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Risk, Clinical Features, and Outcomes of Thrombosis Associated With Pediatric Cardiac Surgery

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Background**—**Thrombosis, usually considered a serious but rare complication of pediatric cardiac surgery, has not been a major clinical and/or research focus in the past.

Methods and Results**—**We noted 444 thrombi (66% occlusive, 60% symptomatic) in 171 of 1542 surgeries (11%). Factors associated with increased odds of thrombosis were age <31 days (odds ratio [OR], 2.0; $P=0.002$), baseline oxygen saturation <85% (OR, 2.0; $P=0.001$), previous thrombosis (OR, 2.6; $P=0.001$), heart transplantation (OR, 4.1; $P<0.001$), use of deep hypothermic circulatory arrest (OR, 1.9 $P=0.01$), longer cumulative time with central lines (OR, 1.2 per 5-day equivalent; $P<0.001$), and postoperative use of extracorporeal support (OR, 5.2; $P<0.001$). Serious complications of thrombosis occurred with 64 of 444 thrombi (14%) in 47 of 171 patients (28%), and were associated with thrombus location (intrathoracic, 45%; extrathoracic arterial, 19%; extrathoracic venous, 8%; $P<0.001$), symptomatic thrombi (OR, 8.0; $P=0.02$), and partially/fully occluding thrombi (OR, 14.3; $P=0.001$); indwelling access line in vessel (versus no access line) was associated with lower risk of serious complications (OR, 0.4; $P=0.05$). Thrombosis was associated with longer intensive care unit (+10.0 days; $P<0.001$) and hospital stay (+15.2 days; $P<0.001$); higher odds of cardiac arrest (OR, 4.9; $P<0.001$), catheter reintervention (OR, 3.3; $P=0.002$), and reoperation (OR, 2.5; $P=0.003$); and increased mortality (OR, 5.1; $P<0.001$). Long-term outcome assessment was possible for 316 thrombi in 129 patients. Of those, 197 (62%) had resolved at the last follow-up. Factors associated with increased odds of thrombus resolution were location (intrathoracic, 75%; extrathoracic arterial, 89%; extrathoracic venous, 60%; $P<0.001$), nonocclusive thrombi (OR, 2.2; $P=0.01$), older age at surgery (OR, 1.2 per year; $P=0.04$), higher white blood cell count (OR, $1.1/10^9$ cells per 1 mL; $P=0.002$), and lower fibrinogen (OR, 1.4/g/L; $P=0.02$) after surgery.

Conclusions**—**Thrombosis affects a high proportion of children undergoing cardiac surgery and is associated with suboptimal outcomes. Increased awareness and effective prevention and detection strategies are needed. **(*Circulation*. 2011;124:1511-1519.)**

Key Words: heart defects, congenital ■ morbidity ■ pediatrics ■ surgery ■ thrombosis

Children with congenital heart disease often undergo several cardiac surgical procedures at a young age and are at risk for important morbidity and mortality. Data on thrombosis associated with cardiac surgery in pediatric patients are very limited. The prevailing opinion is that they are clinically important but somewhat rare occurrences, and thus have not been a major clinical and research focus in the past. Theoretically, pediatric patients undergoing cardiac surgery are an especially high-risk group for thrombosis. Pediatric cardiac surgery is associated with disruption of blood flow,

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platelet dysfunction and activation, inflammation, and blood hypercoagulability, all of which contribute to thrombus formation.[1,2] Factors further complicating the health of young patients include an immature coagulation system that exhibits a low capacity to inhibit clot formation and a high resistance to anticoagulation.[1–3] Finally, blood circulation for many types of congenital heart lesions is dependent on shunts that are prone to thrombotic and/or stenotic occlusions.[4,5]

Clinical Perspective on p 1519

The exact incidence of thrombosis in this context is currently not known, reflecting a lack of clinical suspicion, reporting biases, and/or the inappropriate/insufficient use of diagnostic tests. In a clinical research context, these patients are seldom considered as a separate group, and are often combined with other pediatric patients at high risk of thrombosis but with completely different types of disease and associated factors.[2,6] To date, most studies have used hospital discharge coding rather than focused review for the identification and quantification of thrombosis in pediatric patients, a method that is highly susceptible to both ascertainment bias and reporting bias.[7] We hypothesized that thrombosis in pediatric patients undergoing cardiac surgery is more common than previously reported and that, within this population, some subpopulations are at higher risk than others. In addition, we hypothesized that, in this context, children with thrombosis are at high risk of severe complications and have suboptimal outcomes compared with those without thrombosis.

Methods

Surgical Procedure Inclusions/Exclusions

This retrospective study included all pediatric patients (<18 years of age) with congenital heart disease who underwent cardiac surgery with or without the use of cardiopulmonary bypass between September 1, 2004, and December 31, 2007, at The Hospital for Sick Children, Toronto. Multiple discrete surgical procedures required as part of the primary management strategy were included. Early reoperations for surgical complications and delayed sternal closure were excluded. In the event of multiple procedures performed on an individual patient during the study time interval, all procedures were treated as independent entities, and the entire data collection process was repeated for each procedure. We excluded isolated closures of patent ductus arteriosus, placement or removal of an implantable cardioverter-defibrillator or pacemaker, implantation of a ventricular assist device, cannulation or decannulation for extracorporeal membrane oxygenation, and any noncardiac operation requiring the use of cardiopulmonary bypass. The study protocol was approved by The Hospital for Sick Children Research Ethics Board; the requirement for individual patient consent was waived for this study.

Surgical Characteristics

For every included surgery, we recorded from the medical record the patient's underlying cardiac anatomy (primary and secondary diagnoses), extracardiac anomalies, clinical medical history (including previous history of thrombosis), previous catheterizations, previous surgeries, and clinical status at diagnosis and immediately before the procedure. Specific details of the surgical procedure, including the use of central and peripheral lines (location, duration of use, and line size), blood transfusions (type and volume), laboratory investigations, postoperative diagnostic imaging, and detailed surgical outcomes, were also collected. Cardiac anatomy and cardiac surgeries were classified according to the International Nomenclature for Congenital Heart Surgery, and the Aristotle score was used to determine case complexity.[8,9] Standard postoperative thromboprophylaxis strategy in this population is to heparinize the arterial and central lines. Prophylaxis antithrombotic therapy is used postoperatively for high-risk patient populations such as those with an aortopulmonary shunt or mechanical valve.

