Cardiol Young 2002; 12: 513–518

ISSN 1047-9511

Original Article

Low prevalence of femoral venous thrombosis after cardiac catheterizations in children: a prospective study

Ellen Ruud, Solveig Natvig, Henrik Holmstrøm, Finn Wesenberg

Departments of Pediatrics and Radiology, National Hospital, Oslo, Norway

Abstract *Objective:* Cardiac catheterization is an important and frequent diagnostic intervention in children, but few systematic studies have explored the associated venous thrombotic complications. We have prospectively evaluated the prevalence of venous thrombosis, diagnosed by ultrasonography, in children catheterized at our department. *Materials and methods:* We examined 50 children with weight greater than seven kilograms for thrombosis of the femoral vessels. Prophylactic anticoagulation was given to half of the children who were to undergo left-sided catheterization. The enrolled children had ultrasonography of the site of puncture the day before, and the day after, the cardiac catheterization. During catheterization, blood samples were taken from 33 of the children for analysis of thrombophilic agents. *Results:* The children, with a median age of 34 months, had been catheterized 103 times, comprising the 50 current and 53 previous procedures. Over the course of the current procedure, interventions of various types were performed in 18 children (36%). We diagnosed thrombophilic predispositions in four patients. Despite the thrombophilic tendencies, and a high frequency of interventions, we did not encounter a single case of femoral venous thrombosis. Nor did we find any evidence of arterial thrombosis. *Conclusion:* Our study indicates that catheterization procedures in children are currently associated with a low prevalence of femoral venous thrombosis. Continuous assessment of vascular complications, nonetheless, is still required to prevent late effects, and to ensure the best quality of cardiac catheterisations in children.

Keywords: Congenital heart disease; radiology; clinical investigation

THE FOCUS ON, AND AWARENESS OF, THROMBOSIS in childhood is growing due to an increasing incidence of pediatric thromboembolism.[1] The increase of childhood thromboses is mainly caused by rapid progress in the field of intensive care medicine, which constantly makes possible more complicated strategies for treatment. The unwanted consequences, and side effects, of these progressive steps are a rising number of children susceptible to thrombosis.[2,3]

Children with congenital cardiac malformations may have multiple predispositions for thrombosis, and children at special risk are those with the Fontan circulation along with those having mechanical valvar prostheses.[4,5] International recommendations on anticoagulation for children in general are available,[6] but the scientific documentation is limited, and new studies are requested. Furthermore, many questions remain unresolved in the issue of childhood thromboembolism.

Cardiac catheterization is a vital component of the evaluation and treatment of children with congenital cardiac diseases.[7] The procedure is attended with complications, and the most common adverse events are vascular.[8]

Prevalence, prophylaxis, and treatment of femoral arterial thrombosis are thoroughly described,[9–11] but there are few reports about venous thrombosis after cardiac catheterizations in children. It was the purpose of our study to evaluate the prevalence of venous

Correspondence to: Ellen Ruud, Dept of Pediatrics, The National Hospital, 0027 Oslo, Norway. Tel: 0047 23 07 45 24; Fax: 0047 23 07 45 57; E-mail: ellen.ruud@rikshospitalet.no

Ellen Ruud receives financial support from the Norwegian Cancer Society

Accepted for publication 23 July 2002

thrombosis associated with procedures and equipment in general use for paediatric cardiac catheterizations. To our knowledge, this is the first study published that prospectively evaluates the potential association of femoral venous thrombosis with cardiac catheterization in children.

Material and methods

From March to November 2000, 68 children with congenital cardiac disease, consecutively admitted to the National Hospital in Norway for cardiac catheterizations, were invited to participate in the study. Because of refusal of participation, cancellation of catheterizations, or missed post-catheterization ultrasonography, 18 of these patients did not enter the study. Thus, finally, there were 50 children properly examined according to our protocol. We excluded children with bodyweight greater than 7 kg, both due to practical reasons and to achieve a more homogenous cohort, as discussed later.[12,13] Ongoing anticoagulation was another criterion for exclusion, but none of the invited children were on anticoagulation. The local ethics committee approved the study, which is in accordance with the Helsinki Declaration. Prior to inclusion, the patients and their parents received individualised oral and standardised written information, and inclusion required parental consent.

