgical eras.[1,2] Freedom from reoperation or transplantation also remains good at >90% at 10 years with a good quality of life in most survivors.

A true estimate of the occurrence of thrombosis and embolism is hard to ascertain, as the majority of these events are "silent," i.e., without any symptoms. Different studies report varying incidence of thrombosis and embolism ranging from 4% to 20%[3] and this variation is related to small sample size; different methods of detection (i.e., transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or planar imaging), differing end points (i.e., clinical TE vs. detection of thrombus on routine imaging), and different therapeutic strategies of thromboprophylaxis with several earlier studies having substantial number of patients who were not on any thromboprophylaxis.

There is little doubt that the burden of thromboembolism post-Fontan surgery is significant with clinical TE being reported in up to 20–30% in some older series.[4-6] A meta-analysis of around 1200 patients' post-Fontan surgery reported an incidence of TE of 11.8%.[7] Although the incidence of thromboembolism is highest in the 1st year after Fontan surgery, there remains a persistent risk several years later.[6] Cerebrovascular events, which carry significant morbidity, have been reported in around 5% of patients post-Fontan.[6-9] In addition, silent

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Address for correspondence: Dr. Sangeetha Viswanathan, SRM Institute of Medical Sciences, Chennai, Tamil Nadu, India.
E-mail: sangeetha.viswanathan@gmail.com

thrombi have been detected on TTE and TEE in up to 33% of patients, raising concerns regarding the long-term efficiency of the Fontan circuit.[10-12]

In summary, the reported incidence of thromboembolism in patients following Fontan surgery is variable, but significant with a persistent risk several years postsurgery. In addition to clinical thromboembolism, which often presents with catastrophic outcomes, there is a high incidence of silent TE, which is of long-term concern.

WHAT ARE THE OUTCOMES OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH FONTAN CIRCULATION?

Thromboembolism carries a substantial morbidity and mortality with numerous reports of patients who develop significant events such as stroke, myocardial infarction, and pulmonary embolism resulting in death or adverse clinical outcomes post-Fontan completion.[8,9,13,14] Over 50% of patients with cerebrovascular events post-Fontan are likely to die or have severe neurological sequelae.[8]

WHY ARE PATIENTS WITH FONTAN CIRCULATION PRONE TO THROMBOEMBOLIC EVENTS?

The sluggish circulation and stagnation as a result of the absence of the right ventricular pump are an obvious substrate for thrombus formation. In addition, it has been long recognized that patients undergoing single ventricle palliation have significant alterations in both pro- and anti-coagulant factors compared to normal participants. In an elegant series of papers, Odegard *et al.* studied patients with single ventricle physiology at three stages; before bidirectional Glenn surgery, before Fontan completion, and following the Fontan operation.[15-17] They found coagulation abnormalities early in the course of single ventricle palliation even before cavopulmonary anastomosis.[14] Concentrations of protein C, factors II, V, VII, IX, and X, plasminogen, fibrinogen, and antithrombin III were significantly lower in the pre-Glenn infants compared with the age-matched control participants. The interval between Glenn surgery and Fontan completion was found to be associated with the degree of coagulation factor derangement in these patients.[16] Following Fontan completion, Factor VIII levels were found to be increased, and this may be related to the higher venous pressures in these patients resulting in liver-related alterations in the levels of this factor which is linked with an increased risk of TE.[17]

In summary, sluggish flow in the absence of a pump, flow turbulence related to the anatomical considerations of the Fontan operation, and coagulation abnormalities predispose these patients to thromboembolism.

IS THERE A DIFFERENCE IN THE INCIDENCE OF THROMBOEMBOLIC EVENTS BETWEEN LATERAL TUNNEL FONTAN AND EXTRACARDIAC TOTAL CAVOPULMONARY CONNECTION?

A retrospective review by Coon *et al.* of 592 patients who had undergone Fontan surgery showed no significant difference in the incidence of TE between the lateral tunnel, atriopulmonary, and extracardiac conduit type of Fontan on TTE. Freedom from thrombus was 92%, 90%, 84%, and 82% at 1, 3, 8, and 10 years, respectively, after Fontan operation. The majority of patients in this series, however, underwent lateral tunnel Fontan (82%) with only 5% having an extracardiac total cavopulmonary connection (TCPC).[18]

A secondary study by McCrindle *et al.* from a randomized trial of 111 patients post-Fontan showed freedom from thrombus formation of 69% at 2.5 years post-Fontan completion. The majority of these patients had TE surveillance for thrombus formation. As many as 28% of patients with thrombi presented as a clinical TE. In this study, the majority of patients underwent extracardiac TCPC (85%) and the remainder lateral tunnel Fontan, and there was no demonstrable difference between the two groups in the incidence of thrombus.[4] A retrospective review by Dabal *et al.* of a cohort of 207 patients who had undergone extracardiac TCPC showed freedom from TE of 98% at 20 years.[1] However, the more recent extracardiac TCPC series has a lower duration of follow-up as compared to the older types of Fontan surgery, which might partly contribute to the lower cumulative incidence of thromboembolism.