Thrombosis Identification and Characteristics

All intrathoracic, extrathoracic venous, and extrathoracic arterial thrombi identified after the procedure before hospital discharge (or before any subsequent surgery if not discharged between the 2 procedures) were included. No systematic screening protocol for thrombosis was in place at that time; hence, all diagnostic imaging tests were ordered at the discretion of the attending physician. Only thrombi confirmed by ultrasonography, computed tomography, magnetic resonance imaging, echocardiography, angiography, or surgical or autopsy findings were considered. Thrombi found outside the vasculature, including those removed from the chest cavity, mouth, trachea, and chest drainage tubes, were excluded. Loss of indwelling access line functionality, regardless of whether it was related to the thrombosis or not, was excluded. Previously known thrombi (such as those associated with previous surgeries) or newly identified thrombi with a high degree of calcification (presumably older thrombi) were excluded.

Diagnostic imaging reports were reviewed for each thrombus to assess the exact location and degree of occlusion (subjective categorization of occlusion was applied as nonocclusive, partially occlusive, or fully occlusive). In rare cases in which a thrombus extended into multiple vessels, thrombus location was assigned on the basis of the responsible radiologist report and follow-up studies. Surgical and intensive care unit records were reviewed to determine whether thrombi were identified in a location used for placement of an indwelling access line. Finally, daily progress notes were reviewed to determine whether the patient showed classic symptoms of venous or arterial thrombosis. These included limb swelling, generalized red/purple limb discoloration, mottled darkening of the skin, limb pain for deep extremity veins, cold limb temperature, delayed capillary refill (>2 seconds), weak peripheral pulse (for peripheral arterial vessels only), abdominal swelling, hepatosplenomegaly and/or increased periumbilical collaterals (for portal/umbilical veins thrombosis only), poor cardiac function/arrhythmia (for intracardiac thrombi only), or neurological symptoms for either cardioembolic arterial ischemic strokes or sinovenous stroke immediately before or at thrombus diagnosis.

Serious Complications of Thrombosis

We defined serious complications of thrombosis as acute, clinically important events associated with a completely or partially obstructive thrombus that are potentially life threatening or that carry a high risk of long-term sequelae. These include cardioembolic arterial ischemic stroke, sinovenous stroke, pulmonary embolism, superior vena cava syndrome, thrombectomy (catheter or surgical), vessel obstruction treated with thrombolytics, and cardiopulmonary arrest or death associated with thrombosis. A combination of clinical observations, clot location, and timing of diagnoses was used to assign serious complications to specific thrombus. Use of anticoagulants and thrombolytics and mechanical thrombus removal (defined as catheter or surgical thrombectomy or removal/replacement of ventricular assist device or extracorporeal membrane oxygenation circuit because of thrombosis) were recorded. Clinical notes and autopsy reports were reviewed (when available) for all patients who had early reoperations, early recatheterization, or cardiac arrest or who died. The clinical assessment from the staff physician provided important information on whether thrombosis was a potentially contributing factor. Thrombotic events were considered causal and/or associated with death only if listed as such in the final autopsy report signed by the responsible pathologist. For patients who survived to hospital discharge and were followed up locally, outcomes of thrombosis (resolution or persistence) were assessed from follow-up investigations in the Thrombosis Clinic at the Hospital for Sick Children. All patients were followed up until confirmation of thrombus resolution or until their last follow-up (at least 2 years after surgery).

Statistical Analysis

Data are presented as means with SDs, medians with 5th and 95th percentiles, or frequencies as appropriate. Basic comparisons between patients with and without thrombosis were performed by use of Student *t* tests and Fisher exact tests. To identify factors associated with thrombosis, exploratory analyses were performed in univariable logistic regression models with thrombosis as the outcome and all other collected variables as potential associated factors. This allowed the removal of collinear variables, ill-conditioned variables, or variables with an unacceptable amount of missing data. All potential variables associated with the outcomes (univariable $P<0.30$ and excluding variables removed in exploratory analyses) were then included in a bootstrap-bagging algorithm (1000 random subsamples) for variable selection. Variables with high reliability (selected in >50% of the random subsamples) were then included in multivariable logistic regression models adjusted for repeated measures with a compound symmetry covariance structure and backward elimination of variables to obtain a final model. Factors associated with serious complications of thrombosis were sought in logistic regression models adjusted for repeated measures (unit of analysis, surgeries) through a compound symmetry covariance structure. Variable preselection was performed in univariable regression models, and variables with statistically significant associations were then included in a multivariable regression model with backward elimination of variables to obtain a final model. The same methodology was used to identify factors associated with thrombus resolution in patients who survived to hospital discharge and were followed up locally. For this model, thrombi that were removed mechanically were also excluded. Immediate postsurgical clinical outcomes of patients with thrombosis were compared with those of patients without thrombosis in multivariable log-linear (continuous outcome) and logistic (categorical outcome) regression models as appropriate. All of these regression models were adjusted for the patient's age at surgery, type and complexity of surgery, and postoperative use of extracorporeal membrane oxygenation/ventricular assist device (selected from ≈150 clinical and surgical characteristics in stepwise regression models). All statistical analyses were performed with SAS statistical software version 9.2 (SAS Institute Inc, Cary NC).

