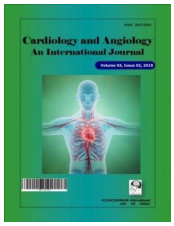

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Thrombosis of Extra-cardiac Fontan, an Institutional Experience

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Authors' contributions

This work was carried out in collaboration between all authors. Author HA managed the cases, collected the data and wrote the first draft of the manuscript. Authors AA-K and JA-A managed the cases, did the cardiac catheterization and managed the literature searches, author MA-B managed the literature searches, and wrote the final draft of the study and author AJ revised the article and did the surgical part. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Thromboembolism can complicate Fontan surgery. There are few well designed studies in the literature to determine the epidemiology of thrombosis after Fontan.
Methods: We report the experience of King Faisal Specialist Hospital & Research Center- Jeddah, Kingdom of Saudi Arabia; regarding thrombosis of extra-cardiac Fontan pathways in 3 of our

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patients; two patients were post- Fontan operation and one patient was post- Kawashima procedure & hepatic vein incorporation.
Results: The first and second patients developed thrombosis of Fontan pathways at one month & one year postoperatively respectively. In both patients, stenting of the extra-cardiac contegra re-established the patency of Fontan circuit and saved the risks of redo-surgeries. In the third patient, conduit occlusion was diagnosed 5 months postoperatively. Several attempts of cardiac catheterizations failed to penetrate the thrombosed conduit. Surgical re-intervention was inevitable.
Conclusions: The threshold for diagnostic and interventional cardiac catheterization should be lowered in post Fontan operation. Chronic oral anticoagulation may not prevent development of thrombosis despite therapeutic international normalized ratio (INR).

Keywords: Children; fontan; kawashima; thrombosis.

CORE TIP

Fontan surgery can be complicated with thromboembolism. We report the experience of King Faisal Specialist Hospital & Research Center- Jeddah, Kingdom of Saudi Arabia regarding thrombosis of extra-cardiac Fontan pathways in 3 patients; two patients were post-Fontan operation and one patient was post-Kawashima procedure & hepatic vein incorporation. The threshold for diagnostic and interventional cardiac catheterization should be lowered in post Fontan operation. Chronic oral anticoagulation may not prevent development of thrombosis despite therapeutic international normalized ratio (INR).

1. INTRODUCTION

The introduction of the Fontan operation dramatically improved the management of children with a functional single ventricle [1]. Hemodynamic fluctuations and thromboembolic complications are significant areas of concern during the postoperative care and follow up of patients with Fontan operation. Thromboembolic events may occur both in early and late periods after the Fontan procedure at a frequency higher than any other cardiac surgery in children other than prosthetic valve replacement and contribute to the failure of Fontan physiology. Occurrence of these thromboembolic events is not only because of hypercoagulable states but also due to the interaction of different factors including low flow states, stasis in the venous pathways, right-to-left shunts, blind cul-de-sacs, prosthetic material, and atrial arrhythmias [2,3]. The incidence of thrombosis after Fontan surgery has not been determined by prospective trials despite that some cross sectional surveys using transesophageal echocardiography found that the prevalence of thromboembolism following Fontan surgery ranges between 17% and 33% [4]. The current article reported 3 cases with thromboembolic complications after Fontan and Kawashima procedures.

2. PATIENTS AND METHODS

We reported our own experience of Fontan circuit blockade in 3 patients. The medical records, laboratory data, serial echocardiograms and angiograms of the patients were reviewed by two separate investigators.

2.1 Patient 1

An 8 year old female child presented with the diagnosis of double outlet right ventricle, subpulmonic ventricular septal defect, pulmonary and sub-pulmonary stenosis, d-malposed great arteries and a tiny patent ductus arteriosus. The right ventricle was bipartite with no trabecular portion. The tricuspid valve annulus was overriding the ventricular septum with chordal attachment to the crest.

