Anticoagulation in Children Undergoing Cardiac Surgery

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ABSTRACT

Advances in medical and surgical care have resulted in improved survival of patients with congenital heart disease (CHD). Parallel to these progresses, an increasing number of immediate and long-term complications have been recognized. One important complication in CHD is the development of thrombosis. Children with a single functional cardiac ventricle usually require sequential steps of surgery: the initial Blalock-Taussig shunts (BTS) during the neonatal period, followed by the Glenn shunt, and finally, the Fontan shunt, the "definitive palliative" procedure. Surgery mostly involves cardiopulmonary bypass (CPB), which also affects the coagulation system and causes an inflammatory response. This article will review surgical procedures, such as BTS, Glenn shunt, and Fontan shunt, prosthetic mechanical valves, and CPB, and their risk of thrombotic complications. There is insufficient evidence and no consensus for optimal anticoagulant prophylaxis or treatment in children with CHD. Current recommendations are mostly based on adult data.

KEYWORDS: Pediatric cardiology, cardiac surgery, thrombosis, thromboprophylaxis, anticoagulation

Congenital heart disease (CHD) affects ~1% of all live births. One important complication in survivors of CHD is the development of thrombosis, arising within the cardiac chambers, on the valves, vessel walls, or on implanted devices.[1] Thromboembolic complications, such as intracardiac thrombi, pulmonary embolism, and systemic embolism, particularly to the central nervous system, have been reported as a major cause of morbidity in children with CHD.[2] According to the Canadian Childhood Thrombophilia Registry, CHD was the underlying disease in 19% (75 of 405) of children with reported venous thromboembolism. Thrombosis-associated mortality in the subgroup with CHD was 7%.[3]

Children with a single, functional ventricle usually require sequential steps of surgery: the initial Blalock-Taussig shunt (BTS) during the neonatal period, followed by the Glenn shunt, and the Fontan shunt, which is the final procedure.[4–6] The risk of thrombosis differs with each surgical procedure.[1] Surgical advances for treatment of CHD have resulted in an increased use of anticoagulants in children in recent years. Nowadays, the majority of children requiring primary anticoagulant prophylaxis are those with CHD or acquired heart disease.[2] Optimal treatment strategies for prevention of thrombotic complications have been widely discussed over the last decade with little evidence for either strategies.[2,7] Most of the evidence for anticoagulation

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for mechanical prosthetic valves is extrapolated from adult studies with limited data from small pediatric studies and case reports.[8,9]

This article will review surgical procedures, such as BTS, Glenn shunts, Fontan shunts, prosthetic mechanical valves, and cardiopulmonary bypass (CPB), their risk of thrombotic events (TE) and current recommendations for anticoagulation.

BTS

The original BTS was a systemic-to-pulmonary shunt created by anastomosing the subclavian artery end-to-side to the ipsilateral pulmonary artery.[4] This "classic BTS" has largely been replaced by the modified Blalock-Taussig shunt (MBTS) which was originally designed for situations in which a classic BTS could not be performed, such as in infants less than 3 months of age.[10] In a MBTS, an artificial graft is placed between the subclavian artery and the ipsilateral pulmonary artery.[11] The most common indications in which BTS are used include tricuspid atresia, pulmonary atresia, and tetralogy of Fallot in some centers.[12] In hypoplastic left heart syndrome, MBTS can be performed as part of a more complex surgical intervention, for example, Norwood procedure.[13] An MBTS is commonly performed in the neonatal period to increase pulmonary blood flow. The graft tube may be as small as 3 to 4 mm, depending on the size of the infant.[14]

Risk factors for thrombosis include patient age, graft size, and cardiac malformation.[10–17] The incidence reported for thrombotic occlusion of MBTS ranges from 1 to 17%.[15,18] Shunt failure by occlusion in the postoperative period in patients with shunt-dependent pulmonary circulation can result in life-threatening hypoxia, acute respiratory distress, hypotension, and death. Therapeutic options are thrombolytic therapy, balloon angioplasty, stent implantation, and surgical revision.[19]

In any cardiac shunt procedure, maintaining shunt patency is obviously critical to the success of the treatment. However, currently there is no established approach to the prevention of shunt occlusion.

