SURGERY FOR CONGENITAL HEART DISEASE

CENTRAL VENOUS THROMBOSIS AFTER CARDIAC OPERATIONS IN CHILDREN

Jari Petäjä, MD^a
Ulla Lundström, MD^a
Heikki Sairanen, MD^a
Eino Marttinen, MD^a
John H. Griffin, PhD^b

To evaluate the incidence, mortality, late outcome, and cause of central venous thrombosis after pediatric heart operations and other operations performed with cardiopulmonary bypass, we identified patients with postoperative central venous thrombosis during a 10-year period at a single pediatric hospital. There had been 1591 open heart (with bypass) and 1086 closed heart (no bypass) procedures and 13 operations with cardiopulmonary bypass for extracardiac indications. There were 20 patients with central venous thrombosis, yielding incidences of 1.1% and 0.2% after cardiopulmonary bypass and after closed heart operations, respectively. When neonates were compared with older children (1 to 119 months of age) undergoing heart procedures, a tenfold increase (5.8% vs 0.6%) ($p < 0.001$) in the incidence of central venous thrombosis was observed. The mortality was eight of 20 (40%). Central venous thrombosis contributed to seven deaths and it was a direct cause of one death. Ten patients were reinvestigated 5 to 108 months after central venous thrombosis. The outcome of surgery was excellent in eight. Two had residual thrombosis, but this was not hemodynamically significant to the cardiorespiratory condition of the patients. During or preceding thrombosis, low levels of antithrombin III and/or protein C and high levels of the plasminogen activator inhibitor were observed in five of the patients. A congenital thrombotic risk factor, "resistance to activated protein C," was found in two of 12 tested patients with central venous thrombosis (17%). In conclusion, central venous thrombosis, especially in neonates, is an important cause of morbidity and mortality after cardiac operations. The cause is multifactorial, with contributions from multiple acquired thrombophilic coagulation abnormalities, and resistance to activated protein C may act as a risk factor for thrombosis already during neonatal period. (*J Thorac Cardiovasc Surg* 1996;112:883-9)

Thrombosis of central venous circulation (CVT) after pediatric cardiac operations is a life-threatening complication. The postoperative phase is associated with multiple independent situational risk

factors for thrombosis. These include central venous catheters, surgically traumatized blood vessels, altered hemodynamics, and multiple coagulation disturbances caused by cardiopulmonary bypass (CPB).¹⁻⁸ The role of congenital thrombophilic abnormalities in this context remains unknown. Deep venous catheters in children, irrespective of the child's specific disease, have been associated with thrombosis in 13% to 26% of cases.⁹⁻¹¹ Venous thrombi occurring late after Fontan operations are a recognized complication and demonstrate the significance of altered venous hemodynamics associated with thrombophilic coagulation abnormalities.^{12, 13} However, the specific clinical entity of CVT during the acute phase after pediatric cardiac operations has received little attention.^{9, 14}

This study was undertaken to analyze the inci-

From the Children's Hospital, University of Helsinki, Helsinki, Finland,^a and the Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, Calif.^b

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Address for reprints: Jari Petäjä, MD, Department of Molecular and Experimental Medicine, The Scripps Research Institute, 10666 North Torrey Pines Rd., SBR-5, La Jolla, CA 92037.

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Table 1. Characteristics of 20 patients with central venous thrombosis