A bidirectional Glenn shunt, pulmonary artery banding, atrial septectomy & patent ductus arteriosus ligation were performed at the age of 5 months. Till the time of her Glenn surgery, the patient had sinus rhythm then episodes of junctional rhythm & junctional tachycardia were reported and became more frequent later on. After her Glenn shunt, the patient was kept on aspirin.

An extra-cardiac Fontan operation was done at the age of 4.5 years using a contegra size 20 mm to connect the inferior vena cava to the pulmonary arteries confluence. In the intensive care unit, the patient had a history of early post-operative hemothorax, sluggish inferior vena cava flow and low urine output. Cardiac catheterization elucidated stenosis at the junction of the inferior vena cava to contegra,

sluggish inferior vena cava flow, a mean pressure of 16 mmHg at Fontan circuit, patent Glenn shunt & a right ventricular end diastolic pressure of 10-12 mm Hg. At this point no intervention was done as there was no gradient across the Fontan stenosis. The patient was managed to be extubated & discharged home in a stable condition. After Fontan operation, warfarin was added for a target PT- INR of 2-3.

Two weeks later, she presented with persistent vomiting & abdominal pain. Chest x-ray showed significant pleural effusion. Echocardiography showed mild pericardial effusion, dilated inferior vena cava and distal hepatic vein (Figs. 1 and 2) and patent Fontan connections with reduced flow velocity. The INR for the patient was within the therapeutic range over the last 6 months before the event.

She had significant hepatomegaly not responding to conservative management, therefore, cardiac catheterization was performed revealing thrombotic blockade of the entire Fontan circuit and the left pulmonary artery. Tissue plasminogen activator infusion was given at the intensive care unit for 48 hours. Repeat catheterization showed significant declotting of Fontan connections with improved but still sluggish blood flow. Two 45 mm covered stents were used to stent the Fontan circuit (Fig. 3). After stenting, the liver size and abdominal pain showed some improvement and the echocardiography confirmed the patency of Fontan connections with reduced laminar flow velocity in inferior vena cava and hepatic veins, patent right Glenn shunt, with no superior or inferior vena cava dilatation (Fig. 4). At the time of her discharge, liver size regressed to 3 cm below the right costal margin in mid-clavicular line with better oral feeding tolerance and no more abdominal pain.

2.2 Patient 2

An 8 year old boy was diagnosed to have mesocardia, double inlet left ventricle, L-malposed great arteries, and pulmonary and sub-pulmonary stenosis. He presented to us at the age of 8 months with a remarkable desaturation (Oxygen saturation down to 20%); therefore an urgent Glenn shunt was performed. An extra-cardiac Fontan was done at the age of 3.7 years using a contegra size 14 mm with augmentation of proximal left pulmonary artery by bovine pericardium. Similar to the first patient, aspirin was started after the Glenn and warfarin was added after Fontan procedures.