Results

Prevalence and Characteristics of Thrombosis

A total of 1542 surgeries in 1361 patients were included. Of those 1542 surgeries, 171 (in 155 patients, 11%) were associated with 444 thrombi (Table 1). Extrathoracic venous thrombosis was the most common (7.9%), followed by intrathoracic thrombosis (4.2%) and extrathoracic arterial thrombosis (2.7%); 3.4% of patients had thrombi in more than one of the above-listed categories. In extrathoracic veins, thrombi were evenly distributed between the upper and lower limbs, whereas in the extrathoracic arteries, thrombi were concentrated in the lower limbs. Intrathoracic thrombi were most often seen in the inferior or superior venae cavae, followed by the cardiac chambers and valves, pulmonary veins/arteries, and surgically created cardiac shunts (Table 1). Median time from surgery to detection of thrombosis was 11 days for extrathoracic venous thrombi, 7 days for extrathoracic arterial thrombi, and 16 days for intrathoracic thrombi, with 85% of thrombi diagnosed within 1 month of surgery. Indwelling access lines were present in 70 of the thrombosed vessels(16%), and the majority of thrombi were partially or fully occlusive (66%) and symptomatic (60%). Distribution of thrombi in selected high-risk subpopulations is presented in Table I in the online-only Data Supplement.

Table 1. Prevalence and Characteristics of Thrombosis in Pediatric Patients Undergoing Cardiac Surgery (n=1542)

	n (%)
Any thrombosis	171 (11)
Thrombosis in multiple locations*	53 (3.4)
Extrathoracic venous thrombosis	122 (7.9)
Cerebral venous sinus thrombosis	5 (0.3)
Internal/external jugular vein	62 (4.0)
Subclavian vein	17 (1.1)
Cephalic/brachiocephalic vein	39 (2.5)
Intra-abdominal veins (portal/renal/umbilical)	18 (1.2)
Iliac veins (common, internal, external)	44 (2.9)
Femoral vein	29 (1.9)
Other lower limb veins†	4 (0.3)
Extrathoracic arterial thrombosis	41 (2.7)
Cerebral arterial circle of Willis	9 (0.6)
Internal/external carotid artery	5 (0.3)
Iliac arteries (common, internal, external)	20 (1.3)
Femoral artery	14 (0.9)
Other arteries‡	7 (0.5)
Intrathoracic	65 (4.2)
Superior or inferior vena cava/intrathoracic veins	38 (2.5)
Cardiac chambers/valves	12 (0.8)
Pulmonary veins/pulmonary arteries	13 (0.8)
Aorta/descending aorta/intrathoracic arteries	5 (0.3)
Fetal shunt	4 (0.3)
Surgically created shunt	5 (0.3)
VAD circuit/ECMO circuit	4 (0.3)
Thrombi characteristics (n=444)	
Indwelling access line in vessel	70 (16)
Partially/fully occlusive clot (vs nonocclusive)	291 (66)
Symptomatic (vs asymptomatic)	265 (60)
Limb swelling	58 (13)
Generalized red/purple limb discoloration	31 (7.0)
Mottled darkening of skin	64 (14)
Limb pain	7 (1.6)
Cold extremity	40 (9.0)
Abdominal swelling	13 (2.9)
Delayed capillary refill/weak peripheral pulse	115 (26)
Low cardiac output/arrhythmia	53 (12)
Neurological symptoms	16 (3.6)

VAD indicates ventricular assist device; ECMO, extracorporeal membrane oxygenation.

*In 2 or 3 locations of intrathoracic, extrathoracic venous, or extrathoracic arterial.

†Popliteal (n=2), saphenous (n=1), and profunda femoris (n=1).

‡Subclavian (n=1), axillary/brachial (n=3), mesenteric (n=1), renal (n=1), and anterior tibial (n=1).

Patient and Surgical Characteristics Associated With Thrombosis

Patient characteristics stratified by presence or absence of thrombosis are reported in Table II in the online-only Data Supplement. Many patient and surgical characteristics were associated with increased odds of thrombosis, although many

Table 2. Factors Associated With Increased Odds of Thrombosis in Multivariable Logistic Regression Model Adjusted for Repeated Measures (n=1542)

Factor	Reliability, %	OR (95% CI)	*P*
Younger age at surgery	78		
0–31 d		2.0 (1.3–3.0)	0.002
>31 d–<1 y		Reference	
1–9 y		0.4 (0.2–0.7)	0.002
≥10 y		0.5 (0.2–1.0)	0.06
Oxygen saturation <85%	53	2.0 (1.3–3.1)	0.001
Previous thrombosis	89	2.6 (1.6–4.1)	0.001
Heart transplantation	67	4.1 (2.1–7.9)	<0.001
Use of deep hypothermic circulatory arrest	50	1.9 (1.2–3.0)	0.01
Longer cumulative time with central lines (/5 d)	87	1.2 (1.1–1.3)	<0.001
Postoperative use of VAD/ECMO	98	5.2 (2.8–9.6)	<0.001

OR indicates odds ratio; CI, confidence interval; VAD, ventricular assist device; and ECMO, extracorporeal membrane oxygenation.

of those potential risk factors were strongly correlated with each other. Multivariable risk factor analysis for thrombosis is reported in Table 2. Similar risk factors were identified if patients who underwent heart transplantation and/or postoperative extracorporeal membrane oxygenation/ventricular assist device were removed from the analysis. Previous cardiac surgery, preoperative hemostasis, and cardiac diagnosis were not associated with thrombosis. Increased surgical complexity and perioperative transfusions of red blood cells and platelets were associated with increased thrombosis risk but were also highly correlated with age at surgery.

Thrombosis Management and Serious Complications of Thrombosis

Thrombosis in this population was treated in 87% of patients, with 108 patients (63%) treated with low-molecular-weight heparin, 76 (44%) treated with unfractionated heparin, and 12 (7.0%) treated with warfarin. Thrombolytics were used for 9 patients (5.3%) with 19 obstructed vessels, and mechanical thrombus removal was performed in 25 patients (15%) with 28 obstructed vessels/intracardiac thrombi. Serious complications occurred with 64 thrombi (14%) (47 of 171 patients, 28%); details of the individual complications are provided in Table 3. Overall, 32 patients had 1 complication, 10 patients had 2 complications each, and 4 patients had 3 complications each. Multivariable factors associated with increased risk of serious complications are listed in Table 4. Patient and surgical characteristics, including patient age at surgery and hemostatic system activity, were not associated with risk of serious complications.

Association Between Thrombosis and Clinical Outcomes

In multivariable regression models, thrombosis was associated with increased length of intensive care unit and total hospital stay and increased odds of cardiac arrest, early catheter reintervention, early reoperation, and in-hospital mortality (Table 5).