Few controlled studies are available to guide the antithrombotic management of MBTS patients.[20] Table 1 summarizes studies on thromboprophylaxis in BTS patients. In the postoperative period, strategies vary between heparin administration for 2 to 5 postoperative days[14,17,21] and no heparin.[11,22] Fenton reported identical mortality rate of patients after MBTS discharged on aspirin (11%) compared with those discharged on no anticoagulation (12.3%).[23] A retrospective case series of 546 MBTS procedures revealed shunt failure in 9.1% with heparin given intraoperatively and postoperatively versus 13.6% without heparin administration. Aspirin given during the further course, nonsignificantly reduced shunt failure from 11 to 6.7%.[14] Another small study showed a decrease of MBTS thrombosis in patients treated with aspirin.[24] Whether patients benefit from long-term anticoagulation is unclear. Some studies report lower shunt failure rates using aspirin during follow-up period.[11,14] Other studies suggest that more important risk factors for shunt failure are the underlying heart defect, age, and weight at the time of surgery, and the size of the graft in MBTS.[10,12,17] A recent prospective, multicenter, observational study of 1004 infants with systemic-to-pulmonary shunts including right ventricular-to-pulmonary artery shunts reported an overall incidence of shunt thrombosis of 12%. Use of aspirin was associated with a significantly decreased risk of shunt thrombosis and death.[25] A recently completed multicenter, randomized trial (CLARINET) in 906 infants with systemic-to-pulmonary shunts compared clopidogrel in a dose of 0.2 mg/kg versus placebo on top of aspirin therapy given to 88% of patients. The study found an overall incidence of shunt thrombosis of ~5% and mortality of 13%. There was no significant difference between treatment arms in the composite primary outcome and its components (mortality, shunt thrombosis, cardiac procedure) before 120 days of age due to a thrombotic event. Bleeding rates were also similar between arms. Thus, adding clopidogrel (at the chosen dose) to aspirin did not result in a significant benefit in children with systemic-to-pulmonary shunts.[26]

GLENN SHUNTS

The bidirectional cavopulmonary shunt (BCPS) is an end-to-side shunt between superior vena cava (SVC) and right pulmonary artery. This palliative procedure is created to increase pulmonary blood flow and, thereby, oxygen saturation, without increasing the workload of the systemic ventricle.[5] The Glenn shunt is used as intermediate step in patients with single ventricle anatomy before definitive Fontan surgery.[20,27]

Via the Glenn shunt, blood flows directly from the SVC into the pulmonary arteries and the lungs. Any reduction of SVC flow due to thrombotic occlusion will dramatically reduce pulmonary blood flow. The main concern after Glenn shunts are pulmonary emboli with the danger of increased pulmonary resistance, which may result in being unsuitable for Fontan surgery.[1,28] One rationale is that anticoagulation after Glenn shunt may reduce the risk of pulmonary emboli. However, available data have infrequently reported thrombotic complication after Glenn shunts.[29–31] Therefore, currently there are no data to support routine thromboprophylaxis. Current clinical approaches vary and include no anticoagulation, heparin followed by aspirin, or heparin followed by vitamin K antagonists (VKA). There is no evidence to support either of these approaches.[20]