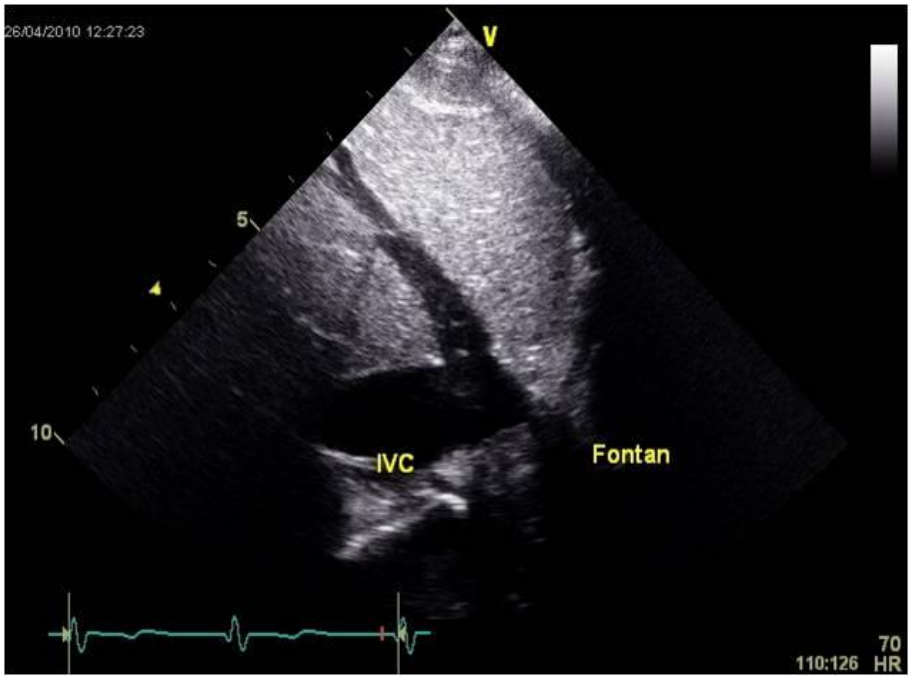

Fig. 1. Two-dimensional image of first patient showing dilated IVC and distal hepatic vein

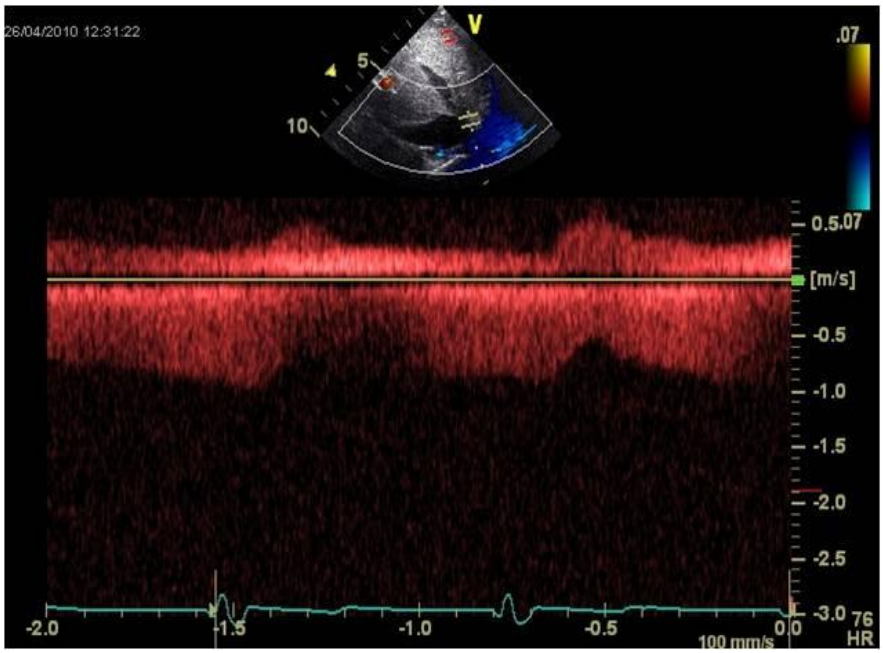

Fig. 2. Pulsed wave Doppler interrogation of IVC in first patient showing preserved respiratory related variation of IVC flow