The enrolled children had a spectrum of congenital cardiac diseases, and both diagnostic and interventional catheterizations were studied (Table 1). All children had general anaesthesia during the procedure, and the catheterization technique was in accordance with general accepted principles.[7] Introduction sheaths (Terumo, Belgium) were used routinely during all catheterizations. Depending on body size, the standard size of sheaths in arterial position was 4 or 5 French, and sizes varied from 5 French in newborns to 7 French in adults for venous catheterization. The procedures were accomplished by use of standard fluid-filled catheters. An overview of the interventional procedures, sizes of sheaths, and body weight is presented in Table 2.

Heparin sulfate, 75 IU/kg, was given intravenously at the beginning of each arterial catheterization, and the dose was repeated every second hour during the procedure. Heparin sulfate was not used in standard venous catheterizations. Patients with a positive family history of thrombosis, or known thrombophilic alterations, were supposed to have heparin during venous catheterizations, but none of the enrolled children were classified in this manner. Exclusively venous catheterizations were performed in 26 children, while 24 children had combined venous and arterial catheterizations. In those undergoing left-sided procedures, about one half of the children, anticoagulation was the rule. The site of insertion of the catheters was mainly the right groin, in 82%, but nine children had punctures in both groins. Nonionic Omnipaque® 300 mg iod/ml (Nycomed Imaging AS,

Table 1. Diagnoses and interventions in current and previous catheterizations.

Group	Main diagnoses	n	Current interventions (n)	Previous interventions (n)
Left to right shunt	VSD	2	0	0
	PAD	12	10	1
	ASD	3	2	0
Pulmonary stenosis	Valvar PS	5	1	1
	TGA	2	0	1
VSD + RVOTO	Fallot	4	0	0
	DORV	3	1	0
	VSD + PS	3	0	1
Functionally univentricular heart	Ind.	11	2	2
Left sided obstructions	CoA	2	1	0
	AS	1	0	0
Miscellaneous	Ind.	2	0	0
Total number		50	18	6

Abbrevations: VSD: ventricular septal defect; PAD: patent arterial duct; ASD: atrial septal defect; PS: pulmonary stenosis; TGA: transposition of the great arteries; RVOTO: right ventricular outflow tract obstruction; DORV: double outlet of the right ventricle, Ind.: individual, CoA: coarctation of the aorta, AS: aortic stenosis

Table 2. Diagnoses, body weight and introducer sizes in interventional procedures.

Diagnosis and procedure	Body weight (kg)	Introducer size (F)	
		Venous	Arterial
ASD, Amplatzer device	11.6	11*	#
ASD, Amplatzer device	15.3	9	#
ASD, Amplatzer device	15.9	8	#
PAD, Amplatzer device	8.8	6	4
PAD, Amplatzer device	12	5	4
PAD, Amplatzer device	12.2	6	4
PAD, Amplatzer device	19.4	7	5
PAD, Amplatzer device	21	6	5
PAD, coil	9.7	5	4
PAD, coil	13.5	5	4
PAD, coil	15.5	5	4
PAD, coil	18.2	5	4
PAD, coil	22.9	6	5
Aorticopulmonary collateral, coil	30	5	#
PS, balloon dilation	8.3	9	#
PS, balloon dilation	16	7	#
PS, balloon dilation	49	10	#
CoA, balloon dilation	62.1	#	6

*A large sheath was required because a defect device had to be removed.
Abbreviations: ASD: atrial septal defect; PAD: patent arterial duct; PS: pulmonary stenosis; CoA: coarctation of the aorta

https://doi.org/10.1017/S1047951102000938 Published online by Cambridge University Press

Table 3. Patients with thrombophilia (n = 4) and borderline thrombophilia (n = 10).