Table 1 Primary Thrombosis Prophylaxis after BTS

Study/Year	Design (Period)	Pt. No.	Shunt Size	Shunt Failure/ Occlusion *n* (%)	Anticoagulation/ Platelet Inhibition	Conclusion
Mullen JC et al, 1996[22]	Prospective	24 Shunts in 23 pt.	5 mm	0	1. Postop UFH single dose (20 IU/kg) after anastomosis 2. ASA $n=2$ (due to small pulmonary arteries)	-Mean f/u 18 mo -Three deaths not shunt related -100% shunt patency without heparin
Al Jubair KA et al, 1998[14]	Retrospective (1983–1995)	546 Shunts in 472 pt.	4–6 mm -128 classical BTS -418 MBTS	-With UFH: 9.1% vs. without UFH: 13.6% -With ASA: 6.7% vs. without ASA: 11%	-MBTS 173: UFH 100 IU/kg up to 48 h postop (individual decision by surgeon) -All MBTS: ASA 1–2 mg/kg/d	-Significant relation between early shunt failure and: 1. age <1 wk 2. weight <3 kg - Heparin-reduced early and late mortality
Li JS et al, 2007[25]	Prospective (2001–2005)	1004 pt.	4 mm MBTS including RV to PA shunt	Shunt thrombosis: 99/806 (12.2%)	ASA: 3–5 mg/kg: 806 of 1004 pt.	With ASA: Significant lower risk of shunt thrombosis and death
Wessel et al, 2010[26]	RCT (2001–2005)	906 (age 0–3 mo)	MBTS inclusive PDA stents	Shunt thrombosis: -Clopidogrel group: 26 (5.4%) -Placebo group: 21 (4.8%)	Clopidogrel (0.2 mg/kg): 479 Placebo: 439 Concomitant ASA: 792 (88%)	No differences between groups for -shunt thrombosis -bleeding events

BTS, Blalock-Taussig shunt; pt., patients; postop, postoperative; UFH, unfractionated heparin; ASA, acetylsalicylic acid; mo, months; MBTS, modified Blalock-Taussig shunt; h, hours; d, days; wk, weeks; RV, right ventricle; PA, pulmonary artery; RCT, randomized controlled trial.

FONTAN SHUNT

The Fontan procedure is the definitive palliative surgical treatment for most univentricular heart defects. After numerous modifications, the basic principle remains the same: both the SVC (done in the first stage BCPS) and inferior vena cava are anastomosed to the right pulmonary artery.[6] Consequently pulmonary blood flow is totally passive without interposed ventricle or valves, depending on venous flow mechanisms (negative intrathoracic pressure with inspiration, venous valves). Thereby, the single ventricle functions as left ventricle, generating systemic blood flow. A modification is the creation of a fenestration (Fontan tunnel to atrium) to allow decompression of the venous system by right-to-left shunting. Such modifications reduce perioperative mortality.[28,32–34] However, Fontan shunts are associated with relevant morbidity.

Important complications are TE, reported with prevalences between 5 and 33%.[35–41] Most studies reporting on the incidence of thromboembolic complications after Fontan surgery so far have been retrospective. Three cross-sectional surveys, using transesophageal echocardiography reported prevalences of 17, 20, and 33%, respectively.[38,42,43] All three studies demonstrated increased sensitivity with transesophageal echocardiography (TEE) compared with transthoracic echocardiography. The frequency of TE was increased in recent studies compared with earlier studies, reflecting increased survival, longer duration of follow-up period, improved diagnostic tests as well as increased awareness of the potential for TE. The retrospective design and limited follow-up period may explain the variability in reported incidences, which may still be an underestimation. Table 2 summarizes studies on primary thrombosis prophylaxis after Fontan operation.