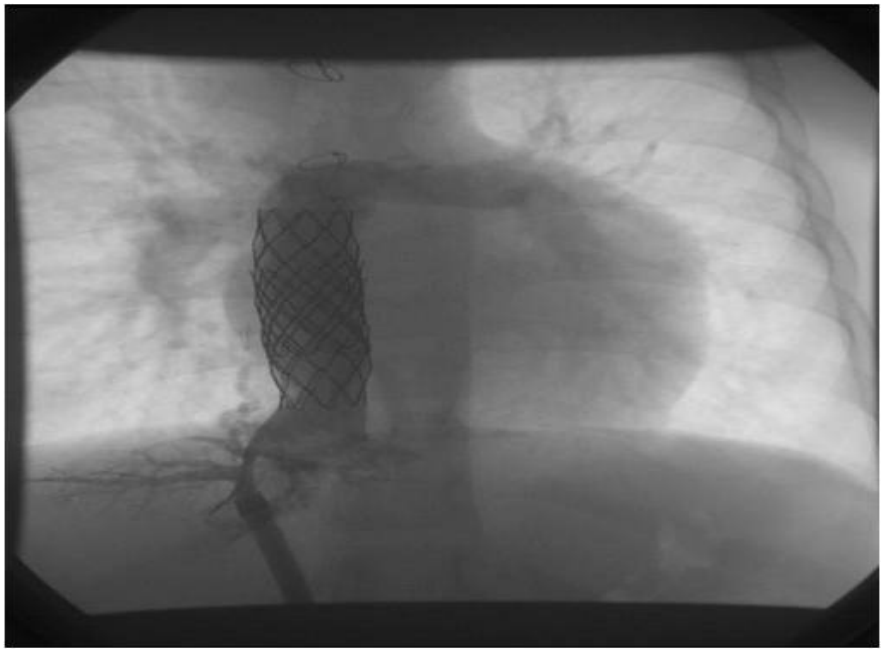

Fig. 3. Stenting of EC fontan contegra in first patient with angiography showing patency of fontan pathways

One year after Fontan operation, during one of the post-operative clinic visits, the family gave a history of an episode of jaundice, dark urine & leg swelling of one week duration and diagnosed as hepatitis at another hospital. On clinical examination, he was found to have an oxygen saturation of 95%, prominent superficial veins over the chest wall with filling from below upwards with an otherwise unremarkable chest examination, grade 1/6 systolic ejection murmur,

no hepatomegaly, no lower limb edema, and INR was within the therapeutic range. Echocardiography revealed reduced flow velocity in the inferior vena cava with prominent flow in a hemiazygous vein versus an abnormal venous channel. An urgent cardiac catheterization was arranged to rule out presence of inferior vena caval obstruction and to delineate the venous anatomy. The INR for the patient was within the therapeutic range over the last 6 months before the event.

Cardiac catheterization revealed an inferior vena caval mean pressure of 18 mmHg, and superior vena caval mean pressure of 20 mmHg. Inferior vena caval angiograms showed totally obstructed Fontan contegra with blood clots and aneurysmal dilatation of the contegra. The systemic venous drainage was reaching the pulmonary circulation via dilated azygous & hemiazygous veins and multiple small collateral venous channels. Right internal jugular angiogram showed patent Glenn shunt & good size of right pulmonary artery. The contegra was stented with 2 covered stents 8 x 45 mm and 8 x 39 mm dilated to 15 mm (Fig. 5). After stenting, angiograms revealed stent protrusion into the left pulmonary artery directing the superior vena caval flow to the right pulmonary artery; however, there was a good flow to left pulmonary artery as well. Serial echocardiograms after stenting of the contegra showed patent Fontan connections (Fig. 6). Shortly after stenting; a lung perfusion scan showed preferential flow to the right lung; 86% compared with 14% for the left lung. Repeat lung perfusion scan 8 months later showed improved left lung perfusion; 71%.

2.3 Patient 3

A 12 year old girl presented shortly after birth with polysplenia, unbalanced atrioventricular septal defect, double outlet right ventricle, and pulmonary stenosis. Her mitral valve was atretic, the ventricles were l-looped, left ventricle was hypoplastic & inferior vena cava was interrupted.

A left bidirectional Kawashima shunt was constructed together with pulmonary arterial banding at the age of 8 months. Three months later; cardiac catheterization revealed multiple large abdomino-pelvic veno-venous malformations. Lung perfusion scan showed no pulmonary arterio-venous malformations.

ECG demonstrated atrial rhythm with sick sinus syndrome at the age of 6 years. Hepatic vein incorporation was performed at the age of 9 years using a fenestrated extra-cardiac Dacron tube size 18 mm to anastomose the hepatic vein confluence to the right pulmonary artery.

