The use of anticoagulation in pediatric cardiac disease

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Abstract
Palliation and repair of increasingly complex congenital heart defects as well as the emergence of novel contexts has led to multiple scenarios in which a real or potential risk of thromboembolism may exist. While various anticoagulation methodologies have been well defined for adults, there are few studies relating directly to pediatric patients. This article reviews a number of specific pediatric disease states, the representative pediatric literature, and, where appropriate, the corresponding adult literature. In so doing, the art and science of pediatric cardiac anticoagulation is defined with the hope to engender further thought regarding future directions of study and therapy.

MeSH: heart defects, congenital, warfarin, heparin, aspirin, thromboembolism, shunt

Introduction
As medical and surgical care for patients with congenital heart disease progresses, an increasing number of immediate and long-term complications have been recognized. One important complication is the development of thrombus arising within the chambers, on the valves, or in the walls of the heart, or on implanted devices and prosthetic material placed in the heart or its downstream arteries or upstream veins. These clots can cause local complications, such as their mass effect obstructing flow through chambers or vessels, or impairing valve function. They can also lead to embolic events, such as coronary artery obstruction with myocardial infarction, cerebrovascular accident, or mesenteric artery obstruction. (Figure 1)

Figure 1 Large pedunculated thrombus in the left atrium as well as thrombus across the foramen ovale and into the right atrium, presumably from placement of an umbilical venous catheter across the foramen ovale. The left-sided portion of the thrombus subsequently embolized to the descending aorta, resulting in the patient's demise.

Much of what is known regarding cardiac thrombotic phenomena derives from adult studies. In fact, many of the recommendations that pediatric cardiologists use are either empirically derived and then passed on by tradition or based on adult data, with little or no supporting evidence from pediatric studies. Some of these prevention and treatment plans are probably reasonable, as there is fairly good correlation
between certain adult and pediatric pathophysiologic states. Furthermore, a number
of these studies may never be done, as the patient population is small and the risk-
benefit ratio is unclear. Yet, various pathophysiologic and anatomic states are
germane to pediatric and adolescent patients. Specifically those patients with
complex congenital heart defects (e.g. the Glenn and Fontan physiology and the
Blalock-Taussig shunt) that have undergone palliative operations, which place them
at high risk for thromboembolism. These require long-term study. Further
complicating matters are the changes in the normal levels of prothrombotic and
antithrombotic proteins with age. This article will review the topic of anticoagulation in
various pediatric cardiac intervention and disease states where both art and science
simultaneously operate. The aim here is to provide the practitioner with general
guidelines as well as define areas in which several legitimate methods exist.
Anticoagulation of prosthetic valves will not be discussed here, as this can be
considered a fundamentally unique indication with its own extensive body of literature
in which there is overall consensus on the approach to anticoagulation without
significant distinctions drawn between pediatric and adult patients.

**Principles and agents of anticoagulation**

Advances in pediatric cardiac intervention have demanded broader expertise in
applying principles of anticoagulation to a new and diverse set of indications. Initially,
much of the understanding and principles of use for coagulation inhibiting agents that
are used in children was derived from adult data; in fact, this still continues for newer
medications. Only recently has a greater understanding of the age-related
differences in the hemostasis pathway led both to more effective use of these agents
as well as furthering pediatric trials to better define the guidelines for use, monitoring
efficacy, and management of complications.1,2 The use of anticoagulation agents in
other, non-cardiac disease states, such as in thromboembolism and cancer, has
benefited therapeutic regimen design for cardiac-specific uses, as well. The result is
a growing knowledge base upon which further studies lead to frequent updates in
guidelines for use.1

The most frequently used anticoagulation agents are unfractionated heparin and
warfarin (other warfarin-like derivatives include phenprocoumon, which has a much
longer half-life, and acenocoumarol, which has a shorter half-life and increased
bleeding complications). Typically, heparin is used for either short-term
anticoagulation use, due to its relatively short half-life, or for initiation of long-term
anticoagulation therapy in preparation for conversion to warfarin. Heparin is a
mucopolysaccharide that functions as a catalyst in the activation of antithrombin III.
Antithrombin III activation causes subsequent inactivation of thrombin, plasmin, and
factors IX, X, XI, and XII, resulting in impaired coagulation. Typical anticoagulation
regimens include a loading dose of 75 to 100 units/kg followed by a maintenance
dose of 28 units/kg/hour for children under age 1 year and 20 units/kg/hour for
children over age 1 (based on decreased normal infant antithrombin levels).1 The
dose in older children, 18 units/kg/hour, is similar to that in adults. Doses of 50
units/kg given as a bolus, which have been employed in studies and are widely
accepted, were found to be inadequate in establishing appropriate initial
anticoagulation.3 Monitoring of therapeutic efficacy has centered on the use of the
activated partial thromboplastin time, although this method has been difficult to
standardize. Other monitoring methods include achieving heparin concentrations at a
level of 0.2 to 0.4 units/ml by titration with protamine, or anti-factor Xa levels of 0.35
to 0.70 units/ml. However, this has been deemed to be accurate only approximately
70% of the time in children.3 Therefore, when converting to an oral anticoagulant
agent either immediately or after prolonged heparin therapy, it is recommended that
two separate therapeutic measurements of the international normalized ratio (INR)
be obtained before stopping heparin.4 Alternatively, for brief use, such as during
arterial access in the cardiac catheterization laboratory, monitoring with the activated clotting time (ACT) to obtain levels of approximately 200 seconds (double the normal time) can be performed quickly and accurately.5

Low-molecular weight heparin (LMWH) is gaining popularity as a safer and more efficacious alternative than unfractionated heparin for several reasons. Its half-life is longer than that of unfractionated heparin. It can be given subcutaneously without the need for intravenous access. It has a stable, reproducible anticoagulant effect. It has a lower incidence of heparin-associated side effects, including thrombocytopenia and osteoporosis. Dosing of enoxaparin or reviparin depends on whether the patient is younger or older than 2 months of age. For enoxaparin, the initial dose for children less than 2 months is 1.5 mg/kg subcutaneously; children over 2 months receive 1.0 mg/kg every 12 hours. For reviparin, initial dosing for children greater than 2 months is 100 units/kg subcutaneously every 12 hours; children less than 2 months old require 150 units/kg every 12 hours. To achieve maintenance, anti-factor Xa levels are followed with adjustment to keep levels from 0.5 to 1.0 units/ml.

Warfarin, acenocoumarol, and phenprocoumon are all similar oral anticoagulant medications that block the formation in the liver of the vitamin K-dependent clotting factors II, VII, IX, and X. There are age-related adjustments for the use of these agents, as infant vitamin K-dependent clotting factors are 50% of adult levels, and childhood amounts are 80% of adult levels through adolescence. Due to the significantly shorter half-life of acenocoumarol and the longer half-life of phenprocoumon, the medical literature suggests that warfarin is the agent of choice.6,7 Typical loading doses for children are 0.2 mg/kg; these are then followed by dose adjustments based on the international normalized ratio (INR) values of prothrombin times. These dose adjustments relate to the original loading dose, and are dependent upon the target INR range. INR is usually kept between 2.0 and 3.0 for treatment of thromboembolism, and between 2.5 and 3.5 for prophylaxis of thrombosis in patients with congenital heart valves. However, so-called “low-dose therapy,” which keeps the INR between 1.4 and 1.9, has also been studied in children who either have a new thrombus in the setting of a history of recurrent thrombus, or have an older thrombus. Higher dose therapy to keep the INR between 3.0 and 4.5 has been suggested to be efficacious specifically for patients who have recurrent thromboembolism despite appropriate INR measurements between 2.0 and 3.0, or for patients with certain hypercoagulable states, such as protein S or protein C deficiency.8

Aspirin functions specifically as a platelet-inhibiting agent, causing its effects by irreversibly binding to cyclooxygenase. This prevents the eventual formation of thromboxane A2, thus decreasing platelet aggregation. This effect lasts until new platelets with unbound cyclooxygenase are produced and released, which requires seven to ten days after aspirin therapy has ceased. Typical doses that have been used range from 1 to 10 mg/kg/day, although there is little actual data supporting specific pediatric doses of aspirin for platelet inhibition. Most commonly, doses of 3 to 5 mg/kg/day are quoted as “platelet-inhibiting” or “antiplatelet therapy.”9