In summary, most studies have not shown any difference in the incidence of thrombus between the types of Fontan operations although these studies have mainly been retrospective in nature with unequal distribution of patients in the two groups.

AND WHAT ABOUT FENESTRATED AND NONFENESTRATED FONTAN?

Although there were initial concerns regarding the role of fenestration in the incidence of TEs post-Fontan surgery,[19] there has been no reported difference in the incidence of thrombosis or cerebrovascular events between fenestrated and nonfenestrated Fontan circuits in recent series.[4,8]

WHAT ARE THE RISK FACTORS FOR THROMBOEMBOLIC EVENTS IN PATIENTS WITH FONTAN CIRCULATION?

Several factors have been proposed as contributory to thromboembolism post-Fontan surgery in small retrospective series. In McCrindle *et al.*'s prospective trial, pulmonary artery distortion, pulmonary atresia with intact ventricular septum, prolonged use of central lines in Intensive Care Unit, and subtherapeutic international normalized ratio (INR) in patients on warfarin were identified to be significant on multivariable regression analysis.[4] Other retrospective series has identified previous pulmonary artery banding,[8] conduit-related factors, and right to left shunting[19] as potential risk factors. The type of Fontan surgery and presence of arrhythmia have not been shown to be significant risk factors in any of these series, and no specific recommendations regarding thromboprophylaxis have been made in patients with atrial arrhythmia.

In summary, the results of the various studies have been quite variable, and no consistent risk factors have been identified that can be reliably used to risk stratify patients in clinical practice.

WHAT IS THE SIGNIFICANCE OF SILENT THROMBI IN THE FONTAN CIRCULATION?

Silent thrombi have been detected on surveillance post-Fontan surgery in up to 33% of patients.[10-12] Thrombus formation has been noted in both the systemic and pulmonary venous circulation with the potential for embolization to the aorta giving rise to stroke or transient ischemic attack and also into the pulmonary circulation.[6,8-10] A study by Varma *et al.*[20] in a cohort of adult patients, post-Fontan surgery reported the incidence of silent pulmonary embolism detected by ventilation-perfusion (V/Q) scan and computed tomography pulmonary angiography to be as high as 17% and suggested that the long-term hemodynamic consequences of recurrent silent pulmonary emboli could be significant in the Fontan circulation.

WHAT IS THE BEST WAY TO SCREEN FOR THROMBUS IN THE FONTAN CIRCUIT? IS THERE A RECOMMENDED SURVEILLANCE STRATEGY?

TTE is clearly limited in identifying thrombus within the Fontan circuit with only one out of 17 patients with intracardiac thrombus being picked up by TTE in a series by Balling *et al.*[10] Despite this statistics, most clinicians would hesitate to perform routine TEE on asymptomatic patients under follow-up. Review of the literature shows that some studies have employed TTE as the first line investigation followed by TEE if any suspicion regarding thrombus formation was to arise.[21] Others have attempted to universally apply TEE to detect thrombi more effectively.[4,10] The majority of adult patients with congenital heart disease in the Western world are likely to be investigated using imaging modalities such as the magnetic resonance imaging which are noninvasive and radiation-free.[22] In the developing world, however, resource constraints limit the use of these relatively expensive modalities. The mode of surveillance would to some extent depend on whether the findings would alter the thromboprophylaxis strategy.

Currently, there is no standardized surveillance strategy to detect thrombus formation in patients following Fontan surgery, and most units would use TTE routinely with a low threshold for TEE if indicated.

DOES PROPHYLAXIS (ANTICOAGULATION OR ANTIPLATELET THERAPY) DECREASE THE INCIDENCE OF THROMBOEMBOLIC EVENTS IN THESE PATIENTS?