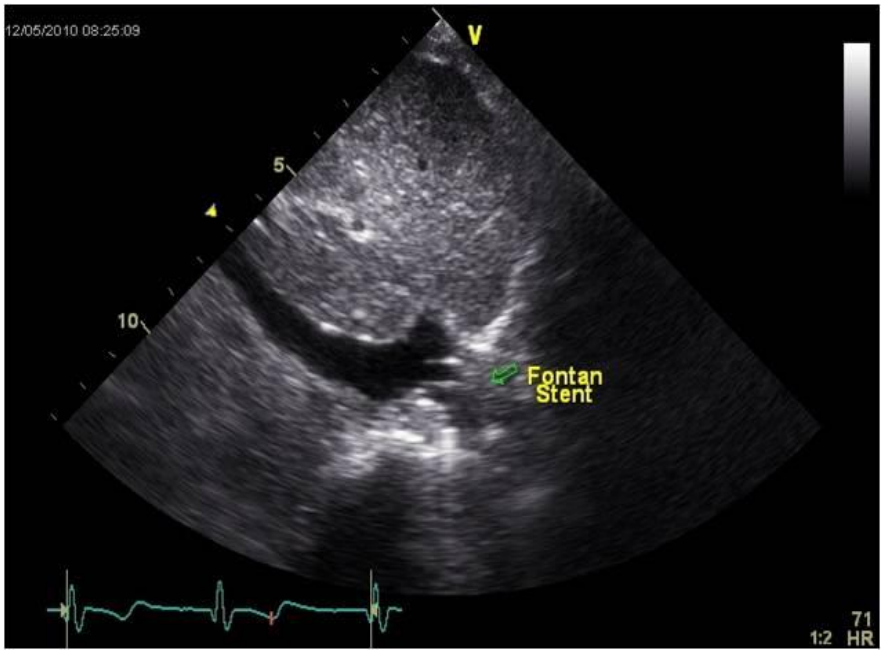

Fig. 4. Two-dimensional image of first patient illustrating the proximal part of Fontan stent with less IVC dilatation compared to Fig. 1

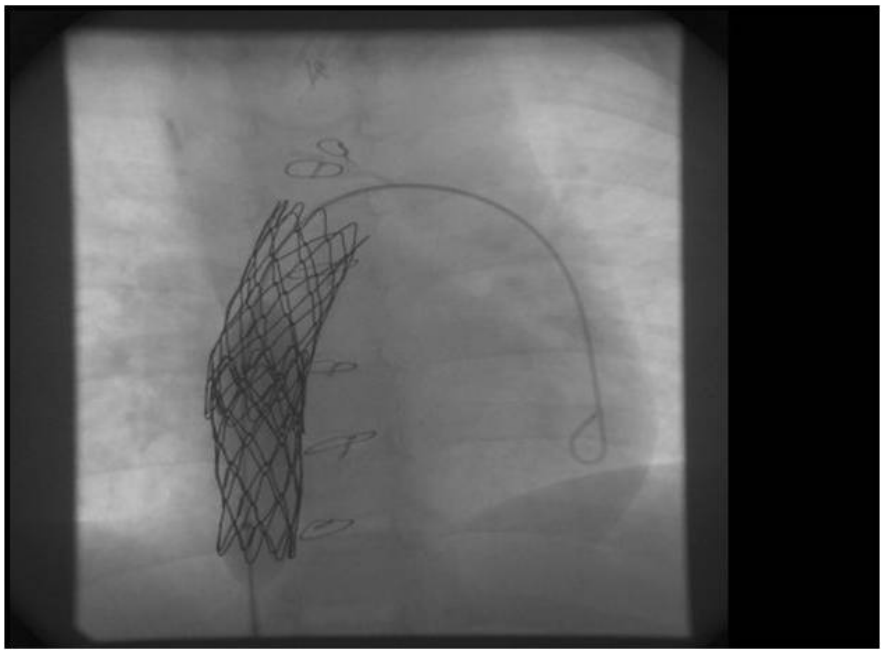

Fig. 5. Stenting of EC fontan contegra in second patient with balloon dilatation of the stent