Heart defects	Operation	Age	Thrombosis site	Treatment	Follow-up (mo)	Outcome
1. TGA	Switch	2 days	SVC, SCV, 4	SK	25	Good
2. IAA, VSD, ASD	PA banding*	1 mo	IV, 14	TE, W3	45	Excellent
3. TGA	Switch	2 days	SVC, 7	SK, W6	18	Excellent
4. TGA, PS	Switch	4 days	RA, 25	SK, W3	52	Moderate
5. TOF	Repair of TOF	7 mo	SCV, 11	SK, W6	73	Excellent
6. TGA, VSD, ASD	Switch	9 days	SVC, SCV, 5	W	20	Excellent
7. AVSD	Repair of AVSD	6 mo	RA, SVC, 18	TE, W1.5	52	Excellent
8. VSD	Closure of VSD	14 mo	RA, SVC, 13	W4	52	Excellent
9. TGA, VSD	Senning, closure of VSD	1 mo	IV, SVC, 12	W1.5	108	Excellent
10. TGA, VSD	Switch, closure of VSD	8 days	IV, 5	SK, W	2	—
11. Taussig-Bing	Switch, closure of VSD	14 days	SVC, 4	SK, W	2	—
12. Tracheal stenosis	End-to-end anastomosis	6 mo	SVC, 6	SK, W5	5	Excellent
13. TGA	Senning	16 days	IVC, SVC, aorta, 15	SK, W	—	Death, C
14. TGA, VSD	Switch, closure of VSD	5 days	SVC, 20	None	—	Death, Co
15. TGA	Senning	9 days	SVC, 4	SK, W	—	Death, Co
16. DILV, PA	Fontan*	119 mo	RA, SVC, 25	TE, SK, W	—	Death, Co
17. AVSD	Repair of AVSD	2 mo	RA, SVC, 27	None	—	Death, Co
18. VSD, ASD, CoA, Ao arch hypoplasia	PA banding*	12 days	SVC, 6	SK, W	—	Death, Co
19. HLHS, CoA	Hemi-Fontan*	6 mo	SVC, DS, 11	None	—	Death, Co
20. TA, TGA, CoA	TCPC*	56 mo	SVC, 19	SK	—	Death, Co†

Heart defects: ASD, Atrial septal defect; AVSD, atrioventricular septal defect; CoA, aortic coarctation; DILV, double-inlet left ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; VSD, ventricular septal defect; PA, pulmonary atresia; PS, pulmonary stenosis; TA, tricuspid atresia; TGA, transposition of great arteries; TOF, tetralogy of Fallot. Operations: PA banding, Banding of pulmonary artery; Switch, arterial switch; TCPC, total cavopulmonary connection. Thrombosis site: DS, Dural sinus; IV, innominate vein; IVC, inferior vena cava; RA, right atrium; SCV, subclavian vein; SVC, superior vena cava. The number after site of thrombosis denotes days between operation and diagnosis. Treatment: SK, streptokinase; TE, thrombectomy; W, number, warfarin, duration in months. The letter after death denotes estimated contribution of thrombosis to death. C, cause of; Co, contributing to death.

*Second to sixth cardiac operation.

†Patient died of intraventricular hemorrhage during SK treatment.

dence, mortality, and late outcome of CVT after pediatric heart operations. In addition, we wanted to test the hypothesis that the multiple operation-associated risk factors of thrombosis would trigger thrombogenesis, especially in patients with congenital deficiencies of physiologic anticoagulants, anti-thrombin III, protein C, and protein S, or with the recently described genetic abnormality of coagulation factor V that causes resistance to activated protein C and thereby is a risk factor for venous thrombosis.¹⁵⁻²⁰

Patients and methods

Patients. The patient population constituted the 1499 pediatric patients (1591 operations with CPB) who underwent cardiac operations and 975 (1086 operations) patients who had cardiac operations without CPB between January 1985 and December 1994 at our Children's Hospital. In addition to the 1591 CPBs for cardiac surgery, 13 operations performed with CPB for extracardiac indications were included. Patients in whom CVT developed (thrombosis of the subclavian veins, innominate veins, superior vena cava, right atrium, or inferior vena cava) during postoperative care were identified by search-

ing through hospital records by three approaches. Computer databases including all diagnoses at discharge, diagnoses during intensive care, and files of the radiology department containing radiologic diagnoses were searched. Twenty patients with CVT were found, and their indications and operations are presented in Table 1. Eight patients had died and 12 were alive. Two patients who received operations in November 1994 were not clinically evaluated for long-term prognosis in January 1995 when the study was completed. The remaining 10 patients were reinvestigated 5 to 108 months (45 ± 10 months, mean $\pm$ standard error of the mean [SEM]) after thrombosis. At reinvestigation, cardiologic evaluation with electrocardiograms, chest x-ray films, and echocardiograms were done. Whether the central veins were patent or still obstructed was evaluated by Doppler echocardiography. In one patient phlebography was also performed. The cardiologist classified the operative result into categories of excellent, good, moderate, and poor (Table 1). To investigate whether clinical parameters concerning the operation and CPB would differ between the patients with and without thrombosis, we compared data of the 20 patients with CVT and data of 73 consecutive infants operated on during 1992. These 73 patients (23 neonates and 50 older children) had been previously analyzed in detail for another study.²¹ None of the control patients had CVT. Neonates with CVT were compared

with control neonates, and older children with CVT were compared with control older children. There was no significant difference in the mean ages of the CVT and control groups. The analysis was also performed comparing the 73 control patients as a whole with the 20 patients with CVT. This did not affect the results to any significant degree (data not shown). A significant change in thrombolytic therapy took place during the study period. Until 1988, streptokinase (SK) whenever used was started with an infusion of 2000 U/kg per hour to a peripheral vein. From 1989, the SK dose has been 50 to 200 U/kg per hour for 1 to 8 days. When possible (whatever the dose), local infusion to the thrombus is first applied, then the indwelling catheter is removed, and the infusion is continued to a peripheral vein.