Table 3. Serious Complications of Thrombosis

	All Thrombi (n=444), n (%)	Patients With Thrombosis Only (n=171), n (%)	All Surgeries (n=1542), n (%)
Any serious complications	64 (14)	47 (28)	47 (3.0)
Cardioembolic arterial ischemic stroke*	9 (2.0)	9 (5.3)	9 (0.6)
Sinovenous stroke†	5 (1.1)	3 (1.8)	3 (0.2)
Pulmonary embolism	5 (1.1)	5 (2.9)	5 (0.3)
Superior vena cava syndrome	7 (1.6)	6 (3.5)	6 (0.4)
Cardiopulmonary arrest associated with thrombosis	7 (1.6)	7 (4.1)	7 (0.5)
Vessel obstruction treated with thrombolytics	19 (4.3)	9 (5.3)	9 (0.6)
Thrombectomy/intervention (catheter/surgical)‡	24 (5.4)	21 (12)	21 (1.5)
Death associated with thrombosis§	10 (2.3)	9 (5.3)	9 (0.6)

Reported are the frequencies of serious complications for all thrombi, for patients with thrombosis only, and for all surgeries. Outcomes are not mutually exclusive.

*Three subcortical infarcts and 6 cortical infarcts: 3 secondary to occlusive thrombus in the middle cerebral artery, 1 secondary to occlusive thrombus in the carotid artery, and 5 without a specific cause identified.

†All secondary to occlusive thrombus in the transverse sinus.

‡Surgery: 5 surgical thrombectomies, 4 shunt revisions, 1 shunt takedown, and 3 vessel injury repairs. Catheter intervention: 4 thrombectomies, 3 stent placements (superior vena cava, Blalock-Taussig shunt, and pulmonary artery), 1 thrombectomy with stent placement (pulmonary artery).

§Three cardiopulmonary arrests secondary to shunt occlusion, 2 superior vena cava syndromes, 1 pulmonary embolism, 1 cerebral sinovenous stroke, and 2 multisystem organ failures complicated by liver embolism.

Long-Term Outcomes of Thrombosis

Of the original 171 patients, 33 patients (109 thrombi) did not survive to hospital discharge, and 9 patients (19 thrombi) were not followed up locally (the Figure). The remaining 129 patients (316 thrombi) were available for thrombus outcome assessment. Of those 316 thrombi, 20 (6%) were removed mechanically, 197 (62%) resolved, and 99 (32%) persisted at the last follow-up. Multivariable factors associated with thrombus resolution in patients who survived to hospital discharge and were followed up locally, excluding thrombi that were removed mechanically, are listed in Table 6. Other patient and or surgical characteristics, use of a hemostatic system activity before surgery, and any of the discharge medications were not associated with increased odds of thrombus resolution. As per the clinical protocol, only thrombi at the lowest risk of sequelae were left untreated. Thus, any estimate of treatment effect is strongly biased toward high-risk cases, and unbiased treatment effect estimates cannot be calculated. Treatment with unfractionated heparin was not associated with increased odds of thrombus resolution.

Table 4. Factors Associated With Increased Odds of Serious Complications in Multivariable Logistic Regression Model Adjusted for Repeated Measures (n=444)

Variable	Thrombi With Serious Complications, %*	OR (95% CI)	*P*
Location of thrombosis			<0.001
Extrathoracic venous thrombosis	7.9	Reference	
Extrathoracic arterial thrombosis	19	2.4 (0.7–7.8)	
Intrathoracic thrombosis†	45	9.2 (3.9–22.0)	
Symptomatic (vs asymptomatic)	22	8.0 (1.4–47.7)	0.02
Partially/fully occlusive thrombus (vs nonocclusive)	21	14.3 (3.2–63.0)	0.001
Indwelling access line in vessel (vs no access line)	8.6	0.4 (0.2–1.0)	0.05

OR indicates odds ratio; CI, confidence interval.

*Overall serious complications frequency is 64 of 444, 14%.

†Intrathoracic vs extrathoracic arterial thrombosis (OR, 3.9; 95% CI, 1.3–11.5; *P*=0.02).

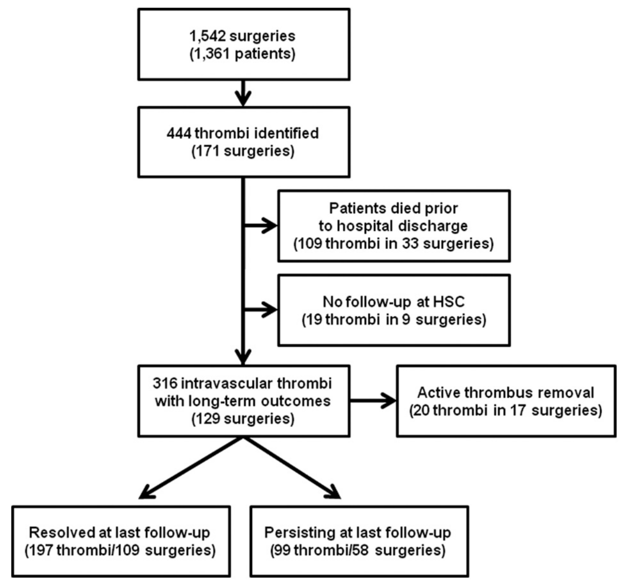

Figure. Thrombosis prevalence and outcomes. HSC indicates Hospital for Sick Children.

Discussion

This study is unique in that it considers pediatric patients who recently underwent cardiac surgery as a unique group with regard to thrombosis rather than amalgamating them with all pediatric patients with thrombosis as most previous studies have done.[2,6] The incidence of thrombosis in this specific population was found to be much higher than previously reported.[10–12] These complications were associated with significant morbidity and suboptimal clinical outcomes. It is clear that the topic of thrombosis in the context of pediatric cardiac surgery needs to be a major focus of clinical management and research efforts.