	Thrombophilia-criteria	Number of positive patients	Number of borderline patients
Antithrombin activity	<75%	0	0
Protein C activity	<40–60%	0	1 (40-60%)
Protein S total activity	<40–60%	0	1 (40-60%)
Protein S free activity	<40–60%	0	7 (40-60%)
Lupus anticoagulants	Positive	0	0
Lipoprotein(a)	>300–400 mg/l	1	1 (300–400 mg/l)
Homocysteine	>15 µmol/l	0	0
Factor V Leiden*	Positive	3	0
G20210A-mutation	Positive	0	0

*Factor V Leiden includes activated protein C resistance

Oslo) was used as the contrast agent, and the average total dose per case was 3 to 5 ml/kg.

The groin vessels of each enrolled child were examined by ultrasonography the day before and the day after the procedure. One pediatric radiologist (SN) was dedicated to this task. Methods and criterions to diagnose thrombosis were discussed amongst the group of pediatric radiologists. The radiologist used an ATL HDI 3000 unit with a linear transducer of 5 to 10 MHz. The real-time observation was performed by use of grey-scale imaging and colour Doppler sonography. The vessels were examined in transverse and longitudinal planes for grey-scale evaluation and compression. Blood flow was observed on colour flow imaging. The radiologist focused on the area for vascular puncture, with the superficial femoral vein being followed for 5 cm in both directions. The compressibility of the femoral vessels, flow in the region of the vessel, and the exact size of any blood clots, were planned to be measured in cases of positive findings.

During catheterisation, blood samples for thrombophilic investigations were taken from 33 patients. Blood samples were randomly missed in 17 children due to poor communication between researchers and the staff of the catheterization room. Thrombophilic investigation included serum analyses for antithrombin, protein C, protein S, activated protein C resistance, Factor V Leiden Mutation, prothrombin G20210A mutation, lupus anticoagulants, homocysteine and lipoprotein(a). In a previous report, we described the methods used to analyse prothrombotic risk factors.[14] The criterions for classifications of thrombophilia are given in Table 3.

We used SPSS 9.0 for Windows for descriptive analyses, and the Fisher's exact test was the method to compare small groups of patients. A two-tailed p value of less than 0.05 was considered significant. Because of limited participants, the statistical power is low for all but effects of very large size, but the absence of positive findings for the main end-point made statistics simple.

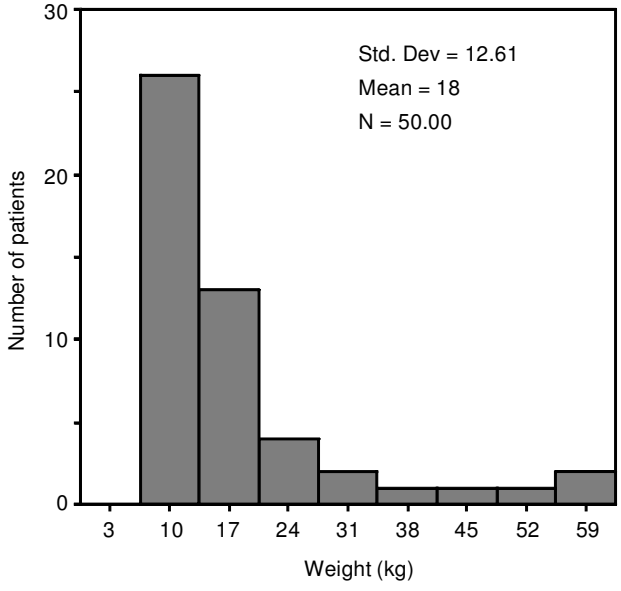

Figure 1.
The weight of the children at time of catheterization.

Results

We examined 50 children for thrombosis of the catheterized femoral vessels. There were 21 girls and 29 boys, their ages varying from 8 months to 16 years. The majority of children aged less than 3 years, and the median age was 34 months. Their body weight ranged from 7.7 to 61.2 kg, with a median of 13.6 kg (Fig. 1). A previous catheterization had been performed in 25 of the children (Fig. 2). Altogether, 53 previous venous procedures had been performed. The current catheterization was exclusively right-sided in one half, with the other half having combined left- and right-sided catheterizations. The diagnoses and performed interventions are presented in Tables 1 and 2.

https://doi.org/10.1017/S1047951102000938 Published online by Cambridge University Press