Dipyridamole, another antiplatelet agent, inhibits phosphodiesterase and increases cyclic adenosine monophosphate, thus decreasing platelet aggregation. Dosing is typically 2 to 5 mg/kg/day, although there is also limited documentation on appropriate dosing and uses in pediatric patients. Most literature supports its use as adjunctive therapy in mechanical prosthetic cardiac valves.10,11

Pentoxifylline, a methylxanthine-derived agent, acts in a novel way by enhancing erythrocyte flexibility and decreasing blood viscosity. It also inhibits platelet aggregation, inhibits tumor necrosis factor alpha, and causes vasodilation. It is not considered, however, a true anticoagulant. Although approved for the treatment of peripheral vascular disease in adults, it has had some initial investigation in pediatric cardiac disease. Doses of 20 mg/kg/day were used in a pilot study to achieve modest improvement of pulmonary blood flow in patients with inoperable cyanotic heart
disease and polycythemia.\textsuperscript{12} It has also been used in conjunction with IVIG and ASA in the therapy of Kawasaki’s disease, with a dose of 20 mg/kg/day leading to a debatable decrease in the formation of coronary artery aneurysms.\textsuperscript{13} There are a number of newer anticoagulation agents, such as platelet inhibition agents (ticlopidine and clopidogrel), which have been gaining popularity, and the glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban), in which there is limited pediatric data. Use and dosing of these drugs will be discussed later in specific sections. Further detailed information regarding all of the anticoagulation and antiplatelet agents mentioned here can be found in both updated reviews on pediatric antithrombosis\textsuperscript{1} as well as in a recent text assessing pediatric thrombosis.\textsuperscript{14} What follows is a discussion of anticoagulation as it relates to various pediatric cardiac disease conditions.

\textbf{Dysrhythmias and anticoagulation}

Patients with congenital heart disease that have had extensive atrial surgery are at greater risk for later development of dysrhythmias, both in the immediate postoperative period\textsuperscript{15} and during long-term follow-up.\textsuperscript{16} With increased sensitivity of transesophageal echocardiographic surveillance, more of these thrombi are now detectable and must be addressed prior to initiation of cardioversion (either electrical or chemical). However, there are no studies specifically involving pediatric patients in which prior anticoagulation of a patient is performed and assessed for relative risk of embolism post-cardioversion versus a patient who has not been anticoagulated. Therefore, specific risk factors are not well described, and prediction of which patients will be at greater risk for embolic events is not possible. There has been speculation, however, that patients in whom spontaneous echocardiographic contrast can be seen, or those with poor ventricular function, are at increased risk for thrombus development.\textsuperscript{16}

Pediatric patients with atrial arrhythmias often will be cardioverted without the use of prior anticoagulation if there is no evidence of intra-atrial thrombus by transthoracic echocardiography, in some cases, or by transesophageal echocardiography. Much of the practice for anticoagulation of pediatric patients in chronic atrial arrhythmias derives from the adult literature, although there is individual variation. Using atrial fibrillation as an example, typical adult patients under age 60, with or without heart failure, no structural disease, and no other systemic risk factors can be prophylactically managed with either no anticoagulation or just aspirin 325 mg per day.\textsuperscript{12} With increased age, coronary artery or valvular disease, systemic diseases, or heart failure, warfarin anticoagulation is initiated, with maintenance of an INR of 2.0-3.0. During elective DC or chemical cardioversion, patients who have had their atrial dysrhythmia for at least 48 hours (or for unknown duration) are given warfarin to maintain an INR of 2 to 3 for three to four weeks prior to as well as after cardioversion. For those patients requiring immediate cardioversion, the recommendation is for urgent heparinization to increase aPTT to 1.5-2.0 times normal prior to cardioversion, followed by oral anticoagulation maintenance as described.

\textbf{Glenn/Fontan anastomoses}

Glenn and Patino first described their vena caval-pulmonary artery shunt over 45 years ago,\textsuperscript{18} and Fontan and Baudet's original article describing the physiologic surgical repair for tricuspid atresia is now over 30 years old.\textsuperscript{19} In that time, numerous modifications to these initial procedures have evolved. However, the basic physiology remains, in that there is direct flow from the vena cavae into the pulmonary arteries without an intervening ventricle and, typically now, without an interposed valve. The lack of these two entities means that there is no active pumping of blood into the pulmonary tree, and no way to prevent retrograde flow or pressure transmission.
Moreover, unlike the description of the original anastomoses, which divided superior and inferior vena caval return between the branch pulmonary arteries, current reconstructive operations maintain continuity between both pulmonary arteries and both vena cavae. This allows any obstruction or downstream pressure load to be transmitted through the entire system. It also allows two oppositely directed flows to dissipate their kinetic energy as they meet. The sequelae of this have led to the modifications mentioned above, so that the majority of the repairs that are undertaken now are no longer the direct right-atrium-to-pulmonary-artery connection, but are more of the lateral tunnel (total cavopulmonary connection) or the external conduit connection.

The other major modification that has been made to the Fontan physiology is that of the creation of a fenestration to allow decompression of the right-sided system by right-to-left shunting. Used by a number of centers, this fenestration can be left as is or later occluded by transcatheater device or by surgical closure. Despite these various modifications, a prominent, and not uncommon, adverse finding in these patients is the development of thrombi and embolic events, with a prevalence of anywhere from 5-33%.20–23 (Figure 2) Of note, the actual incidence of these may be even higher, as several studies show that the sensitivity of transthoracic echocardiography to detect thrombi is less than that of transesophageal echocardiography, even in smaller children,22,24–27 and nearly all of the numerous studies reporting the presence of thrombi were retrospective in nature. Therefore most studies likely underestimate these incidences. An exception is the study from the German Heart Center, in Munich, which performed a partially prospective study of 52 patients. This study demonstrated that transesophageal echo was more sensitive than transthoracic echo, and identified thrombus formation in 1/3 of their patients.22

Figure 2 Older Fontan repair, with a direct atriopulmonary anastomosis, demonstrating spontaneous echocardiographic contrast and a mural thrombus attached anteriorly to the atrial wall.
The etiology of thrombus formation is unclear. Multiple derangements of liver-generated proteins has been noted, most prominently that of a relative deficiency of protein C.20,21,28–33 However, decreased antithrombin III, protein S, prothrombin times, plasminogen, factors II, VII, IX, X, and XIII levels, elevated thrombin-antithrombin III complex, plasmin-antiplasmin complex, D-dimer, prothrombin, activated partial thromboplastin times, factor VIII, gamma glutamyltranspeptidase (GGTP), alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase levels have also been variously reported.20,21,28–33 Note that prothrombin times have been listed as both decreased and increased, depending on the reporting study. Although it has been correctly noted that there are age-related maturational levels of these hemostatic factors and that some of the earlier data did not take this into account,2,14,34,35 much of the later data still demonstrate overall lower absolute measurements and subnormal levels of protein C as well as other decreased anticoagulant factors for age as compared to normal.30–33

The changes in hemostatic factors associated with the Fontan surgery may directly result in protein-losing enteropathy seen in these patients. A small study from Denver, looking at hepatic function in these patients, demonstrated an increased galactose elimination half-life in the entire study group in addition to abnormal GGTP, prothrombin, and factor V levels in over 70% of their study group. Of note, liver biopsies in four of eleven patients demonstrated cirrhosis or varying degrees of fibrosis.36 Hsia and colleagues at Great Ormond Street assessed Doppler flow and/or catheter measurements across the portal vein, hepatic vein, and inferior vena cava of Fontan and control patients, found clues that may lend insight into the pathogenesis of liver damage.37,38 They found that gravity and exhalation adversely affected various aspects of flow both in the older atrioventricular connection Fontan patients as well as in those with the newer total cavopulmonary connections when compared to normals. Between alterations in pulsatility, flow direction, and pressures, they demonstrated central venous, hepatic venous, and portal hypertension in their Fontan patients with a decreased transhepatic gradient, suggesting global congestion of capacitance sinusoids. They suggest that the constant pressure, which was shown to be further increased in certain venous systems in patients with worse NYHA status or protein-losing enteropathy, overwhelms autoregulatory responses and further deranges local flow as well as affecting regional drainage patterns. This may lead to the later GI complications, such as ascites and protein-losing enteropathy. It may also lead to the direct hepatic damage. (Figure 3).