Coagulation studies. Blood for coagulation studies was collected after an overnight fast. Nine volumes of blood were mixed with 1 volume of 0.129 mol/L trisodium citrate. Plasma was immediately separated by centrifugation (1900 g for 20 minutes) and frozen to -70°C until assayed. Buffy coat was also harvested. Antithrombin III activity was measured with an ACL 300 R coagulometer (ACL Inc., Elk Grove Village, Ill.) and an IL test antithrombin III kit from Instrumentation Laboratory S.P.A., Milan, Italy. IL calibration plasma was used as a standard. Protein C activity was measured by means of a chromogenic method with S-2366 (Chromogenix AB, Mölndal, Sweden) as a substrate and protein C activator (American Diagnostica, Inc., Greenwich, Conn.). The functional activity of protein S was measured with an ACL 300 R coagulometer and an IL test protein S kit from Instrumentation Laboratory. A frozen plasma pool of 57 normal donors was taken as 100%. Plasminogen activator inhibitor (PAI) was measured with Coatest PAI (Chromogenix AB). Lupus anticoagulant was screened by mixing equal volumes of patient plasma and normal plasma pool with PTT-LA (lupus anticoagulant-sensitive APTT reagent) from Diagnostica Stago, Ansieres, France. Resistance to activated protein C was assessed by testing for G to A substitution at nucleotide position 1691 in the factor V gene causing the change of Arg 506 to Gln as described.²⁰ Antithrombin III measurements done during the thrombotic event were also used. For antithrombin III, protein C, and protein S, age-specific normal ranges were adopted from the literature.²² PAI was evaluated against adult reference values (upper limit of normal 23 AU/ml). Relevance of this was controlled by measuring PAI in eight control patients. These patients were four boys and four girls, aged from 5 months to 11 years, seen for routine follow-up after cardiac operations. In these children, PAI ranged from less than 5 AU/ml to 8.0 AU/ml (6.0 ± 0.4 AU/ml, mean $\pm$ SEM).

Statistical methods. The two-tailed Student's *t* test for independent samples and the χ^2 test were used for comparisons. A *p* value < 0.05 was regarded as significant.

Informed consent was obtained from the parents of each reinvestigated patient before entry into the study. The study protocol was approved by the ethics committee of the Children's Hospital, University Central Hospital of Helsinki.

Results

Incidence and mortality. The incidence of CVT was 1.1% (18/1604) after all operations (1591 cardiac procedures plus 13 extracardiac operations)

Table II. Incidence of CVT after cardiac operations

	No. of operations	Thrombosis	<i>p</i> Value
Open heart surgery, CPB	1591	17 (1.1%)	—
Open heart surgery, neonates excluded	1436	8 (0.6%)	—
Neonatal open heart surgery	155	9 (5.8%)	$< 0.001^*$
Closed heart surgery	1086	2 (0.2%)	$< 0.01^{\dagger}$

*The incidence for this group was compared with the incidence in open heart surgery after exclusion of neonates.

† The incidence for this group was compared with the incidence in open heart surgery without exclusion of neonates.

performed with CPB (2 of the 20 thrombi occurred after closed heart procedures). CVT occurred much more frequently in the neonates (Table II). The mortality associated with thrombosis was 40% (8/20), which is significantly higher than the general mortality after CPB in our patients who have not had thrombosis ($124/1571 = 8.3\%$) during the past 10 years ($p < 0.001$). For neonates the corresponding mortality figures were 40% with thrombosis and 15% without thrombosis ($p < 0.05$). Thrombosis was a direct cause of death in one patient and contributed to death in seven patients.

