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High incidence of catheter-associated venous thromboembolic events in patients with long gap esophageal atresia treated with the Foker process ☆

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ABSTRACT

Purpose: To determine the incidence of catheter-associated venous thromboembolic events (VTE) in long gap esophageal atresia (LGEA) patients treated at Boston Children's Hospital (BCH) and to identify possible risk factors associated with their development.
Methods: We performed a retrospective analysis of LGEA patients from 2005 to 2012. Symptomatic VTEs with radiographic confirmation were defined as events. Potential risk factors were assessed by univariate analysis and multivariate logistic regression. Covariates included age, weight, initial gap length, cumulative days of pharmacologic paralysis and paralytic episodes, number and type of central venous catheters (CVCs), and number of operations.
Results: Forty-four LGEA patients were identified. The incidence of CVC associated VTE was 34%. Univariate analysis identified age at Foker 1 ($P = .03$), paralysis duration ($P = .01$), episodes of paralysis ($P = .001$), cumulative number of CVC ($P = .007$) and length of stay ($P = .03$) as significant. Multivariate logistic regression identified the number of paralytic episodes as the only significant independent risk factor for VTE ($P < .0001$).
Conclusions: The incidence of symptomatic VTE was 34%, significantly higher than the VTE incidence of 4.5% reported for our other hospitalized children. These data have led to multidisciplinary discussions regarding thromboprophylaxis and development of a consensus-driven protocol. Since the initiation of this protocol, no VTEs have been identified.

The incidence of symptomatic pediatric venous thromboembolic events (VTE) is increasing within pediatric tertiary care facilities. Analysis of VTE rates among hospitalized children reveals a 70% increase in annual rate of VTE from 34 to 58 cases per 10,000 hospital admissions over a 7-year period [1]. It is postulated that the dramatic increase in pediatric VTE at tertiary care centers may be caused by increased exposure to prothrombotic risk factors as a direct consequence of more intensive medical therapy that disrupts vascular and hemostatic health [2]. Of children with VTE, 80% to 90% have one or more underlying risk factor such as malignancy, congenital heart disease or presence of central venous catheters (CVCs) [1,2]. For example, CVCs are a widely accepted risk factor for VTE with the rate of catheter-associated VTE at our institution reported at 4.5% [3].

Treatment of esophageal atresia (EA), a rare congenital anomaly, frequently requires utilization of interventions that may expose patients to prothrombotic risks. [4,5] As early as the 1950s, Dr. Robert Gross proposed a classification scheme based on anatomical variants of esophageal atresia with and without a tracheoesophageal fistula [6]. A subgroup of patients with EA have long gap esophageal atresia (LGEA), which is often defined by a distance between the upper and a lower atretic esophageal segment of greater than three vertebral bodies [7]. This distance ultimately delineates the timing and ease of repair. Foker et al. described the utilization of external traction sutures to promote in vivo growth through tension-induced natural lengthening, and subsequent delayed primary repair, potentially avoiding the need for interpositions [7]. During the Foker process, necessary adjunct therapies may include mechanical ventilation, pharmacological paralysis, sedation and analgesia, and utilization of CVCs to facilitate medication and parenteral nutrition (PN) administration.

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As a referral center for LGEA, Boston Children's Hospital (BCH) provides a unique environment to evaluate the potential effects of exposure to prothrombotic interventions and the development of VTE. We aim to define the incidence of CVC-associated VTE and effects of patient and treatment characteristics on VTE risk in this select, surgical pediatric population.

1. Methods

Following the approval of our institutional review board (IRB no. P00005612), we retrospectively reviewed the medical records of all patients managed utilizing the Foker tension-induced natural growth procedure for LGEA from January 1, 2005 to June 30, 2012 at our institution. Esophageal atresia (EA) patients with or without tracheoesophageal fistula (TEF) were considered to have LGEA when primary anastomosis was not possible because of length of the gap between the upper and lower esophageal segments [8]. All other forms of EA were excluded.

VTEs were defined as incident events when a venous thrombotic event occurred and was clinically symptomatic. Symptomatic VTEs were further defined as events which included unilateral swelling and color changes of the affected limb, as well as those which raised clinical concern by healthcare providers prompting diagnostic imaging. Routine screening imaging for identification of nonsymptomatic VTE was not conducted. LGEA patients who developed a symptomatic VTE were compared to those LGEA patients who did not develop a VTE. Arterial thrombotic events were excluded and only occurred in one patient following a radial arterial line placement (e.g. radial artery thrombosis).