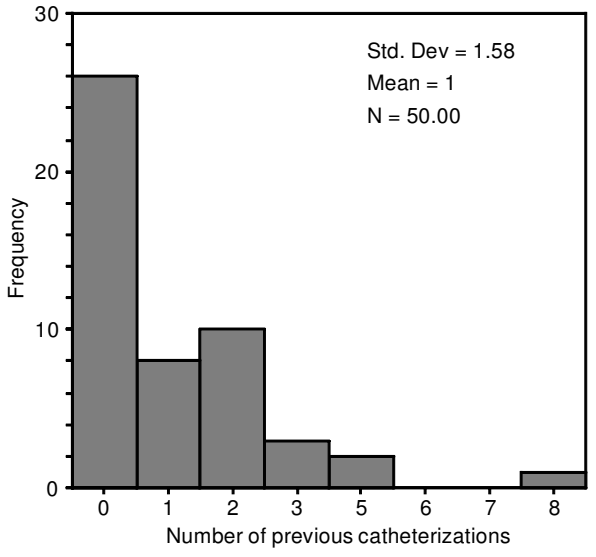

Figure 2.
Number of previous catheterizations.

In those studied, we did not find any events of venous thromboses, neither before nor after the current cardiac catheterization. Nor did we observe any arterial thromboses.

A hematoma was found in 22 children (44%), while 6 patients had edema (12%) revealed by ultrasonography following catheterization. The remaining 22 children (44%) had normal ultrasonography. There was no relationship between previous catheterizations and the presence of either hematomas or edema ($p = 1.0$/Fisher's exact test). There were no excessive bleeding episodes, and none of the enrolled patients had transfusions of blood products. There was no need of further anticoagulation, thrombolysis, or local surgical procedures in those studied, but one girl, aged 10 months, developed reversible cerebral embolic stroke after left-side cardiac catheterization.

Definite thrombophilia was found in 4 (12%) of the 33 children who had biochemical thrombophilic investigations (Table 2). None of these patients had multiple catheterizations, and only one received heparin because of left-sided catheterization. Borderline values were found in 10 children, but they were not defined as thrombophilic in accordance with international recommendations.[13] In spite of thrombophilia, none of our patients developed thrombosis in the femoral vessels. The girl who developed cerebral stroke, nonetheless, had slightly elevated levels of lipoprotein(a) at 324 mg/l.

Discussion

We have studied the potential for femoral venous thrombosis after cardiac catheterizations in children. In all 50 children catheterised, ultrasonographic examination of the femoral vessels proved negative, and there were no signs of thrombosis. Congenital predispositions to thrombosis were identified in 4 children, but the thrombophilic alterations did not contribute to formation of blood clots.

It is well documented that vascular complications depend on equipment, procedures and technique. The size of the catheter compared to the size of the patient is one of the main predictors of vascular complications in children.[8,10,15] In addition, interventional procedures are important contributors to thrombotic complications in children.[8,10,15] We believe that the availability of modern and well-designed equipment is one of the main reasons underlying the totally negative nature of the observations of vascular complications in our children.

Another important issue is anticoagulation. One half of our patients were anticoagulated because of the need for left-sided catheterization. After the first disappointing attempts with aspirin,[16] heparin has become the drug of choice for anticoagulation. From the 1970s, and with growing evidence, heparin sulfate has become recognised as an effective method for prevention of thrombosis in arterial catheterizations.[15,17,18] The dose and type of heparin are matters of discussion,[19] but our strategy for anticoagulation seemed safe and effective. We did not observe any episodes of major bleedings. Neither did we observe thrombosis in the group of children not undergoing anticoagulation.

None of the children we studied with thrombophilia developed thrombosis, but theoretically they are at a special risk. Nevertheless, only four of our cohort were considered at thrombophilic risk, and they did not experience multiple procedures. With regard to thrombophilia, our observations are too limited to draw significant conclusions. Evidence-based strategies for anticoagulation in cardiac catheterizations are desirable, nonetheless, for patients with and without thrombophilia.

Venous ultrasonography is the preferred noninvasive test to establish the diagnosis of venous thrombosis, and has a positive predictive value of 94%.[20] The method of venography, even more sensitive, might theoretically have detected some minor blood clots. The potential side effects, and practical problems, associated with venography were too significant to regard it as advantageous for our study.