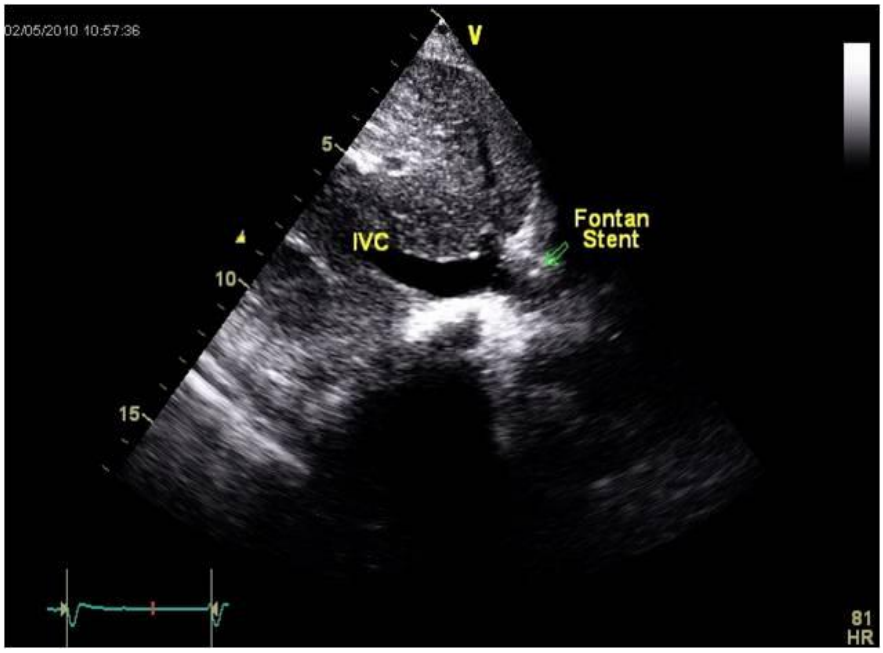

Fig. 6. Two-dimensional echocardiographic image showing the proximal part of Fontan stent in second patient

The main pulmonary artery stump was sutured and closed. A 5 mm fenestration was done between the conduit and the atrium because of the history of recurrent pleural effusion & chylothoraces. A permanent atrial & ventricular pacemaker leads were inserted due to presence of sick sinus syndrome & potential need for pacemaker in future. Postoperative echocardiography confirmed the patency of cavo-pulmonary connections & good ventricular

functions. She was discharged home in a stable condition and ECG showing a normal sinus rhythm fluctuating with an adequate junctional rate.

Five months post-hepatic vein incorporation, she had minimal bilateral pitting lower limb edema and mild abdominal distension. Echocardiography revealed thrombosis involving the lower part of the conduit (Fig. 7). She was admitted to hospital with a normal Prothrombin time (PT)-INR as she missed two doses of her warfarin. However, by heparin infusion & resuming warfarin, PT- INR was readjusted to be therapeutic but worsening of thrombosis was detected by MRI. Lower limb edema progressed to be severe with development of ascites & bilateral pleural effusion.

Several catheterization attempts failed to penetrate the hepatic vein thrombosis despite local tissue plasminogen activator infusion into the clot site using the transhepatic & transjugular approaches. Tissue plasminogen activator treatment was complicated with intracranial haemorrhage that was managed conservatively. Surgical intervention was made for hepatic vein thrombectomy and conduit replacement with a Gortex tube size 16 mm. A permanent pacemaker generator was inserted using the old atrioventricular permanent leads.

3. DISCUSSION

The potential advantages of the extra-cardiac Fontan procedure include avoidance of myocardial ischemia (aortic cross-clamping), atrial incision, and intra-atrial suture lines, and the feasibility of early or late fenestration. However, the capacity of this procedure to reduce late atrial arrhythmias and the longevity of the extra-cardiac conduit remain unproven [5-8].