A retrospective review of medical records evaluated the following preadmission variables: estimated gestational age, initial gap length, age, gender, history of congenital heart disease, prior thrombosis, congenital thrombophilia and family history of thrombosis. Details of each patient's treatment course included weight at time of Foker I process; number of surgeries; and, stage of Foker process when VTEs were diagnosed. Review of medical records also gathered details of ICU therapy including total number and location of indwelling CVCs, number of cumulative days of paralysis, number of episodes of paralysis, total length of stay (LOS) within the ICU, and diagnostic method of VTE (ultrasound, venogram) detection. Surgical and medical therapies, as well as overall thrombotic-related morbidities and thrombotic-related mortalities within the study time period were also documented.

Variables were evaluated as potential risk factors for development of VTEs by univariate analysis. Those statistically significant univariate variables were then evaluated by multivariate Cox logistic regression. Independent risk factors for the development of VTEs were identified by multivariate Cox logistic regression. Statistical analysis was performed using SPSS (version 19.0, SPSS Inc./IBM, Chicago, IL). Two-tailed values of $P < .05$ were considered statistically significant.

2. Results

A retrospective review of medical records identified a total of 44 patients who met the above stated diagnostic criteria for LGEA. The incidence of symptomatic catheter-associated VTE was 34% in this population ($n = 15/44$). Baseline characteristics, surgical and critical care variables are displayed in Table 1. All symptomatic VTEs were detected by health care professionals, with the most common finding being unilateral extremity swelling. Clinically detected VTEs were confirmed with an ultrasonography ($n = 10$), venogram ($n = 2$), or a diagnostic catheterization ($n = 1$). With the exception of two VTEs, all others were associated with the venous catheter. One patient developed a subsequent pulmonary embolism (PE), while the other patient developed superior cava syndrome (SVC) secondary to thrombosis extension.

LGEA patients who developed a symptomatic, catheter-related VTE were compared to LGEA patients who did not develop a symptomatic, catheter-related VTE. Median hospital length of stay at time of VTE diagnosis was 29.5 days (range 3–69 days). Median number of central venous catheters (CVCs) or peripheral inserted central catheters (PICCs) placed was 4 catheters per patient (range 1–9 catheters) in those with symptomatic VTE versus 2 catheters (range 1–7 catheters) in those patients without VTE during duration of overall treatment. Seventy-three percent ($n = 11/15$) of subjects diagnosed with a symptomatic VTE had exposure to both a CVC and PICC during hospitalization. Among subjects who had exposure to only one type of venous catheter during the hospitalization, 22% ($n = 4/18$) of subjects with a PICC developed VTEs while no subjects with a CVC alone ($n = 0/4$) developed VTEs.

The median number of operative procedures prior to VTE detection was 11 (range 3–25) in patients with symptomatic VTE versus 8 (range 2–28) in those who did not develop VTE. The median number of days of pharmacologic paralysis prior to diagnosis of VTE was 15 days (range 1–35). All catheter-related VTEs were diagnosed during the Foker stage I. The median ICU length of stay was 19 weeks

Table 1
Baseline analysis of factors associated with VTE in patients with LGEA.

Variable	VTE detected ($n = 15$)	No VTE detected ($n = 29$)	P value
Gender			1.00
Female	8 (53%)	15 (52%)	
Male	7 (47%)	14 (48%)	
Congenital heart disease	4 (27%)	17 (47%)	.21
Family history of thrombosis	2 (13%)	3 (10%)	1.00
Age at Foker 1 (months)	7 (1–22)	4 (1–48)	.03*
Weight at Foker 1 (kg)	7 (3–11.2)	4.7 (3.2–13.0)	.29
Initial gap length (cm)	5 (1.6–9)	4.5 (1.4–7.3)	.56
Median number of total paralysis days	41 (8–133)	21 (2–73)	.01*
Number of episodes of paralysis	4 (1–13)	1 (1–5)	<.001*
More than 2 episodes of paralysis	10 (67%)	4 (14%)	<.001*
Median number of lines	4 (1–9)	2 (1–7)	.007*
Type of line utilized during Foker 1			.06
PICC	4 (27%)	14 (48%)	
CVC	0 (0%)	4 (14%)	
Both	11 (73%)	11 (38%)	
Median number of Operations	8 (3–25)	9 (2–28)	.21
Length of stay in the ICU (weeks)	19 (8–51)	13 (4–34)	.03*

cm, centimeters; kg, kilograms; CVC, central venous catheters; PICC, peripheral inserted central catheter; ICU, intensive care unit.
* Statistically significant univariate predictor of VTE.

(range 8–51 weeks) for patients with symptomatic VTE versus 13 weeks (range 4–34 weeks) for patients without symptomatic VTE.

