Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion

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Objective: The risk for thrombosis is increased after the Fontan operation. It is unknown whether children with univentricular heart disease have an intrinsic coagulation anomaly or acquire a defect in coagulation during the course of the staged repair. This prospective, longitudinal study evaluated changes in coagulation profiles in a cohort of patients with hypoplastic left heart syndrome from stage I palliation through completion of the Fontan operation.

Methods: Thirty-seven patients with hypoplastic left heart syndrome were enrolled prospectively, and the concentration of factors II, V, VII, VIII, IX, X, proteins C and S, fibrinogen, antithrombin, serum albumin, and liver enzymes were measured before stage I palliation (mean age 4 ± 2 days), before bidirectional Glenn (mean age 5.9 ± 1.8 months), before the Fontan procedure (mean age 27.1 ± 6.6 months), and after the Fontan procedure (mean age 49 ± 17.6months). Healthy children were used as age-matched controls for coagulation factors. Demographic, hemodynamic variables, and elapsed time after the Fontan procedure were evaluated as possible predictors of coagulation abnormalities.

Results: Significantly lower levels of both procoagulation and anticoagulation factors were demonstrated through to completion of the Fontan procedure. After the Fontan procedure, there was a significantly higher factor VIII level ($P < .005$) but no correlation with hemodynamic variables or liver function.

Conclusion: This longitudinal study in patients with identical cardiac disease and staged surgical procedures confirms the increase in factor VIII level after the Fontan procedure. This is an acquired defect, and although the cause remains to be determined, monitoring factor VIII levels after the Fontan operation could indicate a subset of patients at risk for thrombosis.

CHD

As early outcome after the Fontan operation continues to improve, the focus has changed from survival to long-term morbidity, prognosis, and quality of life.[1-3] A major factor contributing to both early and late morbidity and mortality after the Fontan operation is the potential for thromboembolic complications.[1,4,5] The incidence of thromboembolic events in patients with Fontan physiology is uncertain but has been reported to be as high as 20% to 33%.[4, 6-9] The etiology is not completely understood and is likely to be multifactorial, including the nature of the Fontan circulation with elevated central venous pressure, low flow with possible stasis through the atrial baffle and pulmonary circulation, atrial dysrhythmias, ventricular dysfunction, hepatic dysfunction, and altered resting venous tone. It has also been demonstrated that lower levels of both procoagulant and anticoagulant factors precede the Fontan operation, and it has been speculated that a ''functional balance'' may exist that reduces the risk for thrombosis during the earlier staged palliation for single ventricle cardiac defects.[10,11]

A possible hypercoagulable state after the Fontan procedure predisposing to thrombus formation has been postulated, secondary to low levels of the naturally occurring anticoagulants protein C, protein S, and antithrombin,[12,13] and elevation of factor VIII.[14] Interpretation of these studies is limited because they included heterogeneous patient populations, often with various modifications of the Fontan operation, and at a variable point in time after the Fontan procedure.

The purpose of this single-center, prospective, longitudinal study was to follow up a homogeneous cohort of children with hypoplastic left heart syndrome (HLHS) undergoing identical staged procedures from the Norwood operation to after completion of the Fontan operation to determine whether there may be an intrinsic or acquired anomaly in the coagulation profile causing hypercoagulability in these patients.

METHODS

After institutional review board approval and informed parental consent had been obtained, 37 neonates with the diagnosis HLHS were enrolled in this single-center prospective study. Patients were followed up from 1998 to

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Received for publication April 11, 2008; revisions received July 28, 2008; accepted for publication Sept 11, 2008.

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J Thorac Cardiovasc Surg 2009;137:934-41
0022-5223/$36.00

doi:10.1016/j.jtcvs.2008.09.031

Abbreviations and Acronyms
BDG = bidirectional Glenn
HLHS = hypoplastic left heart syndrome

2006; patients were excluded if they had other known congenital abnormalities or syndromes and had pre-existing or known family history of hematologic disorder or coagulopathy.

All patients underwent identical staged surgical procedures. Neonates underwent initial stage I palliation with a Norwood procedure using a 3.5-mm polytetrafluoroethylene (Gore-Tex; W. L Gore & Associates, Inc, Flagstaff, Ariz) right modified Blalock–Taussig shunt. The second stage operation was a bidirectional Glenn cavopulmonary connection (BDG) performed on cardiopulmonary bypass. The Fontan procedure consisted of a fenestrated lateral tunnel, cavo–cavo–pulmonary connection, performed with a 0.4-mm thickness polytetrafluoroethylene cardiovascular patch and fenestrated with a 4-mm punch hole.