Other putative associated risk factors for thrombosis that have emerged include: bilateral discordant sized superior vena cavae employed in the creation of a cavopulmonary anastomoses, postoperative low mean arterial saturations,39 atrial dysrhythmias,43,39 large fenestrations (> 4 mm),41 and protein-losing enteropathy through direct loss of clotting regulatory proteins.20 These associated factors have been suggested, but given the relatively small numbers of patients their presence may be circumstantial and not causal.

As is so common in many of these pediatric cardiac disease entities, long-term double-blind, randomized, placebo controlled studies of anticoagulation efficacy and outcome do not exist. Several empiric methods for dealing with this increasingly recognized complication exist. Andrew's Canadian study group suggests initial perioperative anticoagulation followed by no anticoagulation, by warfarin, or by aspirin for six months.4 Some centers do not anticoagulate at all, unless patients have dysrythmias or prosthetic valves.42 There are centers that give warfarin for three months followed by life-long aspirin.43 Some treat with warfarin for six months followed by no anticoagulation or by ASA.44 One center in Rome, however, continues their oral anticoagulation for at least one year and then initiates ASA.45 Others use aspirin six months post-operatively.46 Finally, there are those who give warfarin or aspirin life-long. Of those who treat with warfarin indefinitely, many treat for an INR of...
2.5 to 3.0 while others attempt to achieve and maintain an INR of 3.0-4.5. However, there is reported use of a combination of ASA 10 mg/kg/day plus warfarin to maintain an INR of 1.5. By and large, the centers reporting their anticoagulation were not performing comparisons of various regimens, and were reporting retrospectively. Of note, thrombus formation has been demonstrated while patients were on “low-dose” aspirin, warfarin, dicoumarol, or heparin. At the present time, there is a multicenter prospective study in Canada and Australia that is addressing these issues whose results are pending.

Figure 3 Angiographic and echocardiographic demonstration of complete occlusion of the Fontan anastomosis by thrombosis, with development of collateral circulation bringing lower extremity flow to the branch pulmonary arteries. The Glenn anastomosis is patent.

Interventional catheterization

Balloon angioplasty

Interventional cardiac catheterization has expanded significantly since its inception to include: balloon valvuloplasty, balloon angioplasty, angioplasty plus placement of one or multiple stents in both arterial and venous vessels, placement of occlusion devices in the ductus arteriosus, atrial septum, and other abnormal arterial or venous connections, transseptal puncture, endomyocardial biopsy, and radiofrequency ablation. Due to concern for thrombus formation at sites of intimal rupture or at prosthetic device placement as well as concern for neointimal proliferation, anticoagulation has been used in several specific situations. In one study from the Royal Brompton Hospital, patients with pulmonary atresia and stenotic aortopulmonary collateral vessels underwent balloon angioplasty and stent placement to improve pulmonary flow. Patients were heparinized in the catheterization laboratory, then had their heparin continued until they were orally anticoagulated to an INR of 2.5-3.0. This was maintained for 3 or 6 months in a total of 11 patients. One patient, who was noncompliant with anticoagulation therapy, had restenosis at the distal end of the stent after systemic saturations were noted to be significantly lower by three months post-intervention. It was unclear whether this stenosis was due to thrombus or neointimal hyperplasia, although it was surmised to be due to the former, as the other patients who underwent later catheterization
(median 11-month follow-up) demonstrated no evidence of neointimal hyperplasia. Their institutional recommendation is to anticoagulate with warfarin for 6 months post-intervention, despite having had no patients develop any complications when treated with 3 months of warfarin. Two multicenter studies have used a combination of aspirin and dipyridamole empirically for stent placement in larger pulmonary arteries post-surgery.\textsuperscript{50,51} The Royal Brompton study, however, mentions that their choice of anticoagulation is due to their patients having a higher hemoglobin plus smaller, tortuous vessels with low or non-pulsatile flow.

Much of the research in this area is driven not by pediatric “large vessel” intervention therapies but by adult coronary arterial intervention, with attempts to devise models of atherosclerosis as well as mechanisms of inhibition of re-occlusion of coronary arteries after balloon angioplasty with or without stenting. Therefore, the use of post-interventional anticoagulation regimens appears to be anecdotal at best. For example, research with heparin administration by either continuous infusion or by release by perivascular polymer matrices have demonstrated not only inhibition of post-interventional thrombus formation but also decreased neointimal proliferation after stenting of rabbit arterial vessels.\textsuperscript{52,53} Further direction may come from the adult studies, as newer modalities such as brachytherapy (the use of intracoronary radiation),\textsuperscript{54} sirolimus (and other drug)-eluting stents,\textsuperscript{55} and combination antiplatelet therapies have been used in attempting to decrease thrombosis and the need for either reintervention or revascularization. These may be interesting models of therapy to consider when choosing a short- or long-term anticoagulation treatment post-stenting. Two studies have demonstrated that aspirin plus ticlopidine after stenting reduced the occurrence of cardiac death, myocardial infarction (MI), coronary bypass surgery, or repeat angioplasty over aspirin plus IV heparin plus phenprocoumon,\textsuperscript{56} or reduced the combined incidence of death, MI, or repeat revascularization, plus bleeding complications.\textsuperscript{57} A third study, the STARS trial, demonstrated that the composite endpoint of death, revascularization, thrombosis, or MI was least in patients treated with aspirin plus ticlopidine as compared to aspirin alone or aspirin plus warfarin.\textsuperscript{58}

Clopidogrel has also been shown in randomized trials to be as effective as ticlopidine after stenting.\textsuperscript{59,60} Ticlopidine has been used rarely in pediatric patients, although it has been used in the treatment of coronary thrombosis in Kawasaki's disease\textsuperscript{61} and several other vascular entities, such as Kasabach-Merritt syndrome\textsuperscript{62} and even in adolescent with primary pulmonary hypertension.\textsuperscript{63} Dosing has been 5-8 mg/kg BID in combination with low-dose aspirin; peak response is up to 14 days of treatment (though it can be seen in 2 to 5 days after loading dose), and has been associated with GI disturbance, rash, neutropenia, agranulocytosis, and thrombotic thrombocytopenic purpura in adults.\textsuperscript{64} There are no specific studies or reports that utilize clopidogrel in the treatment of children. Peak response is in 3 to 7 days of initiation of treatment; diarrhea, rash, and pruritus have been seen, although the amount of GI hemorrhage is reportedly less than that associated with ticlopidine.\textsuperscript{64,65} The study of glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa) has opened up the use of a new set of adjunctive therapeutic sites that, when inhibited, decreases aggregation of platelets by antagonizing the binding of fibrinogen and other adhesion proteins with platelets. Their use, as with the other drugs above, has been studied primarily in the setting of coronary angioplasty. They have been demonstrated to decrease the occurrence of ischemic complications post-intervention. However, there have been inconsistent results with these agents, as well as an overall lack of efficacy in the orally administered inhibitors.\textsuperscript{66} Abciximab, a chimeric human-mouse monoclonal antibody FAb fragment, was used along with ticlopidine in elective coronary artery angioplasty with stenting, and was found to decrease the endpoints of death, MI, or revascularization at 30 days as compared to angioplasty without stenting or angioplasty plus placebo.\textsuperscript{67} It has been used in the pediatric treatment of Kawasaki's disease in the setting of large coronary artery aneurysms containing thrombi, with
resolution of aneurysms and clots without development of ischemia,\textsuperscript{68} and is suggested to enhance vascular remodeling as well as speeding aneurysm resolution.\textsuperscript{69} Abciximab is administered as a bolus dose of 0.25 mg/kg 10 to 60 minutes prior to intervention, then given continuously 0.125 mcg/kg/min for up to 12 hours, with bleeding as its main complication.\textsuperscript{66,70} Eptifibatide and tirofiban have not been reported as being used in children in the literature. The concomitant use of these agents with heparin have allowed for the reduction in overall heparin dosing in coronary angioplasty,\textsuperscript{71} although the need for the higher activated clotting times seen in adult coronary intervention appears to be not as relevant in pediatric balloon interventional catheterization.