The thrombotic episode. Thrombosis was diagnosed at 4 to 27 days (12.6 ± 1.7 , mean $\pm$ SEM) after the operation. Thrombosis was diagnosed by phlebography in 12 patients. All these patients had symptoms of superior vena cava syndrome. Thrombosis was discovered accidentally by echocardiography in three and during reoperations in two patients who were free of symptoms of thrombosis. Three patients had thrombotic symptoms and the diagnosis was confirmed at autopsy. All patients had had deep central venous catheters for 2 to 20 days (7.6 ± 1.0 , mean $\pm$ SEM). In 15 patients the catheter was placed transcutaneously via an internal jugular vein, in four it was placed transcutaneously via a subclavian vein, and in one the catheter was placed in the innominate vein during the operation. Ten patients had thrombosis at the site of the catheter tip and/or along the catheter route. In the rest of the patients, the thrombi were more central than the location of the tip of the catheter at the time of diagnosis. For example, in six patients the catheter tip was in the internal jugular vein whereas the thrombosis was in the superior vena cava. Twelve patients had heparin in the fluids infused through the central venous catheters.

The hemodynamic condition of the patients between the operation and the diagnosis of CVT was

Table III. Coagulation studies in patients with CVT

	During thrombosis			At reinvestigation				APCR
	AT III (%)	PC (%)	PAI (AU/ml)	AT III (%)	PC (%)	PS (%)	PAI (AU/ml)	
1	—	—	—	89	59	99	<5	neg
2	—	—	—	93	66	79	7.4	neg
3	—	—	—	112	88	106	<5	neg
4	—	—	—	89	73	89	6.6	neg
5	—	—	—	101	74	90	6.6	neg
6	—	—	—	100	62	50*	8.7	pos
7	—	—	—	86	96	102	<5	neg
8	—	—	—	102	64	98	7.4	neg
9	—	—	—	104	95	101	7.7	neg
10	27*	19*	100†	40*	23	42	<5	neg
11	24*	15*	700†	52	30	71	22.5	neg
12	—	—	—	106	—	—	7.7	pos
13	36*	—	—	—	—	—	—	—
18	36*	—	—	—	—	—	—	—
20	20*	—	—	—	—	—	—	—

Numbering of the patients is the same as in Table I. APCR, Patients with resistance to activated protein C (APCR) who were positive (*pos*) were heterozygous for factor V gene mutation of R506Q.

*Decreased level of antithrombin III (AT III) activity, protein C (PC) activity, or free protein S (PS) activity against age specific normal range.¹⁶

†Increased level of PAI. In patients 10 and 11, the "at reinvestigation" values are those measured preoperatively and "during thrombosis" values are those measured postoperatively 2 to 3 days before CVT.

evaluated by taking into consideration the relevant clinical data including the arterial blood pressure, central venous pressure, and need for inotropic and volume support. As a result, 11 patients were considered to have normal postoperative hemodynamics, whereas five had moderately decreased and four severely decreased cardiac outputs.

CPB time, aortic clamping time, doses of heparin and protamine, degree of hypothermia, and postoperative chest tube drainage of the 20 patients were compared with those of a group of 73 infants operated on during 1992. Neonates with CVT ($n = 10$) were compared with control neonates ($n = 23$) and older children with CVT ($n = 10$) were compared with control older children ($n = 50$). Postoperative use of blood products was also analyzed. The only significant difference between the patients with thrombosis and the control patients was the postoperative use of fresh frozen plasma. For neonates, 50% of patients with CVT and 13% of control patients received fresh frozen plasma after the operation ($p < 0.05$). For older children, the figures were 40% and 8% ($p < 0.05$), respectively.

The treatment of thrombosis is shown in Table I. SK was used in 12 patients. Recanalization after SK was observed in six of 12 patients (50%). In two patients in whom SK was ineffective, recanalized venous circulation was later observed after warfarin treatment. SK resulted in two major bleeding complications (both after 1989 and with smaller SK

dose) and one minor (in 1988) (25%) bleeding complication. Two patients had intracranial hemorrhages. One of these was fatal, and the other caused hydrocephalus and spastic hemiplegia. The mortality was 42% (5/12) among SK-treated patients and 38% (3/8) in the patients who did not receive SK.

Reinvestigation. Individual follow-up times are shown in Table I. The general outcome of the operation in long-term survivors was regarded as excellent in eight patients, good in one patient, and moderate in one patient. None of the patients had cardiac insufficiency or cyanosis. The patient with a moderate outcome had undergone a reoperation because of anastomotic stenosis. The stenosis had developed to the homograft. The patient with a good outcome had mild pulmonary stenosis after an arterial switch operation. The venous circulation was unobstructed in eight patients. In the two patients with residual thrombosis (one confirmed with phlebography and one by echocardiography), dilated superficial veins were present but no significant sequelae to the general cardiopulmonary condition were seen.