The etiology of thrombus formation after Fontan surgery is unclear. TE may occur any time following the Fontan procedure but often presents months to years later. Hemostatic changes peri- and postsurgery have been considered to impact on thrombosis development. Data from a German study showed an imbalance between procoagulant and anticoagulant factors occurring during CPB in children with complex CHD.[44] High levels of procoagulant factors, such as prothrombin fragment $1+2$, were not counterbalanced by anticoagulation factors, such as tissue factor pathway inhibitor and antithrombin. According to these authors, this imbalance was considered to enhance the risk for TE during and after surgery, particularly in patients after univentricular palliation. Further risk factors for TE are a low postoperative arterial saturation,[45] dysrhythmias,[39,45] large fenestrations >4 mm,[46] and protein-losing enteropathy, potentially through direct loss of clotting factors.[36]

There is no consensus regarding routine primary prophylaxis for patients after Fontan palliation. Some centers do not anticoagulate, unless patients have dysrhythmias or prosthetic valves,[47] others give VKA for 3 months, followed by lifelong aspirin.[48] Further examples of clinical practice are VKA for 1 year, followed by aspirin[49] or aspirin only for 6 months postoperatively,[50] and finally aspirin or VKA as lifelong treatment. Target international normalized ratio (INR) ranges differ between centers, some target for INR between 2 and 3, others for INR between 3 and 4.5.[38] Of note, TE have been demonstrated while patients were on "low-dose" aspirin, heparin, or VKA.[39,51] A multicenter, randomized, controlled trial in Canada and Australia compared VKA (INR 2 to 3) versus aspirin (5 mg/kg/d) started immediately after Fontan surgery in 111 children. The primary outcome was TE detected clinically or by screening with TEE after 3 months and 2 years. The overall incidence of TE in the first 2 years was 23% with only about one-third clinically symptomatic thromboembolism. There was no significant difference in TE incidence between VKA and aspirin arms. The conclusion was that the risk of TE in Fontan patients is high despite anticoagulant prophylaxis.[7] Currently, neither treatment modality has proven superiority and longer-term trials will be needed.

MECHANICAL PROSTHETIC HEART VALVES

Mechanical prosthetic valves (MPV) are placed surgically or, recently, also by catheter intervention in children with congenital or acquired valve disease. Due to the presence of foreign material, mechanical valves have a significant thrombogenic potential. Reported incidences of TE in children with mechanical valves vary widely and there are no consistent differences between different anticoagulant modalities or no anticoagulant prophylaxis (summarized in detail in the American College of Chest Physicians [ACCP] guidelines).[20] Most of the evidence for anticoagulation in patients with MPV is extrapolated from adult studies in whom primary thrombosis prophylaxis with VKA has been demonstrated to reduce the risk of TE, although at an increased risk of bleeding.[8,9,52,53] Current recommendations for adults as well as children are to use VKA with a target INR between 2.0 and 3.0 for aortic MPV and a target INR of 2.5 to 3.5 for MPV in mitral position or for aortic MPV associated with dysrhythmia. For children who experienced TE under VKA therapy and in those with contraindications to full-dose VKA, the ACCP guidelines recommend adding aspirin.[20]

ANTICOAGULATION IN CHILDREN UNDERGOING CPB

During CPB the goal is adequate preservation of the coagulation system, preventing thrombosis and consumption of coagulation factors and with that minimizing postbypass coagulopathy. Upon initiation of CPB,

Table 2 Primary Thrombosis Prophylaxis after Fontan Operation

Study, Year	Design (Period)	Pt. No.	Follow-Up	TE *n* (%)	AC/Platelet Inhibition	Major Hemorrhage	Conclusion
Seipelt RG et al, 2002[41]	Retrospective (1986–1998)	85 (three groups)	Mean: 5.7±3.5 y	No AC: 10/45 (22) ASA: 1/14 (7) VKA: 1/26 (4)	No AC: 45/85 (53) ASA: 14/85 (16) Heparin followed by VKA: 26/85 (31)	None reported	-TE peak in first postop year and 10 y postop -VKA most efffective in TE prevention
Kaulitz R et al, 2005[35]	Retrospective case series (1988–2002)	142 pt.	Mean 91.1 ± 43.9 mo	VTE: 10 (7) AIS: 2 (1.4)	No AC: 40 (28) ASA: 74 (52) VKA: 28 (20)	None reported	No need for routine AC in patients after Fontan
Chun DS et al, 2004[41]	Retrospective (1988–2000)	139 post Fontan	13 y	Seven strokes in 5/139 (3.6) pt. -Unfenestrated Fontan:3 -Fenestration: 2 -No intracardiac thrombi	- ASA + VKA: 2 -ASA: 2 -No AC: 3	*n* = 1 on ASA and VKA: -Epistaxis and GI bleed	Previous pulmonary artery banding as risk factor for stroke
Monagle P et al, 2011[7]	Prospective (1998–2003)	111 pt.	2 y	After 2 y: 23%	Randomized: - ASA: 57 - VKA: 54	*n* = 1 (ASA group) *n* = 1 (heparin/VKA group)	No significant differences between both groups regarding TE and bleeding