An interesting new development is the use of activated protein C polymer coating on stents. Animal trials in a rabbit iliofemoral artery injury model have shown that the stents with polymerized activated protein C had no evidence of occlusion as compared to uncoated stents or those coated with bovine serum albumin.\textsuperscript{72}

Since coronary arteries are relatively smaller vessels, it is difficult to compare outcomes and methods in these small vessels with those of larger vessels. Recent data from Texas Children's Hospital suggest that neointimal growth and restenosis are uncommon for as much as 10 years after initial placement of Palmaz stents.\textsuperscript{73} Moderate (1 to 1.5 mm) or severe (>1.5 mm) neointimal proliferation occurred in 1.8%, and restenosis occurred in 2% of their patients. Restenosis was felt to occur due to several risk factors: lack of overlap of tandem stents, sharp angulation of the stent within the vessel, stent overdilation, and stent placement in abnormal tissue substrate (e.g. patients with Williams syndrome). They felt that the risk of neointimal proliferation increased with overdilation of the stent when it was initially placed, which has been previously suggested in the setting of coronary artery stenting.\textsuperscript{74} Another recent study of stenting in pulmonary arteries of patients with pulmonary atresia/VSD from San Francisco, distal pulmonary arteries that were approximately the size of coronary arteries showed a greater rate of restenosis and even occlusion within the stent, although their overall numbers were smaller.\textsuperscript{75} Other studies using Wallstents demonstrated intimal proliferation at a rate of 28%, using growth >30% of the vessel diameter as their definition.\textsuperscript{76} Although they did not define their specific anticoagulation regimens, they did report that there was no difference in neointimal proliferation between patients treated with aspirin and those treated with warfarin. And, as another potential confounding factor, they referenced a study in which Wallstents were found to be more thrombogenic than Palmaz stents in intrahepatic portosystemic shunts.\textsuperscript{77}

So, what of using the stenting of larger arteries, such as adult iliofemoral arteries, as a better model? Again, a number of studies exist that use different regimens, different stents, and have different outcomes. An Australian group used 5000 units of heparin during the placement of Strecker or Wall stents in femoral or popliteal arteries, then aspirin 150 mg/day on discharge; their results demonstrated acute thrombosis (within 48 hours) in 6.3%, late occlusion in an additional 12.9% from 2 to 18 months, and stenosis in 22.5% of their patients from 4 to 15 months post-placement.\textsuperscript{78} Another group, who stented iliofemoral veins with Wall, Palmaz, and Gianturco stents, used intraprocedural heparin of 5000 units, then maintained systemic heparinization post-stenting for three days to keep aPTT 75 to 100 seconds.\textsuperscript{79} They then overlapped warfarin therapy for 3-6 months. Their study showed no significant thromboembolic phenomena, but had occlusion in 32% and stenoses in 22% of their stented vessels. An interesting case report, in which an adult with heparin-induced thrombocytopenia and thrombosis syndrome was anticoagulated with argatroban during carotid artery stenting, had a successful outcome (with no recurrence of neurologic symptoms at six-month follow-up).\textsuperscript{80} Their regimen consisted of an initial argatroban bolus of 350 µg/kg followed by continuous infusion of 25 µg/kg/min, which was later decreased to 15 µg/kg/min when the initial ACT was greater than 700 seconds. After conclusion of
the procedure, the patient was treated with ticlopidine 250 mg twice a day for 6 weeks and aspirin (no dose given) indefinitely. In choosing an established adult model for anticoagulation in balloon angioplasty with stenting, it must be realized that there are multiple confounding factors. Certainly, one of the most important confounders is the size and type of vessel. Stenotic or hypoplastic pulmonary arteries with little atherosclerotic load or damage but possibly very abnormal growth characteristics may respond, heal, interact with the clotting system, and endothelialize very differently from a formerly fully patent iliac or coronary artery with local plaque formation as well as damage from concurrent tobacco use or infection. As well, the stent size, the use of overdilation, the underlying characteristics of the vessel (such as cystic medial necrosis), and residual compliance of the vessels all impact on long-term outcomes. At this point, the use of a randomized, placebo-controlled study of various anticoagulation regimens for stent placement may be difficult, in that the accepted practice is the use of some form of antiplatelet therapy at a minimum for some period of finite or unlimited time.

**Occlusion devices**

Anticoagulation strategies for the placement of steel coils and larger devices to occlude the ductus or septal defects have developed along divergent pathways. Except for the routine heparinization associated with the arterial catheterization, anticoagulation after placement of Gianturco steel coils in the ductus arteriosus or other vessel with the intention of occlusion is not desirable. The coils have Dacron fibers arrayed from them, which act specifically as a procoagulant backbone for platelets and other clotting factors to quickly create a thrombus. So, after a combination of mass effect causing gross occlusion plus successful thrombosis, the coil becomes endothelialized. The Rashkind occlusion device, although larger, seems to have had the same anticoagulation strategy.  

Atrial septal occlusion devices, which have been described now for over 25 years, have taken a different tack toward anticoagulation. The large array of devices that are now available or that are in clinical trials create large profile thrombogenic surfaces in the atria, which are also sites of low velocity flow. Yet, fibrin-platelet deposition is the initial backbone onto which the eventual complete endothelialization of the device occurs, which has been demonstrated in multiple devices. Transesophageal echocardiographic evaluation of adults three days after placement of the ASDOS device have demonstrated layers of echodense material on the both surfaces, which remained constant or decreased over time with follow-up. Mobile and pedunculated thrombi were also seen in at least 25% of the patients that were followed clinically and with echocardiography until resolution. There were no adverse embolic events noted, and neither the presence nor absence of atrial enlargement, residual shunting, or sinus rhythm had any effect on the formation or resolution of these clots, which stabilized in the vast majority by six months. Despite this need for rapid thrombosis, though, the presence of thrombosis in this location confers a higher risk in the non-anticoagulated patient, and may add risk to even those patients who are platelet inhibited. Patients with coagulation disorders can also develop gross thrombus with embolic phenomena; in this specific case report, as in others mentioned in previously mentioned clinical circumstances, the thrombus was missed by transthoracic echocardiography, and was only diagnosed by transesophageal study. This patient, who suffered from factor XII deficiency, had been anticoagulated with heparin and had started phenprocoumon at the time of an acute cerebrovascular accident. Residual shunts also are felt to be risk factors for formation of thrombi, especially in the setting of occluding a foramen ovale for presumed recurrent paradoxical embolism. This study assessed five different devices, and found that aspirin dosed at 100 mg/day for three to six months after placement did not appear to increase or
decrease risk of recurrent embolism. But, even a warfarinized INR of 3.5 in a woman six weeks after placement of a device for an atrial septal defect did not prevent a subsequent embolic event; she was found not to have any disorders of thrombosis. Therefore, though anticoagulation appears to be necessary for placement of septal defect occlusion devices, and may need to be continued longer pending complete closure of residual defects with the history of paradoxical embolism, it may still be incomplete to prevent thrombosis.