Incidence of Thrombosis

Pediatric patients undergoing cardiac surgery are at an increased risk of developing thrombosis compared with other hospitalized children. In a recent study, the incidence of venous thrombosis reported from hospital discharge summaries (all admissions regardless of cause) was found to have increased from 34 to 58 events per 10 000 pediatric admissions between 2002 and 2007,[10] which is much lower than the 7.9% incidence of venous thrombosis found in this population. Our estimate of 11% total incidence of thrombosis is most likely to be an underestimation because there were no protocols for systematic detection of thrombosis during the study period. Therefore, only clinically evident complications were identified.[13] Determining the exact incidence of thrombosis in this context through systematic screening of at-risk vascular systems should be an important future research focus in this population.

Factors Associated With Thrombosis

Cardiopulmonary bypass presents a hemostatic challenge associated with an abundance of prothrombotic risk factors.[14] Exposure of blood components to a large synthetic surface causes disturbances in platelet function, coagulation factors, fibrinolytic system, and physiological inhibitors of coagulation.[15] This ultimately leads to platelet activation, which is also exaggerated by the use of deep hypothermic circulatory arrest.[16] Activated platelets provide important procoagulant activity by expressing binding sites for specific coagulation

Table 5. Postoperative Clinical Outcomes Stratified by Thrombosis Occurrence

	No Thrombosis (n=1371)	Thrombosis (n=171)	*P*	Estimate (95% CI)*	OR (95% CI)*	*P*
Total intensive care unit stay, d	3 (1–17)	11 (2–86)	<0.001	+10.0 (9.4–10.7)		<0.001
Total hospital stay, d	7 (3–43)	25 (7–159)	<0.001	+15.2 (14.3–16.0)		<0.001
Cardiac arrest, n (%)	24 (1.8)	30 (18)	<0.001		4.9 (2.3–10.2)	<0.001
Early catheter reintervention, n (%)	34 (2.5)	21 (12)	<0.001		3.3 (1.6–6.9)	0.002
Early reoperation, n (%)	52 (3.8)	26 (15)	<0.001		2.5 (1.4–4.4)	0.003
In-hospital mortality, n (%)	23 (1.7)	27 (16)	<0.001		5.1 (2.3–11.3)	<0.001

CI indicates confidence interval; OR, odds ratio.

*All models adjusted for age at surgery, stage 1 single-ventricle palliation, heart transplantation, oxygen saturation <85%, Aristotle score, total cardiopulmonary bypass time, use of deep hypothermic circulatory arrest, and use of ventricular assist device/extracorporeal membrane oxygenation.

Table 6. Factors Associated With Increased Odds of Thrombus Resolution at the Last Follow-Up in Patients Who Survived to Hospital Discharge, Who Were Followed Up Locally, and Whose Thrombus Was Not Removed Mechanically: Multivariable Logistic Regression Model Adjusted for Repeated Measures (n=296)

Variable	Percent of Thrombi Resolved at Last Follow-up*	Intrathoracic vs Extrathoracic Arterial Thrombosis†	OR (95% CI)	*P*
Location of thrombosis				<0.001
Extrathoracic venous thrombosis	59.9%			Reference
Extrathoracic arterial thrombosis	89.4%		6.4 (2.3–17.3)	
Intrathoracic thrombosis‡	75.0%		1.9 (0.7–4.8)	
Nonocclusive thrombus (vs partially/fully occlusive)	73.8%		2.2 (1.2–4.1)	0.01
Older age at surgery, y		+0.3 y	1.2 (1.0–1.4)	0.04
Higher white blood cell count in postoperative period, cells/L		$+1.3\times10^9$	1.1 (1.0–1.1)	0.002
Lower fibrinogen in postoperative period, g/L		−0.4	1.4 (1.1–2.0)	0.02

CI indicates confidence interval; OR, odds ratio.
*Overall resolution frequency is 197 of 296 (66.5%).
†Difference in variables means between resolved and persisting thrombi.
‡Intrathoracic vs extrathoracic arterial thrombosis (OR, 0.3; 95% CI, 0.1–1.1; *P*=0.06).

proteins. The activation period tends to be longer and its intensity more pronounced in children with cyanotic congenital heart disease than in healthy infants.[17] Along with direct activation of the coagulation cascade, cardiopulmonary bypass triggers a global inflammatory response in a positive feedback mechanism, leading to further activation of the coagulation system and other systemic manifestations.[14,18–21] Neonates already have low levels of antithrombin, protein S and protein C activity (typically between 20% and 60% of adult levels), contact factors (XI, XII, PK, HMWK), and vitamin K-dependent factors (II, VII, IX, X) (all <70% of adult values).[3] Many of these differences are associated with lower capacity to inhibit thrombin generation, increased heparin clearance,[22] and decreased sensitivity to anticoagulants,[23] particularly to standard heparin, the most commonly used agent during and after surgery. The initiation of cardiopulmonary bypass can result in a further 50% decrease in circulating coagulation factors and antithrombin levels, in addition to a 70% drop in platelet counts.[24] In addition to the newly acquired hypercoagulable state and functional resistance to anticoagulation, physical factors increase the risk of thrombosis in this population. The presence of an indwelling access line is generally considered one of the most important risk factors for thrombosis in pediatric patients, and ≈20% of patients with an indwelling access line will develop a related thrombus.[2] Line-related thrombi are the most common source of pulmonary embolism[25] and arterial thrombosis in children.[26] Turbulent blood flow and areas of flow stasis are well documented in many patients with congenital heart disease. Blood flow disturbances are due to many mechanisms, including hypoplastic ventricles with limited inflow/outflow, dilated atria, and the presence of sutures, shunts, and thrombogenic artificial material, creating an environment conducive to thrombus formation.