Coagulation studies. The results of the coagulation studies are shown in Table III. All patients had normal thrombin time and no lupus anticoagulant was detected in any patient (data not shown). Protein C levels at reinvestigation were within age-specific normal ranges in every patient. Because it is

not known how protein C levels develop during childhood in subjects who are genetically deficient in protein C, the parents of three patients with low normal values (patients 1, 2, and 8) were investigated. Protein C values were within normal ranges in all of them. The protein S level in patient 6 was reinvestigated and was 68%; both his parents had normal protein S values, suggesting no protein S deficiency. In two of 12 patients, the factor V mutation causing resistance to activated protein C was found. Heterozygous resistance to activated protein C was also found in one of the parents in one family. In the other family both parents had normal findings, raising the possibility of a spontaneous mutation in the child.

Discussion

CVT is an important complication after pediatric heart surgery and showed an overall incidence of 1.1% in this study of 1591 consecutive cardiac operations. One major finding was significant clustering of CVT in the neonates, whose thrombotic risk was tenfold greater than that of older children. This may be partly explained by the fact that cardiac operations in neonates are technically more demanding, necessitating longer CPB times.²¹ Further, the hemostatic system of the neonate is immature and may be more prone to disturbances than that of older children.²²⁻²⁴ CVT is known to often be asymptomatic.⁹⁻¹¹ In the present study five of the 20 patients with CVT did not have symptoms of venous obstruction, and the diagnosis was made either by follow-up ultrasonography or accidentally at reoperation. Thus it is most probable that thrombus formation is even more common than reported in the present study.

CVT is life-threatening. In our series, eight of the 20 patients with CVT died. This is similar to the findings of Berman and associates,¹⁴ who reported in a retrospective study nine deaths in 18 patients with CVT after cardiac operations. In prospective studies of catheter-related thrombosis, fatalities were not reported.⁹⁻¹¹ This difference may be due to several reasons. First, early detection of thrombosis results in prompt treatment. Second, the only prospective study concerning cardiac operations did not include patients under 2 years of age,⁹ and six of our eight patients who died were neonates or small infants. Third, the surgically treated heart has a limited capacity to compensate for the hemodynamic deterioration caused by occluded venous return. Even neonates with CVT seem to have a good prognosis if the heart has not been operated on.^{10, 11}

In contrast to the high mortality associated with

CVT during the immediate postoperative phase, the long-term prognosis after CVT seemed good. In reinvestigation, only 20% of the patients had residual thrombosis and, even in these patients, the thrombosis was not a major determinant of the cardiorespiratory performance.

Central venous catheters are a widely recognized triggering factor of thrombus formation.^{9, 11} In the present study, the anatomic correlation between catheter and thrombus locations was evident; 10 patients had thrombosis at the site of the catheter tip and/or along the catheter route. Even in the rest of the patients the catheter and thrombi were close enough to each other to make a triggering effect from the catheter highly likely. Thus, in planning the strategy to decrease the incidence of CVT, evaluation of the practice with central venous catheters must have high priority. In our patient series it was obvious that using heparin in the infused solutions was not protective enough; 12 of 20 patients with CVT received heparin in their catheters. An attempt was made to recognize perioperative or postoperative clinical factors that would differ between patients who were to develop CVT compared with those with convalescence without thrombosis. The only factor identified was the more frequent postoperative use of fresh frozen plasma in patients with CVT. The retrospective setting of the study makes definitive conclusions about this finding impossible, but it seems likely that the increased use of fresh frozen plasma reflected unspecifically the deteriorated postoperative condition of the patients with CVT. Its logical to expect that low cardiac output for any reason would favor thrombus formation in the central veins and, conversely, thrombus formation would make it more difficult to maintain adequate cardiac output. In accordance with this, five patients with CVT had moderately diminished cardiac output and four had severely diminished cardiac output. Therefore, in clinical practice, a patient with postoperative low cardiac output should be considered to be at increased risk for CVT.