There is a number of varying anticoagulation methods that seems to be based more on institutional practice than the actual device used. All groups used heparinization during the actual procedures, then diverged from there. A multicenter study in Germany using the Das Angel Wings device recommended the use of aspirin at a dose of 2-3 mg/kg/day over six months. Sievert, at his institution in Frankfurt, Germany, employed warfarin or aspirin for two to six months post-procedure with the ASDOS device in adults. Later, as the head of a multi-institutional German study, he divided anticoagulation into a pediatric regimen, using aspirin for six months and an adult regimen, using warfarin for six months. Hausdorf's group at Berlin, also using the ASDOS, used heparin 600 u/kg/d IV the first day, 400 u/kg/d the second day, and 200 u/kg the third day to keep the antithrombin III greater than 90%, then gave aspirin 2 to 3 mg/kg/day for six months post-procedure. The multicenter international study groups placing the Sideris buttoned device used aspirin 5 to 10 mg/kg/day in children and 325 mg/day in adults for a total of three months. The German CardioSEAL trials in Hannover used 2-3 mg/kg/d of aspirin daily for six months post-occlusion. When Hausdorf evaluated its replacement, the self-centering STARflex, patients in this multi-center trial were also treated with the same heparin, then aspirin, regimen that he used while at Berlin using the ASDOS. There have been several side-by-side device comparison studies, as well. A British study comparing the Amplatzer and the buttoned devices in children used a flat dose of aspirin 75 mg/day in all their children (some up to 91 kg) for 3 to 6 months. Two more comparative studies in adults used, presumably, platelet-inhibiting doses of aspirin in their adults for 3 to 6 months. Few of these studies demonstrated any concern for residual thrombosis or embolic phenomena. Of the two listed above that did, the first article reported blood clots seen by transesophageal echo on the devices in two adult patients at two and six weeks, respectively, after intervention. They were treated with warfarin and had no specific sequelae. The second reference lists 9 out of 139, or 6%, of their adult patients noted to have thrombus formation seen by TEE in the first two weeks post-procedure. One of these patients, who had a factor XII deficiency, had a cerebral embolism within two days of the procedure; however, the thrombus self-resolved within one month. One patient underwent surgical removal for an asymptomatic thrombus, and the remainder had theirs resolve within three to five weeks. Of interest, none of these patients had residual shunting noted, none of the thrombi were seen by transthoracic echo, and none of the pediatric patients had thrombotic complications.

Radiofrequency ablation

Radiofrequency ablation involves the creation of an endocardial burn to cause tissue disruption within an abnormal electrical cardiac focus, such as accessory pathways, automatic foci, etc. This is achieved by applying alternating current through a catheter in contact with the endocardium. The current causes the burn by creation of resistive heating within local tissues. There is heat transfer to the surrounding blood, which is increased in scenarios of poor myocardial-catheter tip contact. To a lesser extent, there is also heat transfer to deeper tissue and epicardial coronary arteries that is dependent on duration of exposure. Therefore, thrombus formation can occur in the blood pool, at the direct site of ablation, and in epicardial coronary arteries adjacent to the ablation site. Pathologic studies have, in fact, demonstrated
fibrinous collections and even thrombi at the ablation site. Reported thrombotic complications, though, have been few and on the order of 0.6 to 2.8%, depending on the location of the lesion and the type of tachycardia. These include microthrombus formation with embolism and coronary artery thrombosis due to local energy application from an intracardiac or intravascular catheter. Systemic thrombotic and embolic phenomena secondary to instrumentation or prolonged immobilization associated with the ablation procedure, leading to venous occlusion, cerebral or pulmonary embolus, and deep venous thrombosis, are recognized thrombotic complications as well. Mechanisms to control and direct the amount of thermal injury have included temperature monitoring of the catheter tip, manual or automatic impedance monitoring mechanisms, and newer saline-cooled catheters. Anticoagulation during radiofrequency ablation has been typically similar to that of left-sided pediatric cardiac catheterization, with heparinization at 100 u/kg bolus given initially followed by maintenance with either continuous infusion of 15-20 u/kg/h, or repeated bolus of 20-50 u/kg/h, or as dictated by ACT. Some groups will maintain the ACT greater than 300. This is continued until the catheters are removed. There have been varying protocols for maintenance of prophylactic anticoagulation post-ablation. Different institutions will give aspirin 3-5 mg/kg/day for two to six weeks post-ablation, although one facility treated for three months, and another did not treat at all. Nevertheless, the occurrence of thromboembolic events appears to be independent of the anticoagulation protocol. No double-blind, randomized, placebo-controlled studies exist evaluating the efficacy or even the need for anticoagulation agents after ablation.

Figure 4 Thrombus formation in the left main coronary artery after inadvertent direct application of radiofrequency energy to the left coronary artery ostium of a teenager during radiofrequency ablation of a left-sided pathway. Image courtesy of Amy Martin, M.D., Office of the Medical Examiner, Denver, CO.
Post-catheterization vessel occlusion

Cardiac catheterization has evolved from a mostly diagnostic procedure to a more interventional use. Its utility has increased for patients who require some sort of intervention, but may be able to rely on the new generation of non-surgical techniques that can either increase or decrease flow, as appropriate. Since the femoral artery has been the major entry vessel of choice, one of the significant complications is femoral arterial occlusion. Strategies that have reduced the incidence of arterial occlusion include the use of percutaneous access over arteriotomy, indwelling arterial sheaths to keep vessels patent for catheter exchanges, smaller balloon and catheter profiles to create less vessel damage, and double-balloon valvuloplasty techniques to reduce exposure of the arteries to larger catheters. Typically, the background incidence of arterial complications is felt to be higher in patients 5 years of age, or younger. The mechanism of occlusion is complex, and felt to be due to combinations of spasm, thrombus formation at the catheter or sheath, or intimal disruption and flap formation with varying degrees of complicating polycythemia, small size, and low cardiac output. These lead to either transient or complete loss of pulse. Routine systemic heparinization during the catheterization has significantly reduced the incidence of this problem. Typical anticoagulation at the start of arterial cannulation consists of IV heparin 50-100 units/kg given as a bolus. Subsequently, heparin can be given empirically at another 50 units/kg IV bolus for each subsequent hour. Alternatively, ACT levels can be monitored, with maintenance at >200 seconds as adequate anticoagulation. A study looking to further reduce this occurrence using intraarterial papaverine was too small to demonstrate significant effects. However, it was able to demonstrate that ultrasound diagnosis of femoral arterial occlusion, using specifically the pulsatility index, could be made with good sensitivity and specificity if the pulsatiily index was less than 3.34.

Once loss of pulse is determined, by clinical findings such as decreased distal pulses, cool extremity, edema, and color change and/or by abnormal ultrasound findings, using an algorithmic intervention scheme can be quite helpful. Repeat systemic heparinization is usually performed with 100 units/kg bolus IV followed by continuous infusion of 20 units/kg/hour IV for four hours. If pulse has not returned despite improved perfusion, check an aPTT bolus and adjust the heparin infusion to attain an aPTT 2.5 times control values. If there is still no improvement, thrombolytic therapy with either streptokinase, at 1000 units/kg bolus and 1000 units/kg/hour for 6 hours, or rTPA, at 0.7 mg/kg bolus and 0.2 mg/kg/hour for 6 hours OR 0.1-0.5 mg/kg/infusion without initial bolus but with incremental 0.1 mg/kg/hour increases, can replace the heparin. Baseline prothrombin and thrombin times, hemoglobin, fibrinogen, repeat aPTT, and type and cross for one unit of packed red blood cells should be obtained. End points include return of pulse, entry point site bleeding, internal bleeding, or no response or worsening of the limb’s status. Continuing to surgical embolectomy or intimal flap repair is dependent upon whether viability of the leg is still in concern or if adequate thrombolysis fails despite fibrinogen levels <1.9. If thrombolysis successfully returns pulse and perfusion, continued observation for 24 hours after discontinuing therapy is important to ensure that other hemorrhage does not occur and that arterial patency is maintained.