Several studies have reported a significant difference in the incidence of TEs between patients on thromboprophylaxis and those on no prophylaxis.[7,23-25] In a meta-analysis of 1200 patients post-Fontan those who received TE prophylaxis with either aspirin or warfarin had lower incidence of TE than those with no prophylaxis (odds ratio [OR]: 0.425, 95% confidence interval [CI]: 0.194–0.929, $P < 0.01$, $I^2 = 37\%$).[7] The overall incidence of TE in patients receiving no prophylaxis was 18.6% compared with 8.6% when aspirin was used and 9% when warfarin was used. An isolated series from Germany in which patients had Fontan pathways that were fashioned wholly or partly with autologous pericardium found no difference in the incidence of TEE in patients without prophylaxis and advocated that thromboprophylaxis should be tailored to the surgical strategy employed.[21] A cohort study from the New England registry of 210 patients post-Fontan surgery where approximately 50% received no thromboprophylaxis showed a significantly higher incidence of TE in these patients when compared to therapy with either aspirin or warfarin (hazard ratio 8.5, 95% CI: (3.6–19.9), $P < 0.001$).[24]

Overall, there is fairly strong evidence that patients who have undergone Fontan operation require some form of thromboprophylaxis to prevent thromboembolism.

ARE ANTICOAGULANTS LIKE WARFARIN SUPERIOR TO ANTIPLATELET THERAPY IN REDUCING THE INCIDENCE OF THROMBOEMBOLIC EVENTS IN PATIENTS WITH FONTAN CIRCULATION?

There remains considerable uncertainty about which form of thromboprophylaxis is best suited for patients post-Fontan surgery with some studies suggesting that anticoagulation with warfarin particularly early after Fontan surgery is better than antiplatelet therapy with aspirin in preventing TE[23] and others finding no difference in the incidence of TE between the two groups.[4,7,24] The meta-analysis by Alsaied *et al.* which included 1200 patients post-Fontan showed that the incidence of thromboembolism was significantly lower in patients who received aspirin compared with no thromboprophylaxis (OR: 0.363, 95% CI: 0.177–0.744, $P < 0.01$, $I^2 = 0\%$) and who received warfarin compared with no TE prophylaxis (OR: 0.327, 95% CI: 0.168–0.634, $P < 0.01$, $I^2 = 2.5\%$). There was, however, no significant difference in the incidence of early or late TEE between warfarin and aspirin therapy (OR: 0.936, 95% CI: 0.609–1.438, $P = 0.54$, $I^2 = 0\%$). A study by Jacobs *et al.* of 72 patients who had undergone Fontan surgery and were placed on only aspirin prophylaxis showed no evidence of TE at a mean follow-up of 40 months.[26]

The complications of warfarin therapy in children and difficulties in monitoring therapy are well documented in the literature. Most studies on warfarin use demonstrate a relatively low bleeding risk of <1–2% per year; however, the outcome of such events can be catastrophic. In a study of 319 children on warfarin over 391 treatment years, age independently influenced all aspects of therapy. When compared with older children, the younger age groups required increased warfarin doses, longer overlap with heparin, longer time to achieve target INR ranges, more frequent INR testing and dose adjustments, and fewer INR values in the target range.[27] In another study of 45 children on warfarin therapy mainly for congenital heart disease, during a follow-up period of 602 patient months target INRs were achieved on only 62% and 39% of visits for children with low (2.0–3.0) and high target INR (3.0–4.0), respectively.[28] The study by McCrindle *et al.* has demonstrated that subtherapeutic warfarin therapy may be associated with an increased risk of thrombosis in Fontan patients.[4] It showed, in addition, poorer compliance in the warfarin group compared to the aspirin group.

Currently, there is no evidence that anticoagulation with warfarin is superior to antiplatelet therapy in preventing thromboembolic events in patients post-Fontan surgery. Given the difficulties in optimizing, monitoring, and regulating warfarin therapy in children, aspirin thromboprophylaxis might be the most effective strategy with better compliance and lower impact on the quality of life of these patients who already spend a significant amount of time visiting hospitals.

CONCLUSIONS

An exhaustive review of literature over the last two decades was carried out, and it was surprising to note that there are no clear guidelines to guide the clinician on thromboprophylaxis in patients following Fontan surgery. In the absence of guidelines, a systematic review of existing literature was carried out which included small early series of patients who had undergone the atriopulmonary or lateral tunnel Fontan operation, larger later series with growing experience and volumes in centers around the world of mainly extracardiac Fontan surgery and a few meta-analyses on the subject.

It is clear that patients who have undergone the Fontan operation are at a high risk for TEs. While the risk is highest during the 1st year, it does persist throughout the life of the patient. While devastating complications such as cerebrovascular events are the most common clinical manifestation, most TEs appear to be silent and may contribute to premature Fontan failure. There is, therefore, a strong rationale for thromboprophylaxis.

However, it is not clear as to which agent should be administered to prevent TE. While the available evidence suggests that antiplatelet agents alone may be as good as oral anticoagulants, there is a need for a large multicenter randomized control trial comparing these two common strategies to deliver a clear verdict. The advent of newer oral anticoagulants offers an exciting opportunity for improved therapy in these patients but requires rigorous study before it can be recommended in standard practice.[29]

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Conflicts of interest

There are no conflicts of interest.

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