The use of conduits, either intra-cardiac or extra-cardiac, obviates the need of tunneling and has excellent results in patients with normal inferior vena caval drainage. Long-term patency of these conduits continues to be excellent regardless of the material used whether Gore-Tex, homograft tissue, or autologous pericardium [9]. Constructing a competent valve using the xenograft valved conduit (Contegra) in the extra-cardiac Fontan connection may maintain better forward flow into the pulmonary circulation [10]. The importance of hepatic blood flow for prevention or reversal of pulmonary arteriovenous malformation has been reported [11–14]. Kawashima et al.; reported that pulmonary arteriovenous fistulae develop only rarely in older patients [15]. Arteriovenous fistulae did not develop in any of 14 patients who underwent the Kawashima procedure at age 12 years or older [15,16]. It has been assumed that in older patients, the “putative substance” in hepatic venous blood could be transported to the lung through well-developed systemic-to-pulmonary arterial collaterals [16]. The longevity of the extra-cardiac conduit remains the most controversial aspect of this surgical option. The mechanism of late conduit obstruction is likely longitudinal torsion of the conduit during rapid somatic growth in height. The facility of treating this obstruction by stent placement supports this mechanism [17].

The benefits of prophylactic anticoagulation or antiplatelet therapy for patients undergoing extracardiac conduit (ECC) Fontan procedure still are a matter of debate. Anticoagulant regimens in Fontan patients varied widely with a significant trend for warfarin use in patients with impaired haemodynamics. The options for primary prophylaxis include routine prophylactic anticoagulation with warfarin or antiplatelet agents.

Clearly patients receiving warfarin will have higher probability of bleeding complications compared to those receiving aspirin. Australian data suggests that with a well coordinated pediatric anticoagulation clinic; the annual risk of major bleeding in children on warfarin can be reduced to 0.05% per year. Warfarin requires regular monitoring, that can have a significant impact on family life [18,19]. However, Marrone et al.; evaluated the incidence of thromboembolism among patients undergoing extracardiac (ECC) Fontan procedures who received anticoagulation or antiplatelet therapy. They found that the overall thromboembolism rate was 5.2%. They analyzed the effect of different therapeutic strategies on the occurrence of thromboembolic and bleeding events among those patients. They found that the rate of thromboembolic and bleeding events associated with antiplatelet therapy is similar to that associated with anticoagulation therapy in patient underwent ECC Fontan [20]. A recent study done by Ohuchi et al.; 2015 showed that the haemostatic events occurred in 7% of cases; 45% of these events were haemorrhagic and 55% were thrombo-embolic. They found that low oxygen saturation was the only predictor of early postoperative thrombo-embolic events [21]. Risk

factors for thrombotic complications include chronic systemic venous hypertension, protein-losing enteropathy, passive blood flow, atrial arrhythmias, conduit stenosis, coagulation factor abnormalities, and other several patient characteristics [22]. Some reports raise the prospect of warfarin causing reduced bone density in children although further studies are required to confirm this possible effect [23].

A multicenter, randomized clinical trial compared the use of acetylsalicylic acid versus heparin / warfarin targeting international normalized ratio of 2.0 to 3.0 as a primary thromboprophylaxis in children with Fontan procedure in children. The study found no significant difference between the two regimens in the primary thromboprophylaxis in the first 2 years after Fontan surgery. The thrombosis rate was suboptimal for both regimens, suggesting the need for alternative approaches [24]. Low molecular weight heparin (LMWH) demonstrated its safety with cost effectiveness as compared to other heparins [25]. Jacobs, et al.; assessed the impact of aspirin in reducing thromboembolic events after Fontan operation, initiating aspirin therapy from the first post-operative day. On follow up (over forty months), there were no documented thromboembolic events, hemorrhagic events or aspirin-related complications. It was concluded that low dose aspirin can be used safely and effectively in Fontan patients, and more aggressive anticoagulation may be unwarranted [26]. Saheb et al. found that triple antithrombotic therapy was more efficacious in reducing the occurrence of ischemic stroke in patients indicated for chronic oral anticoagulation, compared with double antiplatelet therapy (with aspirin and clopidogrel). However, it significantly increased the major and minor risks of bleeding [27]. Triple therapy with warfarin, aspirin, and a thienopyridine is advised in presence of atrial fibrillation. However, the safety of this regimen appeared suboptimal because of an increased risk of hemorrhagic complications. On the other hand, the combination of oral anticoagulation and an antiplatelet agent is suboptimal in preventing thromboembolic events and stent thrombosis; dual antiplatelet therapy may be considered only when a high hemorrhagic risk and low thromboembolic risk are perceived. Indeed, the need for prolonged multiple-drug antithrombotic therapy increases the bleeding risks when drug eluting stents are used [28]. Till now there are no convincing data that any prophylactic antithrombotic regimen is effective in reducing thromboembolism. Thromboembolic events can occur in patients receiving heparin, aspirin, warfarin, combinations or none of these.