Serious Complications of Thrombosis and Surgical Outcomes

Patients with established thrombosis are at risk of severe complications, including pulmonary embolism, strokes, hemorrhage, cardiac failure, and even death.[2,6] A review by Henke et al found that the length of hospital stay for cardiac surgical adult patients with thrombosis increased by 68% to 126%.[26a] Venous thrombosis in children after cardiopulmonary bypass is associated with a mortality of ≈7% to 9%.[7,27] Mortality after pulmonary embolism is as high as 20%.[28] In a study of 98 pediatric patients, Monagle et al[29] demonstrated that direct arterial thrombosis-related mortality was 4% in infants and 9% in children in a study of 98 pediatric patients. Outcomes of arterial strokes and cerebral sinovenous thrombosis are poor, with high mortality, and up to two thirds of patients have resulting permanent neurological damage.[30] Occurrence of thrombosis after pediatric cardiac surgery has also been linked to a 3.4-fold increase in mortality.[31,32]

Most of the literature on pediatric thrombosis has focused on specific embolic sequelae, including incidence in the global pediatric population, risk factors, and outcomes.[6,28–30,33] Few studies have focused on thrombosis as the denominator, explored the extent of resulting complications, or focused on the cardiac population, despite their distinctive risk profile. In this series, each type of complications affected a small number of patients. When taken in isolation, they may seem like clinically important but rare complications; as a group, however, they represent a much more prevalent problem. We identified arterial, particularly cardiac, thromboses as factors associated with severe complications. Cerebral arterial thrombosis carries a high risk of cardioembolic stroke, but noncerebral arterial thrombosis also carries substantial risk of ischemic injury.[29] Occlusive and symptomatic thrombi were at higher risk of complications. Finally, thromboses found in vessels where there had been indwelling access lines were at lower risk of complications, which might reflect their localization in peripheral vessels farther from central blood circulation. Our study confirms that thrombosis is indeed associated with suboptimal postoperative outcomes. Questions remain as to whether this association is coincidental, because sicker patients could be at higher risk of thrombosis. Although this very well may be the case, we found that a portion of the morbidity and mortality in this study population was likely attributable to thrombosis; therefore, we do think that thrombosis has an effect on surgical outcomes, even if thrombosis is not completely responsible for the observed difference between groups.

Resolution/Persistence of Thrombosis

A previous study of the natural history of thrombosis in pediatric patients treated with low-molecular-weight heparin found a frequency of thrombus resolution of 53% (95% confidence interval, 46–60),[34] which is similar to that reported in adult studies.[35–38] Arterial thrombi have previously been reported as more likely to resolve in these patients, but the reason for this observation remains unclear. It is likely to be related to higher shear forces present within the arterial vascular tree. Furthermore, there are intrinsic differences in the formation and composition of arterial and venous thrombi. Arterial thrombi are platelet rich with little fibrin, whereas venous thrombi are fibrin rich, with few platelets.[39] Nonocclusive thrombi have also been reported to be more likely to resolve over time,[34] which may be due to the greater exposure of nonocclusive thrombi to the fibrinolytic system.[35,37] Previous studies have not reported age at diagnosis, fibrinogen, or white blood cell count in the postoperative period as factors associated with increased odds of clot resolution. Age at diagnosis may be a factor unique to children with congenital heart disease. Pediatric patients undergoing cardiac surgery include a high proportion of neonates compared with other pediatric groups at risk of thrombosis such as patients with cancer and autoimmune disease. Neonates have developmental immaturity of their coagulation and fibrinolytic system,[3] including lower sensitivity to anticoagulation and decreased fibrinolytic system activity.[1,24] Fibrinogen levels and white blood cell count in the postoperative period are important observations that may reflect the level of activity of the overall fibrinolytic system and should be investigated further as factors associated with requirement for higher anticoagulation doses. For patients with persistent thrombi, long-term complications are frequent and manifest as postthrombotic syndrome.[40,41] Postthrombotic syndrome is still a poorly described and characterized entity in children, and was not part of the patients' follow-up during the study period. Therefore, we could not retrospectively estimate the proportion of patients with residual obstructions who eventually developed postthrombotic syndrome in this cohort.

Limitations

This study is limited by its retrospective nature. Data were limited to the information available in the hospital records, which may be incomplete. Our estimate of an 11% incidence of thrombosis in this population is likely an underestimation, and identified risk factors are more likely to be applicable to symptomatic thrombosis, with undefined relevance to asymptomatic thrombosis. In addition, we cannot be certain that we did not count previous asymptomatic thrombi that went undetected at the time but were identified after the surgery as incident thrombi (previously detected thrombi were not counted as incident cases). However, we believe that the former situation is far more prevalent than the latter and that overall our estimate of thrombosis incidence is an underestimation. Because of the lack of systematic screening protocols in this population, mainly clinically evident thromboses were identified. This reinforces the need for prospective studies with systematic detection protocols for thrombosis. Additionally, our estimate of risk of serious complications is likely an overestimation; the risk would certainly decrease if currently undetected, asymptomatic thrombi were included in the denominator, and ascertainment in this cohort is likely biased toward more complex cases. Finally, although we report the association between thrombosis and morbidity/mortality, it is difficult to determine with certainty how much thrombosis actually contributed to those outcomes. There are substantially more opportunities to identify thromboses in patients having a complicated postoperative course owing to the ongoing need for access or obtainment of ultrasounds in a variety of clinical situations. Furthermore, it might be that being sicker itself predisposes to thrombosis, and that the occurrence and diagnosis of thrombus are time-dependent phenomena. It is therefore possible that the association between surgical outcomes and thrombosis is coincidental rather than contributory.