Postoperative and interstage anticoagulation management was at the discretion of each patient's physician. Blood samples from all patients (7 mL) were obtained the day of the operation before each stage (stage I, BDG, and Fontan) after induction of general anesthesia and in the catheterization laboratory after catheter placement for the post-Fontan evaluation. Those patients receiving aspirin and/or warfarin sodium (Coumadin) as prophylaxis for thrombosis had these drugs withheld for an appropriate time period before procedures. Hemoglobin, hematocrit, platelet count, prothrombin time, and activated partial prothrombin time were measured immediately, and this information was available to clinicians caring for the patients. The remaining plasma was stored at –70°C in 200-μL aliquots for batch analysis of the other coagulation assays; this information was not available to clinicians during the admission of each patient. The circulating anticoagulant factors measured were protein C, protein S, and antithrombin; the procoagulant factors measured were II, V, VII, VIII, IX, X, and fibrinogen. All samples were analyzed by identical techniques, in the same laboratory, and by the same technician (R.A.C.); the techniques for analysis along with coefficients of variation have been reported elsewhere.[10,11,14]

To determine whether the increase in factor VIII levels observed after the Fontan operation could have been due to an acute inflammatory response, we measured the level of von Willebrand factor post hoc in the available remaining frozen serum in 11 of the Fontan patients. An increase in both the factor VIII and von Willebrand factor levels would be expected in an acute phase response. von Willebrand factor level was measured by a immunoturbidimetric assay of von Willebrand factor (STA-Liatest VWF:Ag kit; Diagnostica Stago, Asnieres France; coefficients of variation, 1.9% and 2.7%).

Because altered hepatic dysfunction can contribute to coagulation factor abnormalities, serum alkaline phosphatase, gamma-glutamyl transferase, alanine transaminase, aspartate transaminase, total bilirubin, albumin, and total protein were measured in all patients and compared with normal values for our laboratory.

Hemodynamic Variables

Ventricular, atrioventricular valve, and semilunar valve function was assessed by 2-dimensional and Doppler echocardiographic examination for all patients before data sampling. Cardiac catheterization was routinely performed before the BDG and the fenestrated Fontan procedures, but not before the Norwood procedure in neonates. Catheterization data were also available for all 20 of the post-Fontan patients. Data obtained at the time of cardiac catheterization included superior vena cava oxygen saturation, the ratio of pulmonary to systemic blood flow, superior vena cava pressure, pulmonary artery pressure, pulmonary vascular resistance, and systemic ventricular end-diastolic pressure. The time after the Fontan operation was also examined as a potential variable contributing to coagulation abnormalities.

Age-Matched Control Coagulation Parameters

Developmental hemostasis, or maturation of the coagulation system in infants and children, is widely recognized.[15,16] To establish age-matched reference ranges, we obtained informed written parental consent to draw blood samples for coagulation factor assays in healthy infants and children undergoing minor day surgery. We used published control values for neonates because of a state of Massachusetts requirement limiting research in newborn subjects unless potential direct benefit can be demonstrated by participating in a clinical study. The available normative ranges for neonates and infants vary according to the techniques and reagents used to measure coagulation factor levels,[15,16] and we chose to use the reference range described by Andrew and associates[16] because it provided values (mean age 2 days) with similar age distributions to our patients (mean age 2 days). Beyond neonates, there were a total of 90 control subjects, 30 for each age-matched control group. The mean ages for the groups were 7.8 $\pm$ 2.2 months, 26 $\pm$ 12 months, and 8.3 $\pm$ 2.9 years.

A total of 1.8 mL of blood was taken from each control patient, and after centrifuge, the plasma was stored at –70°C for subsequent batch analyses in the same laboratory using the techniques as described above. Normal ranges in these age-matched control groups were based on the empirical 95% confidence intervals and have been described in a previous manuscript.[17]

Because of technical problems, we were unable to obtain complete samples to measure prothrombin time and activated partial thromboplastin time in all of the control patients, and to use a consistent reference range we chose the range of normal for age as described by Andrew and colleagues.[16]

Statistical Analysis

Factor levels at each stage were compared with values from control patients by the 2-sample Student t test after verifying normality. Univariate and multivariable logistic regression using maximum likelihood estimation was performed to identify potential predictors of a coagulation abnormality. Variables evaluated included age, weight, gender, systemic ventricular end-diastolic pressure, superior vena cava oxygen saturation, superior vena cava pressure, ratio of pulmonary to systemic blood flow, pulmonary artery pressure, pulmonary vascular resistance, ventricular function, atrioventricular valve regurgitation, and time after the Fontan operation. In comparing coagulation factors between patients and age-matched controls, we used a 2-tailed Bonferroni-adjusted P value of .005 as the criterion for statistical significance inasmuch as there were 10 variables ($P = .05/10 = .005$) provided this conservative α-level was chosen to minimize the risk of type I (false positive) errors.[18,19] For those patients in whom we were able to obtain complete coagulation factor levels at each study point, a repeated-measures linear mixed model, with compound symmetry to model the covariance, was applied to assess changes over time in coagulation variables from stage I through post-Fontan completion. Statistical analysis was conducted with the SPSS software package (version 6.0; SPSS Inc, Chicago, Ill).

RESULTS

The study population with the mean age and weight at the time of each procedure is shown in Figure 1. Coagulation factor analysis could not be performed in 1 of the patients at the time of stage I, in 1 BDG patient, and in 1 post-Fontan patient because of sampling error. In addition to death (n = 5) or heart transplantation (n = 1), 11 patients were lost to follow-up because they were out-of-state referrals who had undergone the stage I palliation and/or BDG at our institution and subsequent procedures elsewhere. Post-Fontan patients were followed up at a mean of 27 $\pm$ 17.8 months after