pt., patients; TE, thrombotic events; AC, anticoagulation; ASA, acetylsalicylic acid; VKA: vitamin K antagonists; mo, months; VTE, venous thrombotic events; AIS, arterio ischemic stroke; GI, gastrointestinal; RCT, randomized controlled trial; y, years.

fibrinogen adheres to the artificial surfaces of the circuit. Platelets become activated and bind to fibrinogen and degranulate. Once prematurely activated, platelets are not available for hemostasis after surgery.[54] CPB also causes immense humoral (complement, interleukins) and cellular (neutrophils) inflammatory reactions.[55,56] An ideal anticoagulation regimen would completely suppress coagulation and be completely reversible at the end of the CPB.

Despite achieving inadequate anticoagulation and being associated with ongoing thrombosis formation, unfractionated heparin (UFH) remains the preferred anticoagulant in CPB. Its anticoagulant effect is mostly monitored by the activated clotting time (ACT). However, during CPB, the ACT is also affected by factors other than heparin, such as hemodilution and hypothermia, which may result in overestimation of heparin concentration and ongoing thrombin generation.[57]

Koster et al showed that the "heparin concentration-based anticoagulation management" resulted in significant reduction of thrombin generation, fibrinolysis, and neutrophil activation compared with the ACT-guided heparin management.[58] Further prospective, multicenter studies are needed to evaluate and improve management of anticoagulation in children undergoing CPB.

CARDIAC CATHETERIZATION (CC)

CC is important for diagnosis and treatment in children with congenital and acquired heart disease. Incidences of TE associated with CC in children reported in the literature range from 0.8 to 40% for arterial thrombosis and 0 to 20% for venous thrombosis.[59–65] UFH is used for prevention of TE during CC which is based on an early study that demonstrated UFH to decrease the frequency of arterial occlusion.[59] However, the optimal UFH dose for pediatric CC is not established. Only few studies have compared different UFH protocols and their results are not conclusive.[59–63] Current recommendations are to use a bolus of 100 to 150 U/kg body weight UFH and additional UFH bolus during the procedure,[20] but lower UFH doses may potentially be sufficient. A recently completed randomized controlled trial (HEARCAT study) compared UFH at 100 U/kg bolus followed by continuous infusion versus 50 U/kg bolus.[66] The study screened all patients for TE at puncture site using ultrasound. The overall incidence of TE was low (4.6%) and there was no difference in TE between high and low dose UFH. The conclusion was that 50 U/kg UFH may be considered sufficient in usual situations during pediatric CC.

CONCLUSION

Improved surgical and medical treatments have tremendously improved the outcome of children with congenital and acquired cardiac disease. BTS, Glenn, and Fontan procedures are associated with relevant morbidity and mortality due to TE and thromboembolic complications. There are still limited data on the risk of TE in these conditions and on contributing risk factors. Moreover, there is insufficient evidence and no consensus regarding the optimal thromboprophylaxis. Some randomized trials have recently been performed in these patient populations but feasibility remains a challenge. Nevertheless, further trials are urgently needed to establish optimal thromboprophylaxis for patients with complex congenital heart defects.

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