Blalock-Taussig shunts

The original Blalock-Taussig shunt, a systemic to pulmonary shunt created by anastomosing the subclavian artery end to side to the ipsilateral pulmonary artery, has largely been replaced by the modified Blalock-Taussig shunt, a polytetrafluoroethylene tube graft that is interposed end-to-side between the subclavian and pulmonary arteries, or by a modified central shunt, in which a tube
graft is anastomosed between the ascending aorta and pulmonary artery. However, because of their high flow, short distance, and small diameter, these shunts can thrombose and occlude. Typically, patients who receive these shunts are given heparin intraoperatively to prevent occlusion, although one recent study suggests that it may be a significant risk factor in the development of perioperative seroma. \textsuperscript{127} Some patients are then treated with low-dose aspirin (1-10 mg/kg/day), but there has also been a study concluding that after a single intraoperative low-dose of heparin (20 u/kg), no further anticoagulation is required. \textsuperscript{128} In that study of twenty-five 5 mm shunts, there were no acute shunt failures noted, and only one patient required shunt angioplasty six months after the shunt was inserted. An earlier study reports “shunt failure” in 10 of 55 non-anticoagulated patients (only one was 4 mm; the remainder 5 or 6 mm). \textsuperscript{129} Shunt occlusion was not demonstrated. Five patients experienced proximal suture line stenosis. Furthermore, their definition of shunt failure also included isolated increased serum hemoglobin. Another study from 1985 followed 19 patients who received shunts of four, five, and six millimeters in diameter. \textsuperscript{130} Two patients lost partial or complete patency of their 4 mm shunts; neither of these patients had been treated with anticoagulation therapy of any kind. Two other patients, who also received 4 mm shunts, but received aspirin 10 mg/kg/d, had patent shunts but occlusion of the subclavian artery distal to the shunt. The other three patients who received 4 mm shunts received ASA as well, and had no complications. Patients with 5 and 6 mm shunts had no complications, but were not given any specific therapy. In a study of patients less than three months of age at the time of shunt placement, 20 received 5 mm and 43 received 4 mm shunts. \textsuperscript{131} They were given heparin 1 mg/kg/day in the first three to five postoperative days, then given undefined aspirin therapy for an undefined “long” period of time. A total of 27 shunt failures were noted, with 20 of these in the 4 mm grafts, and five of these failures occurring within the first month. Univariate and multivariate analysis demonstrated that the use of a 4 mm shunt conferred a greater risk of shunt failure than the use of a 5 mm shunt. Nevertheless, approximately 85% of the shunts were adequately functioning one year after implantation. Over the long term, 18% of the 4 mm and 25% of the 5 mm shunts demonstrated distortion of the pulmonary artery, and 10 of the 20 shunts failed secondary to distortion at the proximal anastomoses. Smaller shunts associated with PA distortion did not incur failure of shunt patency more than the larger shunts.

At the present time, the ACCP consensus study recommendation has been to initially give perioperative therapeutic heparin followed by indefinite treatment with aspirin 3 to 5 mg/kg/day. \textsuperscript{1} Certainly, one factor that will play into the need for and duration of shunt survival is the increasingly younger age at which patients receive their definitive repair. Many patients were palliated with shunts and allowed to grow until definitive repair occurred two or more years later. With the advent of better techniques and knowledge of cardiopulmonary support, the time from palliation to complete repair has diminished, thus requiring less overall need for an increased duration of patency of a shunt. As well, this trend toward earlier intervention has led to a bypassing of the use of shunts, opting for early complete repair as initial intervention. To be sure, there will still be complex pulmonary atresia patients and the like who require longer periods of shunt survival to achieve adequate pulmonary artery growth.

**Myocardial ischemia and infarction**

Myocardial ischemia and myocardial infarction (MI/MI) are very infrequent events in children. Hence, there is really no literature that has thoroughly evaluated various anticoagulation treatment regimens in children. Furthermore, the etiologies of MI/MI are typically much more diverse than in adults, who most likely have coronary artery atherosclerosis as their primary etiology. Pediatric etiologies for MI/MI include:
Kawasaki disease, anomalous coronary artery origin, course, or bridging. Congenital heart diseases, cardiomyopathy, genetic disorders, substance abuse, trauma, systemic disease resulting in poor perfusion, iatrogenic intervention (surgical or medical), and idiopathic or premature coronary artery disease.\(^{132,133}\) However, since the majority of these disease states require medical (including inotropic), surgical, or mechanical support, there has not been a drive for studying of anticoagulation in this patient population. Thus, as in many other adult disease-model analogues, the model for care for pediatric patients with MI/MI mirrors that of the adult. Since the use of anticoagulation in adults with MI/MI is based on a consistent and well-studied model in which long-standing atherosclerosis acutely impairs coronary flow, and some pediatric diseases may have a similar picture resulting in coronary artery obstruction, we will briefly summarize adult anticoagulation management of MI/MI.

The principles of anticoagulation therapy in adult MI/MI are to prevent further thromboembolic formation and extension in coronary arteries while not increasing risk to the patient for intracranial bleeding. Active thrombolytic therapy will not be addressed, however, since the need for this in pediatric patients is much more limited. These are used as direct agents in destroying thrombus on ruptured atherosclerotic plaques that have obstructed the coronaries. Yet, the use of platelet-active drugs, antithrombotics, and anticoagulants may be reasonable adjunctive therapy in the management of pediatric MI/MI. These are agents that act to prevent further creation and propagation of thrombus. However, there has been no study of the use of these agents for this purpose in children. Extrapolation of the use of these agents may be made, based on what is known about effective dosing in children.

One of the most useful, and inexpensive, agents studied is aspirin. The study that best proved its effectiveness was the ISIS-2 study, in which 162.5 mg of aspirin was crushed or chewed and taken orally for one month.\(^{134}\) It decreased mortality, risk of reinfarction, and risk of stroke. The first dose was given soon after diagnosis to achieve rapid platelet inhibition, which occurs within one hour. The effective dose is 160 to 325 mg in adults, as lower doses delay the onset of platelet inhibition.\(^{135}\) Subsequent adult doses for long-term platelet inhibition can be as low as 75-160 mg/day.\(^{136}\) Continued therapy has been shown to be protective for up to 1-2 years. Contraindications to aspirin therapy include aspirin allergy, active bleeding (including GI or GU sources), and hemophilia.

Patients who cannot take aspirin may be given ticlopidine or clopidogrel.\(^{136}\) Ticlopidine takes 24 to 48 hours for initial effect, and may not achieve its maximal effect until two weeks. As well, its side effect profile includes GI disturbance and neutropenia. The adult dose that has been used is a loading dose of 500 mg followed by 250 mg twice daily, with required monitoring of white cell and platelet counts. As mentioned previously, ticlopidine has been used in the setting of Kawasaki’s disease with coronary artery involvement.\(^{68}\) Recent data suggest that clopidogrel is as effective as ticlopidine, is better tolerated due to its better safety profile, and actually acts faster as a platelet-inhibiting agent. This can be given as a loading dose of 300 to 600 mg, and then followed with daily therapy of 75 mg/day. There are no data regarding clopidogrel use in children. Medications such as dipyridamole, sulfinpyrazone, and prostacyclin and its analogues have not been shown to be effective for patients with unstable angina or non-ST-segment-elevated MI, and are thus not used.\(^{136}\)

Anticoagulants, such as unfractionated heparin and low molecular weight heparin (LMWH), are adjunctive therapies that are typically used in combination with active thrombolytic therapy. However, older data demonstrate that heparin monotherapy has reduced mortality and risk of reinfarction.\(^{137}\) Yet, since the ISIS-2 study demonstrated that aspirin is effective with heparin as well,\(^{134}\) most studies now will not assess heparin as a single therapeutic agent.\(^{138}\) Looking at it from the reverse, after the evaluation of the GUSTO-1,\(^{138}\) GISSI-2,\(^{139}\) and ISIS-3\(^{140}\) trials, the addition of heparin to aspirin does not appear to confer any advantage over aspirin alone, and
seems to add an increased risk of significant bleeding. Recent reviews on managing adult MIs disapprove of the use of heparin completely, or generally lean away from its use. Interestingly, an update of the American College of Cardiology/American Heart Association Guidelines for the Management of Acute Myocardial Infarction further reviewed the use of LMWH, and referenced several studies showing that various formulations of LMWH were superior to unfractionated heparin plus aspirin or aspirin alone. Furthermore, even suggested consideration of these as individual, and not interchangeable, drugs; nadroparin and enoxaparin were demonstrated to have a higher anti-Xa:anti-IIa ratio in vitro than dalteparin, and may be more effective clinically. Overall, enoxaparin was shown to be better than unfractionated heparin at not only reducing death and serious cardiac ischemia, but also not increasing the rate of major hemorrhage in the short term (under 45 days). There is less overall heparin-induced thrombocytopenia, it can be given subcutaneously (obviating the need for continued intravenous access), and requires no specific monitoring. When used in children, dosing ranges have been described as either therapeutic or prophylactic, with differing doses based on whether the patient is less than two months old or older, and whether the scenario is low or high-risk. Therapeutic doses for patients under two months of age are 1.5 mg/kg every 12 hours; prophylaxis doses are 0.75 mg/kg every 12 hours if low-risk, 1.5 mg/kg if high-risk. For patients between two months and 18 years of age, therapeutic dosing is 1.0 mg/kg every 12 hours and prophylactic dosing is 0.5 mg/kg every 12 hours for low-risk and 1.0 mg/kg for high-risk. High and low-risk definitions were derived from the clinical scenarios in the study for which LMWH was used. Examples of high-risk scenarios included cardiomyopathy, prosthetic mitral valve, cardiovascular shunts, systemic lupus erythematosus, and central venous line-related thrombosis with a previous thrombotic event. Low-risk scenarios included central venous line-related thrombosis with no thrombotic history, and trauma after surgery. MI was not one of the clinical scenarios. The GP IIb/IIIa inhibitors, abciximab, eptifibatide, and tirofiban, have been initially evaluated in the settings of acute coronary syndromes, unstable angina, non-Q wave MI, and percutaneous coronary interventions. However, they have not been evaluated in comparison to each other. When compared as a group to placebo and as an adjunct to aspirin and unfractionated heparin therapy, they appear to decrease the occurrence of MI plus death, or MI plus need for coronary artery bypass or plus death. Dosing guidelines are as listed previously, although as also previously mentioned, any pediatric experience with these medications is extremely limited. Yet, to reiterate a prior discussion, abciximab may have some efficacy in not only the prevention of thrombosis but may confer some improved vascular remodeling.

