Management and Outcomes of Patients with Occlusive Thrombosis after Pediatric Cardiac Surgery

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Objectives To evaluate management and outcomes of thrombosis after pediatric cardiac surgery and stratify thrombi according to risk of short- and long-term complications to better guide therapeutic choices.

Study design Retrospective review was performed of 513 thrombi (400 occlusive) diagnosed after 213 pediatric cardiac operations. Long-term outcomes over time were assessed with the use of parametric hazard regression models.

Results Serious complications and/or high-intensity treatment occurred with 17%-24% of thrombi depending on location, most commonly in thrombi affecting the cardiac and cerebral circulation. Bleeding complications affected 13% of patients; associated factors included thrombolytics (OR 8.7, $P < .001$), greater daily dose of unfractionated heparin (OR 1.25 per 5 U/kg/day, $P = .03$), and extracorporeal support (OR 4.5, $P = .007$). Radiologic thrombus persistence was identified in 30% ± 3% at 12 months; associated factors included extracorporeal support (hazard ratio [HR] 1.9, $P = .003$), venous (HR 1.7, $P = .003$), and occlusive thrombi at presentation (HR 1.8, $P = .001$); greater oxygen saturation before surgery (HR 1.13/10%, $P = .05$) and thrombi in femoral veins (HR 1.9, $P = .001$) were associated with increased hazard of resolution. Freedom from postthrombotic syndrome was 83% ± 4% at 6 years, greater number of persistent vessel segment occlusions (HR 1.8/vessel, $P = .001$) and greater fibrinogen at diagnosis (HR 1.1 per g/L, $P = .02$) were associated with increased hazard.

Conclusions Thrombosis outcomes after pediatric cardiac surgery remain suboptimal. Given that more intensive treatment would likely increase the risk of bleeding, the focus should be on both thrombosis-prevention strategies, as well as in tailoring therapy according to a thrombosis outcome risk stratification approach. *(J Pediatr 2016;169:146-53)*.

Clinically important thrombosis occurs in 11% of patients after childhood cardiac surgery.[1] Complications from thrombosis in this context often are considered rare, even if highly clinically relevant.[2] This impression likely comes from the fact that serious complications of thrombosis represent a heterogeneous mix of clinical entities. As a group, however, they affect 28% of children with thrombosis after cardiac surgery and are associated with important morbidity, mortality, and suboptimal surgical outcomes.[1] Given the risk of serious complications in children with cardiac disease, prompt and often-aggressive treatment of postoperative thrombi has been recommended.[2,3] Rates of thrombosis resolution are suboptimal, with approximately one-third to one-half of thrombi persisting despite treatment.[1,4] Persistent thrombi may compromise future vascular access, an important consideration in these children, who often have multiple interventions throughout their lifetime. Other consequences of thrombus persistence include postthrombotic syndrome.[5,6] Controversy remains regarding the risk of thrombi-related complications associated with specific locations and degree of vessel occlusion.

A host of therapeutic options are available; these vary in their targets (ie, preventing further thrombus growth and/or embolism [anticoagulants] or re-establishing vessel patency [fibrinolytic therapy and/or thrombectomy]), dose intensity, and efficacy but also in their associated complications.[7] Optimally, the intensity of the selected treatment strategies (both therapeutic approach and dosing) should be decided on the basis of the probability of absence of further thrombus growth and/or thromboembolism, thrombus resolution, and risk of adverse effects from therapy. We sought to review the management and outcomes of postoperative thrombosis in children who underwent cardiac surgery to provide a stratification of risk associated with different types of thrombi and guide therapeutic choices in this challenging population.

HR Hazard ratio

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Methods

All cardiac operations performed at The Hospital for Sick Children, Toronto, between January 2002 and December 2009 were reviewed (N = 3043). Operations associated with at least 1 occlusive postoperative intravascular thrombus confirmed by diagnostic imaging (absence of flow and vessel noncompressibility on vascular ultrasound) or found during reinterventions within 1 month of surgery were selected for further review. During the study period, no systematic imaging detection protocol for postoperative thrombosis screening was in place; hence, all diagnostic investigations were ordered at the discretion of the treating physician, either because of suspicion of or specific clinical concern for thrombosis. Nonocclusive thrombi found in enrolled patients were also assessed as part of this study because nonocclusive thrombi may potentially contribute to patient outcomes. The study protocol was approved by the Hospital for Sick Children Research Ethics Board; the requirement for individual patient consent was waived for a retrospective study.