The selection, and the small number, of participants represent limitations of the study. A loss of 18 children from the initial group of 68 invited to participate was also a disadvantage, but we do not think the study was biased significantly. A larger population would increase the possibility of positive findings, especially with regard to arterial blood clots.[8,15] Inclusion of younger children, with body weight less

https://doi.org/10.1017/S1047951102000938 Published online by Cambridge University Press

than 7 kg, might also have led to positive findings. Biochemical thrombophilic investigations were intended to be a part of the study, but the blood volume needed was considered to be too large for children weighing less than 7 kg. This is the main reason for the exclusion of neonates and small infants from our study. Risk factors are also different in neonates compared with older children. The body size of neonates is relatively smaller compared to the size of the equipment, and their immature coagulative systems predispose to thrombosis.[13] We did not, therefore, study our youngest infants, but we encourage others to perform similar studies on vascular complications in the neonatal period.

We observed hematoma and edema in more than half of the children, but these minor vascular complications were not related to thrombosis. The vessels at greatest risk for thrombosis during catheterizations are those that are punctured, and negative findings at the area of puncture can be taken as representative of the conditions of the adjacent vessels. There is a possibility that a thombosis may have occurred within the vessel at the day of catheterization, but had disappeared at the time of ultrasonography the day after. If such thromboses occurred, they would have no clinical implications for the patients.

Venous thromboses in association with cardiac catheterizations in children have been examined to a remarkably limited extent, and there are many unresolved questions. In 1979, Mathews et al.[21] reported a low prevalence of venous thrombosis in children who had multiple cardiac catheterizations. They found venous thrombosis in less than one-quarter of one percent of over 1000 patients. Their method for diagnosis of thrombosis was the detection of occluded veins by venography on follow-up cardiac catheterizations. The patients were not followed-up in a systematic manner. Very few publications, since the introduction of the technique, have reported a low number of venous thromboses following cardiac catheterizations in children.[22,23] On the other hand, a prospective study from 1985 described venous thrombosis in over half of the patients brought to autopsy with a right heart catheter in place in the pulmonary trunk.[24] New studies, with more participants from different age groups, are required fully to clarify the issue.

The outcome of venous thrombosis in children has received minimal attention. Recently, a venous post-thrombotic syndrome has been reported in a significant number of children, up to one-fifth, after a single event of thrombosis.[25,26] The syndrome may appear as late as ten years after the thrombotic event. To prevent late vascular complications, pediatric cardiologists dealing with cardiac catheterizations have to be aware of, and focus on, thrombotic complications in both the arterial and venous vessels.

In conclusion, ultrasonography did not disclose any evidence of femoral venous thrombosis in 50 children after 103 cardiac catheterizations. Thus, we consider our catheterization-procedures to be effective and safe, but recommend a continuing search for potential vascular complications to ensure the best quality of such future interventions in children.

Acknowledgement

Dr Ruud was supported by a grant from The Norwegian Cancer Society. We thank Prof. Brosstad for evaluation of the coagulation-investigations, and Prof. E Thaulow for his enthusiasm and support of the study. We are grateful to Geir Aamodt for his statistical guidance. We thank the nurses, laboratory technicians, and doctors at The National Hospital, with special thanks to the nurses of the Pediatric Cardiology Department.