**Kawasaki Disease**

Kawasaki disease, first described in 1967, is an inflammatory syndrome of the medium-sized arteries that leads to acute coronary artery damage with myocardial infarction, and with the potential for chronic coronary artery aneurysm or stenosis. It has undergone a series of modifications to its therapeutic scheme that culminated in the American Heart Association report on diagnosis and therapy. Besides anti-inflammatory treatment, anticoagulation to prevent coronary thrombosis has been a cardinal feature of the therapies. Management of acute Kawasaki's disease includes administration of IV immunoglobulin at a dose of 2 g/kg over 12 hours plus oral aspirin 80 to 100 mg/kg/day divided QID for up to 14 days from the onset of the illness followed by platelet inhibiting aspirin doses of 3-5 mg/kg/day for 6 to 8 weeks after the acute phase. Initial therapy has been shown to be most efficacious prior to day 10 of the illness. This has been demonstrated to decrease the incidence of coronary artery complications from 20-25% to 5%. A repeat dose of IVIG may be used for initial treatment failure. Previously, use of corticosteroids was believed to
lead to an increased incidence of coronary artery thrombosis. Recent studies, though, suggest that it may be more efficacious, such as in those patients who are refractory to an initial dose of IVIG or have recurrence of symptoms. IV methylprednisolone at a dose of 30 mg/kg/day given over 1-3 days has been successfully used in these patients. Alternatively, oral methylprednisolone, 2 mg/kg/day for two weeks followed by a tapered dosing regimen over six weeks, seems to have been effective in the face of persistent fever, progressive cardiac disease, or worsening vasculitis. Newer therapies, such as antiplatelet agents like ticlopidine and abciximab (mentioned previously in this article), have also been used with increasing success in the acute setting, potentially including enhanced resolution of giant coronary aneurysms. Pentoxifylline, as previously mentioned, has been used in combination with IVIG and ASA with dubious results in aneurysm prevention. Long-term prophylactic anticoagulation of patients who have coronary artery complications includes low-dose aspirin (3-5 mg/kg/day) and warfarin (to maintain an INR of 2.0 to 3.0), depending on the presence and size of the coronary arteries aneurysms and the presence of coronary artery stenoses. Dipyridamole, at 2-3 mg/kg/dose BID to TID, may be used temporarily (typically approximately two weeks) for patients on chronic aspirin therapy who have been exposed to either varicella or influenza. This especially is done in patients at greater risk for myocardial infarction. In patients who have had myocardial ischemia or infarction, or other thrombotic complications, thrombolysis has been successfully performed, variably using exercise plus systemic heparin, or systemic or intracoronary streptokinase, urokinase, or tissue plasminogen activator. There are no randomized, double-blind, placebo-controlled trials that assess the various anticoagulation therapies for Kawasaki's disease. The American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease periodically reviews these agents and reports of their use through the literature, and modifies their treatment recommendations; an update after their recent conference is pending.

Cardiomyopathy

Dilated cardiomyopathy

Unlike in adults, dilated cardiomyopathy in children tends to be idiopathic rather than ischemic in etiology. However, the cardiovascular and pathologic features remain similar, including poor cardiac output and congestive heart failure, varying degrees of mitral valve regurgitation, and risk for left ventricular thrombus with thromboembolism. The incidence of thrombus formation is variably reported ranging between 13-23% and the incidence of systemic embolic events ranges from 8-14%. Pulmonary embolism has also been reported in patients with dilated cardiomyopathy. Since the incidence of pediatric dilated cardiomyopathy is low, the studies that describe the findings in this age group are all retrospective, and have not addressed randomization of anticoagulation regimens. Most reports in pediatric patients discuss the use of either aspirin or warfarin, but often do not address dosing regimens. Many of these are initiated post-hoc when thrombus or an embolic event has already been diagnosed. One case report series from Germany did give their dosing regimen for the treatment of LV thrombus as aspirin 25 mg/kg plus dipyridamole 6 mg/kg; this led to resolution of thrombus (by echocardiography) in five to seven weeks in their three patients. These patients were found to have thrombus either after diagnostic echocardiography for congestive heart failure, or after cerebrovascular accident. The incidence of thrombus formation in their series of patients was 33%. Of note, two of their patients had recurrence of thrombus formation diagnosed by echocardiography, despite continued aspirin and dipyridamole therapy. Unfortunately, intracardiac thrombus in the setting of dilated
cardiomyopathy, as in Fontan patients, is not reliably diagnosed by transthoracic echocardiography and is sometimes only found on autopsy.\textsuperscript{167,168} Adult studies of dilated cardiomyopathy have not looked at randomized regimens of platelet-inhibition versus anticoagulation. A retrospective look at data from the Studies of Left Ventricular Dysfunction (SOLVD) trial demonstrated that warfarin use decreased overall mortality (although again there was no dosing or monitoring information available).\textsuperscript{170} It did demonstrate that they had less aspirin use in the patients who were treated with warfarin as compared to those who were not treated with warfarin, to suggest that aspirin may not have been protective against death overall. Of note, though, only 50% of the patients who had not used warfarin had been on aspirin, and over 75% of both groups were smokers, which may have confounded the findings. In addition, warfarin seemed to confer protection from direct cardiovascular causes of death (e.g. sudden death, death associated with heart failure, and MI) in contrast to death from extracardiac, embolic events (in which there was no actual difference noted between those treated with or without warfarin). A review performed in the same year countered these findings, however, by suggesting that aspirin monotherapy was effective in preventing thromboembolism, stroke, and sudden death in adults.\textsuperscript{171} This study also included data from the SOLVD study, as well as three other major studies and four small studies; all were retrospective and non-randomized in nature.

The mechanism of thrombus formation in the face of dilated cardiomyopathy has been attributed to lower Doppler flow velocities across the mitral valve, to the apex, and outflow from the left ventricle.\textsuperscript{172} In this same study from Maze, et al, mitral regurgitation, with its attendant increased inflow velocities, was suggested as being somewhat protective and lead to decreased findings of LV thrombus in adult patients. This concept has been mentioned in other studies, as well.\textsuperscript{173,174} However, a study from Hong Kong that looked at platelet function and its relationship with mitral regurgitation concluded that MR is a risk factor for thrombus formation, and also provided a possible mechanism.\textsuperscript{175} They demonstrated that patients with mitral regurgitation had higher levels of platelet factor 4 and beta-thromboglobulin, both markers of platelet activation, than patients without valvular leak. Yet another way of approaching the problem was looked at in Vienna, in which the investigators studied flow and clotting factors along with the formation of spontaneous echocardiographic contrast as a precursor to potential thrombosis.\textsuperscript{176} Spontaneous echo contrast was seen more frequently in patients presenting with a thromboembolism, and left atrial appendage flow velocities were found to be lower in patients with atrial thrombus. But, there were patients who had thrombi, and yet had normal velocities. As well, although plasma fibrinogen and plasma viscosity were statistically significantly higher in patients with spontaneous echocardiographic contrast than those without, these data were only slightly different while an entire battery of rheologic variables were otherwise determined to be no different between groups. Therefore, there is no consensus as to the mechanism of thrombus formation. With the contradictory findings in these studies, and the continued demonstration of thrombus formation in patients who have dilated cardiomyopathy regardless of mitral valve function, mitral regurgitation may not be an adequate predictor of the formation of thrombus. Thus future randomized prospective studies in both adults and children will need to be designed, with attention to the ventricular flow characteristics as part of the trial.