For each identified thrombus, data on the exact location, degree of occlusion at diagnosis, and time and modality of radiologic diagnosis were collected separately. At the time of diagnosis, baseline coagulation laboratory values, including complete blood count, prothrombin time/international normalized ratio, activated partial thromboplastin time, and fibrinogen levels were obtained, as this is generally part of standard care for these patients in our institution. Pharmacologic management in the months after diagnosis was reviewed in detail, including dosing and duration of treatment with anticoagulant medications (used either for treatment or thromboprophylaxis). During the study, a standardized antithrombotic protocol was in place, albeit with limited adherence, and the choice of treatment strategy often was at the discretion of the treating medical team. For patients who received thrombolytics and for those who underwent thrombectomy (either catheter or surgical), the indication was noted. Severe bleeding complications were defined as bleeding events requiring allogeneic blood transfusions >1 unit, and/or the use of hemostatic agents (eg, recombinant factor VII), or any of the following events (either clinical occurrence or diagnosed by imaging): pulmonary hemorrhage, cerebral hemorrhage, hemorrhagic stroke conversion, severe gastrointestinal bleeding, or bleeding requiring surgical intervention. Any bleeding event in which a surgical cause was identified subsequently was excluded.

Medically complicated thrombi were defined as thrombi associated with arterial ischemic stroke, sinovenous stroke with or without venous infarction, pulmonary embolism, organ ischemia, cardiopulmonary circulation compromise defined clinically, or removed by thrombectomy. A secondary definition also including thrombi in patients treated with thrombolytics was used to capture all medically complicated thrombi, even though not all thrombi found in patients treated with systemic thrombolytics were equally clinically important.

Long-term outcomes of thrombosis were assessed for all patients who survived to discharge from hospital and didn't undergo active thrombus removal (thrombectomy or thrombolysis). Outcomes of thrombi (persistence or resolution) were assessed after diagnosis, up to thrombosis resolution, or last follow-up. Thrombus resolution was defined as vessel return to patency without signs of vessel occlusion. For patients who were followed as outpatients by our specialized thrombosis service, the presence or absence of postthrombotic syndrome was assessed clinically by use of the modified Villalta scale, which has been described previously.[6]

Data are presented as means with SDs, medians with 25th and 75th percentiles, or frequencies, as appropriate. The proportion of patients who had serious complications of thrombosis (by the use of both definitions as outlined previously) was determined for each thrombus location. Factors associated with increased odds of the patient having bleeding complications were assessed in multivariable logistic regression model with forward entry of variables. Examined factors for this model included all elements reported in **Table I**, along with antithrombotic type, dose, and duration. For patients who survived to hospital discharge and who did not undergo thrombectomy or receive thrombolytics, thrombus resolution over time was modeled in multiphase parametric hazard regression models that divide risk of outcomes in up to 3 distinct phases of risk.[8] Resolution rate by thrombus location was calculated. Given the low number of thrombus resolutions >1 year, the prevalence of

Table I. Patient characteristics at operations

	N	All patients
Patient characteristics		
Age at operation, y	203	0.2 (0.0-7.5)
<1 mo		83 (41%)
1 mo to 1 y		87 (43%)
1-10 y		23 (11%)
>10 y		10 (5%)
Weight at operation, kg	203	4.3 (2.4-22.0)
Oxygen saturation, %	128	82 ± 14
Extracorporeal support before or after surgery	203	48 (24%)
Postoperative hypercoagulable disorder	203	14 (7%)
Hemostatic tests at the time of surgery		
Hemoglobin, g/L	198	128 ± 23
Hematocrit	198	0.383 ± 0.074
Platelet, $\times 10^9$/L	196	252 ± 160
Internal normalized ratio	160	1.4 ± 0.4
Activated partial thromboplastin time test, s	158	40 (26-180)
Fibrinogen, g/L	123	1.89 ± 1.15
Primary operation	203	
BT shunt/Norwood/RV-PA conduit		35 (17%)
Cavopulmonary shunt/central shunt		24 (12%)
Septal defect repair		18 (9%)
TGA repair		18 (9%)
Heart transplantation		14 (7%)
Coarctation repair		13 (6%)
Valve replacement/repair		13 (6%)
Tetralogy of Fallot/DORV/pulmonary atresia		12 (6%)
Aortic arch repair		9 (4%)
Fontan operation		8 (4%)
Other		39 (19%)

BT, Blalock-Taussig; *DORV*, double outlet right ventricle; *RV-PA*, right ventricle to pulmonary artery; *TGA*, transposition of the great arteries.