Thrombolytic therapy in neonates and infants is problematic. The published experience is limited and controlled studies are lacking.²⁵ We prefer to use low-dose SK with local infusion to the clot when possible.²⁶ Even with this approach, intraventricular hemorrhage was observed in two of 12 (17%) patients treated with SK. Furthermore, SK resulted in a recanalization rate of only 50% and could not be shown to reduce the high mortality. Clearly, future studies specifically designed for neonates and infants are needed to compare different thrombolytic

agents, their dosage, and their route of administration in this setting.

Cardiac surgery causes multiple transient coagulation abnormalities. Among these are decreases of antithrombin III and protein C.^{1,5} Acquired deficiencies of antithrombin III and protein C can cause thrombosis during the neonatal period.^{23,24} Low levels of protein C after pediatric liver transplantation have been associated with the development of portal vein thrombosis.²⁷ Also, low protein C has been reported to increase the thrombotic risk after Fontan operations.¹² In the present study, coagulation data preceding or coinciding with CVT were available in five patients. In every one of these subjects, the observed antithrombin III level was consistent with an acquired deficiency state. Especially interesting were the two patients (numbers 10 and 11) in whom abnormally low antithrombin III and protein C associated with high PAI preceded the appearance of CVT. Although it is logical to suspect that any combination of thrombophilic coagulation abnormalities might be more dangerous than any single defect alone, interaction between elevated PAI and low protein C may be of special theoretical interest. Activation of protein C has been shown *in vivo* to be an important anticoagulant mechanism after coronary artery occlusion.^{28,29} Activated protein C probably acts both as an anticoagulant by degrading activated forms of clotting factors VIII and V and as a profibrinolytic agent by inhibiting PAI.³⁰ Thus a low protein C level, in addition to decreasing plasma anticoagulant potential, might potentiate the thrombogenicity of increased levels of PAI. We suspect that several acquired thrombogenic coagulation abnormalities significantly contributed to CVT after cardiac surgery. This is an important consideration inasmuch as substitution therapy for both antithrombin III and protein C is possible, depending on the indications.

In performing this study, we hypothesized that children with congenital predisposition to venous thrombosis would be especially prone to CVT after heart operations. Concerning antithrombin III, protein C, and protein S deficiencies, the study was unrewarding in the sense that none of the patients with CVT apparently had these hereditary conditions. On the other hand, the combined population prevalence of either antithrombin III or protein C deficiencies might be as high as 0.2% to 0.8%.³¹⁻³³ However, it must be noted that the figures for the Finnish general population are unknown. Our patient series probably included several patients with

these deficiencies without subsequent clinical CVT. Therefore preoperative screening for deficiencies of antithrombin III, protein C, and protein S is not indicated. In contrast, it appears that resistance to activated protein C may act as a risk factor for thrombosis during cardiac surgery in infancy. Two of 12 patients (17%) were heterozygous for the factor V mutation causing resistance to activated protein C, with the prevalence of this abnormality being 4% in the asymptomatic Finnish population.³⁴ Resistance to activated protein C can easily and economically be diagnosed by definitive deoxyribonucleic acid techniques. Knowing that a patient has an increased risk for postoperative CVT should affect thrombosis prophylaxis and may decrease the incidence of CVT. Therefore a prospective study is indicated to establish the value of preoperative screening of resistance to activated protein C in patients with congenital heart defects.

Acquired defects in the physiologic anticoagulants protein C and antithrombin III were associated with CVT, but no congenital deficiencies of these proteins were found. This is probably due to the fact that acquired defects are overwhelmingly common compared with the congenital ones and, probably more important, several acquired defects may occur at the same time. This phenomenon may be especially prominent in neonates. We have recently observed that 90% and 60% of neonates show, respectively, abnormally low antithrombin III and protein C levels on the second postoperative day after CPB.³⁵

The strategy to decrease the morbidity and mortality associated with CVT must take into account the multifactorial pathogenesis of thrombosis after cardiac operations. We suggest the following measures. First, especially intensive interventions are needed in neonates. Second, the trauma to the central veins during operations must be minimized. Third, central venous catheters must be removed as early as possible. (It is our aim to remove the catheters during the first 2 to 3 postoperative days.) Fourth, follow-up with echocardiography should be intensified in patients who need the deep vein catheters for longer periods. Fifth, preoperative screening for resistance to activated protein C may prove useful. Sixth, the levels of antithrombin III, protein C, and PAI should be monitored after the operation, and substitution therapy for the observed deficiencies should be considered.

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