An interesting adjunctive therapeutic use was suggested by Sliwa, et al., in which pentoxifylline was used, in combination with digoxin, ACE inhibition, and carvedilol or diuretics, in a series of small prospective, randomized, placebo-controlled, double-blind studies of adult patients\textsuperscript{177–179}. By taking advantage of pentoxifylline's ability to reduce TNF-alpha and Fas/Apo-1, they were able to demonstrate significant increases in LV ejection fraction in the treatment group over placebo after one month as well as falls in TNF-alpha and Fas/Apo-1. In these series, pentoxifylline was not used specifically as a coagulation-modulator. Instead, the investigators took
advantage of one of its side effects to achieve their goals. Since these cytokines are elevated in pediatric cardiomyopathies, larger studies could lead to a potentially exciting therapy for this poorly understood medication.

**Left ventricular noncompaction**

Isolated ventricular noncompaction is considered an unclassified cardiomyopathy by the World Health Organization.\(^{180}\) It has been associated with both pulmonary embolism\(^{181}\) as well as systemic embolism, including cerebrovascular accidents, transient ischemic attacks, mesenteric infarctions,\(^{182}\) and saddle emboli to the abdominal aortic bifurcation.\(^{183}\) Intramural thrombus has been demonstrated by echocardiography,\(^{182,183}\) MRI, endomyocardial biopsy,\(^{181}\) and at necropsy.\(^{183}\) Oral anticoagulation has been recommended for these patients,\(^{182,183}\) although no data exist regarding the long-term outcome of these patients after anticoagulation. Typically, the prognosis for these patients is guarded, as they tend to have progressive ventricular dysfunction and dysrhythmias that cause morbidity and mortality independent of embolic phenomena. There have been no prospective studies in adults or children assessing the efficacy of any anticoagulation regimen.

**Mechanical ventricular support devices**

Ventricular assist devices have been in increasing use in pediatric patients. As with much of the technology, the initial tests and devices were performed on adult patients. With the advent of improved miniaturization, devices were developed for use in children, although the use and study of these in pediatric patients significantly lagged behind adult assist device development since the incidence of children requiring these devices is greatly less than the adult population. As well, using simply scaled-down versions of adult-sized equipment has demonstrated increased thrombogenicity of the smaller devices, despite using geometrically similar models.\(^{184}\) Furthermore, extracorporeal membrane oxygenation (ECMO) has been much more widely used and accepted in children. Improvements in flow studies and understanding of fluid dynamics, however, have led to wider use and advances in their design. Their uses have included a bridge to transplant support function, rescue post-operatively, and support during acute myocarditis. We will not discuss the use of ECMO, as it is beyond the scope of this review. For more information regarding the history and early development of pediatric use of these devices, please refer to the review by Pennington and Swartz from 1993.\(^{185}\)

Left ventricular and biventricular assist devices have been used as early as 1963\(^{186}\), but the majority of the clinical experience has centered on the Biomedicus centrifugal pump system, and the pneumatic pumps, the "Berlin Heart" and the Medos-HIA VAD. Use of the Biomedicus centrifugal pump circuit requires heparin infusion at 10-20 units/kg/h to maintain the activated clotting times between 170 and 200 seconds, or the activated partial thromboplastin time at 1.5 times control value.\(^{187}\) Reported complications include various neurologic sequelae.\(^{188}\) The “Berlin Heart,” a pneumatic pump developed in Germany, has been used since 1992.\(^{189}\) It uses heparin-coated cannulae (although initial uses of the system did not include heparin-coated catheters), and requires systemic heparinization to keep activated clotting times between 140 and 160 seconds. Thrombi were detected in the systems where non-heparin-coated catheters were used; in subsequent patients who had heparin-coated cannulae, there were no further reports of thrombi. In all sets of patients, however, there was evidence of neurologic sequelae and bleeding complications, including hemorrhagic pericardial effusions.\(^{190}\) The Medos-HIA VAD, another pediatric VAD developed in Germany, was first described in 1988.\(^{191–193}\) It is also pneumatically driven, but uses systems that are not heparin-bonded, so that protamine can be administered to discontinue bypass.\(^{194}\) It is heparinized to keep the activated clotting time between 180 and 200 seconds or a partial thromboplastin time.
greater than 50 seconds, with longer runs requiring the addition of aspirin 5 mg/kg/day after removal of chest tubes. Transient minor ischemic attacks and visible thrombi (during a period of inconsistent activated clotting time maintenance), and retroperitoneal bleeding (in the same patient, after increased anticoagulation) have been reported, as well as multi-organ failure. The Hemopump, an axial continuous flow, turbine-style pump, had been used somewhat in children in the U.S., although it was used more extensively in Europe and Canada. It used no anticoagulation, and seemed to be well tolerated overall, by reports. However, the device is no longer available in its present form; a German firm, Impella AG, is reportedly developing a similar intravascular system.

Intra-aortic balloon pumps have been available in pediatric sizes since the early-1980's. The Datascope balloon pump has been used in the setting of heparin infusion to keep the partial thromboplastin time 1.5 to 2 times the normal value. Complications include cerebrovascular accidents, renal and mesenteric ischemia, and saphenous venous thrombophlebitis. They are typically used in larger children, as they are placed transvenously in the femoral vessels and can be quite occlusive to flow, risking long-term patency of the femoral vessels. A recent report from the adult balloon pump benchmark registry showed that smaller BSA (≤1.65 m²) was one of the independent risk factors for serious complications, such as limb ischemia and bleeding, confirming pediatric findings. Furthermore, higher pediatric vascular compliance tends to limit their effectiveness. Despite this, it has been used successfully in children weighing as low as 1.9 kg, with subsequent reports successfully using them in patients as low as 3.1 kg and 4.3 kg. The review from Utah suggested continuous infusion of heparin at a rate of 10 to 15 u/kg/hour, monitoring aPTT. In the latter report, the patients were systemically heparinized to maintain an activated clotting time of 180 to 200 seconds without complications.

A previous report from Utah, describing 18 patients with a majority of the children under 10 kg, also recommended maintaining aPTT at twice normal.

Conclusion

The concept of pediatric anticoagulation has been one that has been simultaneously widely embraced and little understood. Despite increasing use, there is a slowly growing, mostly retrospective or case-reported, experience of how these agents affect children combined with a widening gap between adult and pediatric experience with the emerging therapies. As has been shown here, there remains a dearth of prospective, randomized pediatric data, despite great strides by a number of research centers to deepen the known information about these drugs in children. It will most likely remain that anecdotal uses will continue to lead the foray into effective use of anticoagulation, eventually followed by larger single or multi-center studies that better define the successes and failures of these agents, their doses, and their pharmacokinetics, plus give accurate side-by-side comparisons of these agents. As well, the continued following of the lead of adult practitioners will give, at least, initial insights into which therapies may be adapted for pediatric use. It is the hope that defining some of the adult regimens here will stimulate further thought and utilization of newer agents in children, where appropriate. In the United States, efforts by the Food and Drug Administration since 1998 to obtain more pediatric data on a host of newer medications, by exchanging six extra months of patent protection and “pediatric exclusivity” for the development of this information, has already borne fruit in multiple medications. Further similar efforts may be of benefit down the line for these medications, as well, both from a retrospective standpoint for already released medications as well as for new therapies. In the end, it will be up to both the pediatric research community and to the drug companies, which may even lead to joint efforts,
to make develop unbiased, accurate, and useful data for appropriate deployment of the varied anticoagulation entities available for use.
One sad note: one of the driving forces behind the organization of strong pediatric coagulation research and the maintenance of good pediatric anticoagulation practices, Maureen Andrew, M.D., who died during the production of this manuscript, at the age of 49. Her ubiquitous and pioneering presence throughout the world of pediatric hemostasis, thrombosis, and anticoagulation will be truly missed.

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