References

1. Andrew M, Monagle PT, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton, London: B.C. Decker Inc, 2000.
2. Donnelly KM. Venous thromboembolic disease in the pediatric intensive care unit. Curr Opin Pediatr 1999; 11: 213–217.
3. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994; 83: 1251–1257.
4. Coon PD, Rychik J, Novello RT, Ro PS, Gaynor W, Spray L. Thrombus formation after the Fontan operation. Ann Thorac Surg 2001; 71: 1990–1994.
5. Petaja J, Lunfstrøm U, Sairanen H, Marttinen E, Griffin JH. Central venous thrombosis after cardiac operations in children. J Thorac Cardiovasc Surg 1996; 112: 883–889.
6. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 2001; 119: 344–370S.
7. Allen HD, Clark EB, Gutgesell HP, Driscoll DJ. Moss and Adams' Heart disease in infants, children and adolescents (6th edn). Philadelphia: Lippincott Williams & Wilkins, 2001.
8. Vitiello R, McCrindle BW, Nykanen D, Freedom RM, Benson LN. Complications associated with pediatric cardiac catheterization. J Am Coll Cardiol 1998; 32: 1433–1440.
9. Wessel DL, Keane JF, Fellows KE, Robichaud H, Lock JE. Fibrinolytic therapy for femoral arterial thrombosis after cardiac catheterization in infants and children. Am J Cardiol 1986; 58: 347–351.
10. Burrows PE, Benson LN, Babyn P, MacDonald C. Magnetic resonance imaging of the iliofemoral arteries after balloon dilation angioplasty of aortic arch obstructions in children. Circulation 1994; 90: 915–920.
11. Zenz W, Muntean W, Beitzke A, Zobel G, Riccabonna M, Gamillscheg A. Tissue plasminogen activator (alteplase) treatment for femoral artery thrombosis after cardiac catheterisation in infants and children. Br Heart J 1993; 70: 382–385.
12. Andrew M, Brooker LA. Blood component therapy in neonatal hemostatic disorders. Transf Med Rev 1995; Vol IX(3): 231–250.
13. Andrew M, Monagle PT, Brooker L. Developmental hemostasis: Relevance to thromboembolic complications in pediatric patients. In: Thromboembolic complications during infancy and childhood. Hamilton, London: B.C. Decker Inc, 2000: pp 5–46.

14. Ruud E, Holmstrøm H, Natvig S, Wesenberg F. Prevalence of thrombophilia and central venous catheter-associated neck vein thromboisi in 41 children with cancer – a prospective study. Med Pediatr Oncol 2002; 38: 405–410.
15. Saxena A, Gupta R, Kumar KR, Kothari SS, Wasir HS. Predictors of arterial thrombosis after diagnostic cardiac catheterizations in infants and children randomized to two heparin dosages. Cathet Cardiovasc Diagn 1997; 41: 400–403.
16. Freed MD, Rosenthal A, Fyler D. Attempts to reduce arterial thrombosis after cardiac catheterization in children: Use of percutaneous technique and aspirin. Am Heart J 1974; 87: 283–286.
17. Freed MD, Keane JF, Rosenthal A. The use of heparinization to prevent arterial thrombosis after percutaneous cardiac catheterizations in children. Circulation 1974; 50: 565–569.
18. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters. A meta-analysis of randomised controlled trials. Chest 1998; 113: 165–171.
19. Montalescot G, Cohen M. Low molecular weight heparins in the cardiac catheterization laboratory. J Thromb & Thrombol 1999; 7: 319–323.
20. Taylor A, Beveridge R, Barry M et al. Guidelines for the use of imaging techniques for the investigation of venous thromboembolic disease. J Emerg Med 1998; 16: 663–668.
21. Mathews RA, Park SC, Neches WH, Fricker FJ, Lenox CC, Zuberbuhler JR. Iliac venous thrombosis in infants and children after cardiac catheterizations. Cathet cardiovasc Diagn 1979; 5: 67–74.
22. Kuehl KS, Perry LW, Scott LP. Thrombosis of the inferior vena cava in patients with cyanotic congenital heart disease. J Pediatr 1971; 79: 430–435.
23. Wigger HJ, Bransilver BR, Blanc WA. Thromboses due to catheterization in infants and children. J Pediatr 1970; 76: 1–11.
24. Connors AF, Castele RJ, Farhat NZ, Tomashefski JF. Complications of right heart catheterization. A prospective autopsy study. Chest 1985; 88: 567–572.
25. Monagle P, Adams M, Mahoney M, et al. Outcome of pediatric thromboembolic disease: A report from the Canadian childhood thrombophilia registry. Ped Research 2000; 47: 763–766.
26. Hausler M, Hubner D, Delhaas T, Muhler EG. Long term complications of inferior vena cava thrombosis. Arch Dis Child 2001; 85: 228–233.

https://doi.org/10.1017/S1047951102000938 Published online by Cambridge University Press