Conclusions

Thrombosis associated with pediatric cardiac surgery was found in a significant proportion of patients, carrying clinically important risks. Thrombosis in this population was shown to be associated with an important increase in morbidity and suboptimal postoperative outcomes. We have identified clinical and operative risk factors for thrombosis in this population, and future research is necessary to determine the mechanisms by which these factors are associated with thrombosis by focusing on pathways of coagulation and platelet activation that are stimulated in response to those risk factors. Both thrombus and patient characteristics were associated with increased odds of serious complications and thrombus resolution. This study establishes thrombosis in the context of pediatric cardiac surgery as an important clinical problem and will, we hope, form the basis of further research aimed at better prevention, diagnosis, and treatment of those complications.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Thrombosis in the context of pediatric cardiac surgery is usually considered a clinically important but somewhat rare complication. Thus, awareness has been limited, likely resulting in a failure to identify this potentially important clinical problem, reporting biases, inappropriate/insufficient use of diagnostic tests, and a lack of prospective clinical studies. This topic has not been a major research focus in the past. In a review of 1542 pediatric cardiac surgeries, we found that 171 (11%) were associated with incident thrombosis, with multiple subpopulations at substantially higher risk. There were no systematic detection protocols in place during the study period; thus, it is very likely that our estimated thrombosis prevalence of 11% is an underestimation and that this is a much more prevalent problem than reported here. Thrombosis was associated with a high degree of serious complications (28%), with increased morbidity and worse postoperative clinical outcomes compared with surgeries without thrombosis. Both thrombus and patients' characteristics were associated with increased odds of serious complications and thrombus resolution, and these factors could be used for future risk stratification. Further research is necessary to determine the mechanisms by which the identified factors are associated with thrombosis and its outcomes by focusing on pathways of coagulation and platelet activation. This study establishes thrombosis in the context of pediatric cardiac surgery as an important clinical problem and will, we hope, form the basis of further research aimed at better prevention, detection, and treatment of those complications.

Supplemental Table 1: Burden of thrombosis in high-risk subpopulations

	Norwood/ RV-PA (N=104)	***Heart Transplant (N=58)***	***ECMO /VAD (N=94)***
Any thrombosis	*20 (19%)*	19 (33%)	42 (45%)
Extra-thoracic venous thrombosis	*15 (14%)*	*14 (24%)*	*29 (31%)*
Cerebral venous sinus thrombosis	1 (1.0%)	0 (0.0%)	1 (1.1%)
Internal/external jugular vein	7 (6.7%)	12 (21%)	21 (22%)
Subclavian vein	2 (1.9%)	3 (5.2%)	8 (8.5%)
Cephalic/brachiocephalic vein	5 (4.8%)	6 (10%)	11 (12%)
Lower abdominal veins (portal/renal/umbilical)	3 (2.9%)	2 (3.4%)	4 (4.3%)
Iliac veins (common, internal, external)	4 (3.8%)	7 (12%)	8 (8.5%)
Femoral vein	3 (2.9%)	4 (6.9%)	5 (5.3%)
Other lower limbs veins	1 (1.0%)	0 (0.0%)	1 (1.1%)
Extra-thoracic arterial thrombosis	*7 (6.7%)*	*7 (12%)*	*11 (12%)*
Cerebral arterial circle	1 (1.0%)	2 (3.4%)	3 (3.2%)
Internal/external carotid artery	1 (1.0%)	2 (3.4%)	4 (4.3%)
Iliac artery (common, internal, external)	3 (2.9%)	3 (5.2%)	3 (3.2%)
Femoral artery	2 (1.9%)	2 (3.4%)	2 (2.1%)
Other arteries	2 (1.9%)	0 (0.0%)	0 (0.0%)
Intrathoracic thrombosis	*7 (6.7%)*	*6 (10%)*	*17 (18%)*
Superior or inferior vena cava/intrathoracic veins	4 (3.8%)	3 (5.2%)	6 (6.4%)
Heart	2 (1.9%)	3 (5.1%)	6 (6.4%)
Pulmonary veins/pulmonary arteries/lungs	1 (1.0%)	2 (3.4%)	5 (5.3%)
Aorta/descending aorta/intrathoracic arteries	3 (2.9%)	0 (0.0%)	0 (0.0%)
Extra-anatomic shunts	2 (1.9%)	0 (0.0%)	4 (4.3%)
VAD circuit/ECMO circuit	1 (1.0%)	1 (1.7%)	4 (4.3%)

Supplemental Table 2: Patient and surgical characteristics by presence/absence of thrombosis

	No Thrombosis (N=1,371)	***Thrombosis (N=171)***	***p***
Patients characteristics			
Gender (male)	768 (56%)	96 (56 %)	1.00
Age at surgery (years)	0.60 (0.02-14.2)	0.15 (0.01-11.5)	<0.001
Age at surgery			
0-31 days	291 (21%)	75 (44%)	<0.001
>31 days – <1 year	539 (39%)	70 (41%)	0.68
1 year - 9 years	402 (29%)	16 (9.4%)	<0.001
≥10 years	149 (11%)	11 (5.8%)	0.05
Premature birth (<37 weeks)	152 (11%)	31 (18%)	0.01
Chromosome abnormalities	283 (21%)	26 (15%)	0.16
Previous clinical history			
Previous catheterization			0.40
None	1034 (75%)	123 (72%)	
1	261 (19%)	35 (21%)	
2+	76 (5.5%)	13 (7.6%)	
Previous surgery			0.90
None	987 (72%)	123 (72%)	
1	251 (19%)	30 (18%)	
2+	133 (9.7%)	18 (11%)	
Previous thrombosis	157 (12%)	49 (29%)	<0.001
Preoperative coagulopathy (acquired or congenital)	57 (4.2%)	15 (8.8%)	0.01
Preoperative VAD/ECMO	26 (1.9%)	13 (7.3%)	<0.001
Preoperative antiplatelet therapy	64 (4.7%)	6 (3.5%)	1.00
Preoperative heparin/enoxaparin	107 (7.8%)	35 (21%)	<0.001
Preoperative warfarin	18 (1.3%)	4 (2.5%)	0.30
Preoperative prostaglandins	181 (13%)	49 (29%)	<0.001
Preoperative laboratory			
Hematocrit	0.403±0.067	0.409±0.072	0.31
Hemoglobin (mg/L)	149±59	146±53	0.91
International normalized ratio (INR)	1.3±0.3	1.3±0.4	0.27
Platelet count ($x10^9$/L)	320±138	315±133	0.69
Red blood cells ($x10^{12}$/L)	4.6±0.8	4.5±1.0	0.55
White blood cells ($x10^9$/L)	10.6±4.9	11.2±5.1	0.45
Surgery type			
Septal defect repair	361 (26%)	21 (12%)	<0.001
TAPVD repair	19 (1.4%)	11 (6.4%)	<0.001
Pulmonary vein/artery repair other than TAPVD	55 (4.0%)	5 (2.9%)	0.68
Aortic /mitral valve/LV outflow tract repair	130 (9.4%)	3 (1.8%)	<0.001
Pulmonary/tricuspid valve repair/replacement	30 (2.2%)	4 (2.3%)	1.00
Pulmonary atresia with ventricular septal defect repair	30 (2.2%)	4 (2.3%)	1.00
Tetralogy of Fallot repair	120 (8.7%)	5 (2.9%)	0.02
Transposition of the great arteries repair	120 (8.8%)	15 (8.8%)	1.00
Aortic arch repair excluding coarctation of the aorta repair	48 (3.5%)	12 (7.0%)	0.03
Coarctation of the aorta repair	87 (6.3%)	13 (7.6%)	0.51
Coronary artery repair/bypass/vascular rings	27 (2.0%)	1 (0.6%)	0.36
Blalock-Tausig shunts/central shunt/pulmonary artery banding	72 (5.3%)	17 (9.9%)	0.02
Norwood/Right ventricle-pulmonary artery conduits	84 (6.1%)	20 (12%)	0.009
Cavopulmonary shunt	81 (5.9%)	12 (7.0%)	0.39
Fontan	68 (5.0%)	9 (5.3%)	0.58
Heart transplantation	39 (2.8%)	19 (11%)	<0.001