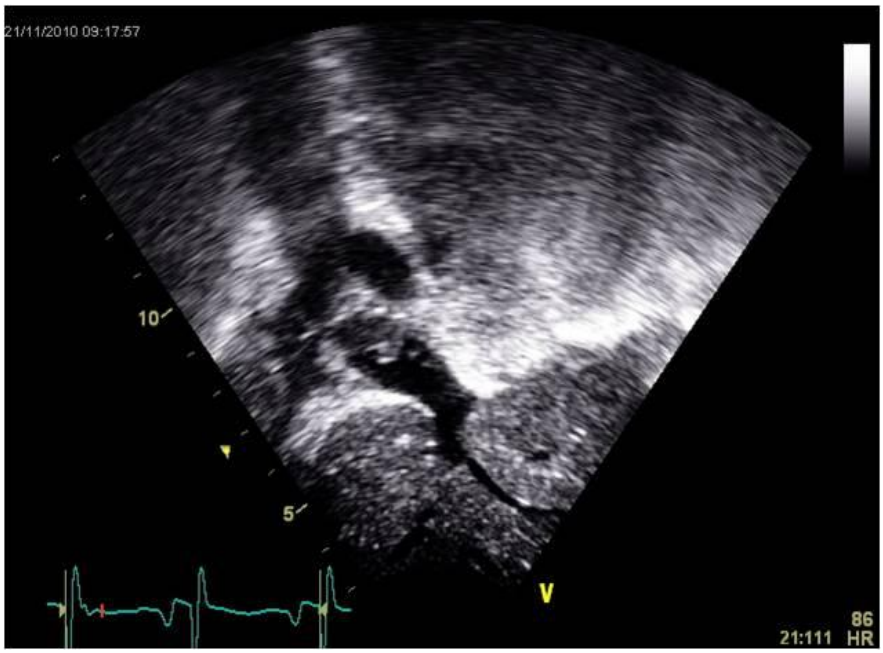

Fig. 7. Subcostal view in the third patient showing thrombosis of hepatic vein. Dilatation of hepatic vein is also noted

4. CONCLUSION AND RECOMMENDATION

The issue of anticoagulation therapy after Fontan procedure remains controversial [9,29]. Oral anticoagulation with warfarin did not prevent conduit thrombosis at least in 3 of our patients; hence, it does not seem reasonable to recommend chronic oral anticoagulation in those patients. However, we cannot draw any conclusion on epidemiology of thrombosis after Fontan from this three cases report and further data are needed to confirm this opinion. Perhaps, a smaller diameter conduit should be used in these patients to prevent stagnation of blood predisposing to thrombosis [9]. We emphasize the importance of careful evaluation of post-Fontan patients for thromboembolic events. Clinically suspicious occurrences must be thoroughly investigated. This may include transesophageal echocardiography when there is an alteration from baseline hemodynamics. The threshold for diagnostic and interventional cardiac catheterization should be lowered post-Fontan even in absence of echocardiographic evidence of inferior vena caval obstruction or lack of significant pressure gradient across contegral stenosis respectively. In agreement with Igor et al. [30], we do believe that multi-centre randomized trials are still needed to outline the methods of decreasing the adverse outcomes. The current uncertainty around the optimal primary prophylaxis regimes should be addressed to reduce the risk of thrombosis among children undergoing cardiac surgery in the future.

CONSENT

All authors declare that 'written informed consent was obtained from the patients' parents for publication of the case series and the accompanying images.

ETHICAL REVIEW BOARD

Approved publication of the case series.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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