	No Thrombosis (N=1,371)	Thrombosis (N=171)	p
Details of surgical procedures			
Oxygen saturation (%)	91±12	83±13	<0.001
Cyanosis (oxygen saturation <85%)	243 (18%)	70 (41 %)	<0.001
Aristotle score	7.7±2.3	8.9±2.6	<0.001
Aristotle score class			
Class I	126 (9.2%)	4 (2.3%)	0.001
Class II	539 (39%)	61 (36%)	0.41
Class III	498 (36%)	61 (36%)	1.00
Class IV	208 (15%)	45 (26%)	0.001
Use of cardiopulmonary bypass	1204 (88%)	139 (81%)	0.02
Multiple cardiopulmonary bypass cycles*	268 (20%)	63 (37%)	<0.001
Total cardiopulmonary bypass time (minutes)*	106±56	124±57	<0.001
Use of cross-clamp	1175 (86%)	140 (82%)	0.21
Multiple cross-clamp cycles	83 (6.1%)	11 (6.4%)	0.87
Total cross-clamp time (minutes)	75±53	107±82	<0.001
Use of deep hypothermic circulatory arrest	122 (8.9%)	49 (29%)	<0.001
Use of low flow cerebral perfusion	43 (3.1%)	14 (8.2%)	0.004
Heparin dose (U/Kg/hour cardiopulmonary bypass)*	403±175	442±194	0.03
Perioperative steroid use	236 (17%)	70 (41%)	<0.001
Antifibrinolytic use			
None	309 (23%)	46 (27%)	0.21
Tranexamic acid	740 (54%)	62 (36%)	<0.001
Aprotinin	323 (24%)	63 (37%)	<0.001
Perioperative use of antithrombin supplement	14 (1.0%)	10 (5.8%)	<0.001
Perioperative use of recombinant factor VIIa	27 (2.0%)	11 (6.4%)	0.002
Chest closure in the operating room	1247 (91%)	129 (75%)	<0.001
Postoperative VAD/ECMO	36 (2.6%)	33 (19%)	<0.001
Bleeding complications	89 (6.5%)	34 (20%)	<0.001
Central and arterial lines			
Total number of central lines	2 (2-3)	3 (2-6)	<0.001
Cumulative time with central lines (days equivalent)	5 (1-29)	24 (4-122)	<0.001
Maximum line size (mm)	1.5±0.3	1.5±0.4	0.92
Line placement in jugular vein (n=595)	460 (88%)	45 (65%)	<0.001
Line placement in femoral vein (n=595)	44 (8.4%)	23 (33%)	<0.001
Line placement in subclavian vein (n=595)	32 (6.1%)	15 (22%)	<0.001
Line placement in radial artery (n=595)	366 (70%)	42 (61%)	0.52
Line placement in femoral artery (n=595)	119 (23%)	21 (30%)	0.03
Perioperative blood transfusions			
Patient given any albumin	1297 (95%)	158 (92%)	0.22
Patient given any fresh frozen plasma	1060 (77%)	145 (85%)	0.02
Fresh frozen plasma (ml/kg)	44.7 (7.1-169.0)	90.2 (24.6-259.2)	<0.001
Patient given any platelets	867 (63%)	98 (57%)	0.18
Platelets (ml/kg)	12.3 (2.2-44.6)	21.3 (7.5-61.2)	<0.001
Platelets (exposures)	2 (0-5)	2 (0-6)	0.21
Patient given any red blood cells	1035 (76%)	157 (92%)	<0.001
Red blood cells (ml/kg)	99.4 (13.3-304.4)	169.1 (34.3-427.0)	<0.001
Red blood cells (exposures)	2 (0-5)	3 (0-7)	<0.001
Patient given any cryoprecipitate	541 (40%)	90 (48%)	0.04
Post-operative blood transfusions (post-operative day 1)			
Platelets	65 (4.7%)	26 (15%)	<0.001
Red blood cells	395 (29%)	90 (53%)	<0.001

	No Thrombosis (N=1,371)	Thrombosis (N=171)	p
Post-operative laboratory (average for 7 days following surgery)			
Hematocrit [N=111]	0.36±0.06	0.37±0.05	0.30
Hemoglobin (mg/L) [N=115]	128±35	131+44	0.79
Platelets count ($x10^9$ cells/L) [N=116]	194±105	207±104	0.14
Red blood cell ($x10^{12}$ cells/L) [N=107]	4.3±0.6	4.1±0.6	0.14
White blood cell ($x10^9$ cells/L) [N=105]	11.9±5.1	12.6±5.3	0.91
Fibrinogen (g/L) [N=114]	2.9±1.4	2.7±1.3	0.67
International normalized ratio (INR) [N=67]	1.4±0.5	1.4±-0.4	0.32

* patients on cardiopulmonary bypass only

Total anomalous pulmonary venous drainage, TAPVD; Ventricular assist device, VAD; Extracorporeal membrane oxygenation, ECMO