Univariate analysis identified age at Foker stage I ($P = .03$), duration of paralysis ($P = .01$), cumulative episodes of paralysis ($P = .001$), cumulative number of CVC ($P = .007$) and ICU length of stay ($P = .03$) as a significant risk factors for a VTE. Multivariate logistic regression analysis presented in Table 2 confirmed that total number of episodes of paralysis was the only independent risk factor for VTE, with patients having more than two episodes, having an estimated risk 12 times higher than those with one or two episodes (odds ratio: 12.5, 95% CI: 2.8–56.3, $P < .001$). The multivariate analysis indicated that patient age ($P = .72$), number of paralysis days ($P = .39$), number of lines ($P = .23$), and length of stay in ICU ($P = .17$) were not significant independent factors associated with development of VTE.

There were no thrombotic-related mortalities among patients during the study time period. Treatment of symptomatic, catheter-related VTE consisted of low-molecular-weight heparin (LMWH), which was not administered immediately prior to or postinterventional procedures. Two patients also required catheter-directed thrombolytic therapy for more extensive clot burden. Complications occurred in three patients during the study period including one case of a pulmonary embolism; one case of an unplanned thoracotomy for hemothorax, which developed while the patient was treated with anticoagulation; and, one case of superior cava syndrome resulting from thrombosis extension.

3. Discussion

We report an incidence of symptomatic, catheter-associated VTE of 34% in this small series of LGEA patients. This is 58-fold greater than the rate of VTE in pediatric inpatients (0.58%) [1] and 8-fold higher than the catheter-associated VTE rate among critically ill patients at our institution who did not receive thromboprophylaxis (4.5%) [3]. While the incidence of thromboembolic complications is greater in adults, both awareness of and detection of these events in pediatric inpatients are rising. Although adult inpatients routinely receive thromboprophylaxis unless contraindicated, hospitalized children may not be considered for these strategies because of the perceived low incidence of thrombosis.

Surveys of thromboprophylaxis prescribing practice for pediatric patients revealed heterogeneity among prescribers [9]. Our results highlight one population of pediatric inpatients deserving of thromboprophylaxis and have raised questions of how to risk stratify pediatric patients for VTE prevention. While the rate of VTE in children is lower than in adults, the rate of bleeding complications is also lower, perhaps improving the margin of safety of prophylactic anticoagulation in children. Of course, thromboprophylaxis does not solely mean pharmacologic anticoagulation. Mechanical devices, physical therapy, minimization of paralysis, adequate hydration and nutrition are important components as well.

CVCs facilitate medical care by allowing for intravenous medication delivery, PN administration and blood sampling via stable vascular access. In our study cohort, patients required prolonged use of CVCs for medication and PN administration. While enteral feeding is the preferred method of nutrition, this was not always feasible in the setting of multiple procedures, gastric dysmotility and esophageal tissue discontinuity. Utilization of CVCs also portends acquisition of prothrombotic risk via disruption of the endothelium and influence on the rate of adjacent blood flow. Most CVC-related VTE events in our series occurred in subjects exposed to both a PICC and CVC during the hospitalization. While no VTE events occurred in those subjects exposed to a CVC alone, this is likely limited by the small sample size and may reflect an overall lower patient morbidity when only one catheter was necessary during the hospitalization. Variable incidence rates of VTE associated with PICC or CVC have been reported and are not conclusive to suggest that one catheter type is safer than the other. [9–13] The use of CVCs, exposure to pharmacologic paralysis, and ICU length of stay during LGEA therapy utilizing the Foker process, correlated with increased risk of VTE.

In our series, use of pharmacologic paralysis was significantly correlated with VTE incidence in both univariate and multivariate analyses. Paralytic episodes remained the only predictor of VTE after multivariate analysis. This may be a surrogate for complicated repair with numerous procedures (e.g. initial esophageal anastomosis, correction of esophageal stricture, repair of esophageal leaks) or unexpected need to reinstitute paralysis. Immobilization is an established risk factor for VTE, though it is rarely sufficient alone to cause VTE in children. During the Foker process, patients may require multiple episodes of pharmacologic paralysis interrupted by periods of unrestricted movement to facilitate growth of esophageal tissue.

Utilization of paralysis necessitates both the use of mechanical ventilation and central venous access, which may serve to further increase thrombotic risk. The association of paralysis with catheter-associated VTE highlights the synergy of multiple risk factors to produce VTE in pediatric inpatients. Avoidance of pharmacologic paralysis is not feasible in all patients because of risk of esophageal disruption during tissue growth induction. This small series highlights paralysis as a risk factor for VTE and suggests that immobility be minimized to the extent possible and that use of thromboprophylaxis be considered among such patients.

Limitations of our study include its retrospective nature, relatively small sample size and data collection at a single institution. Other risk factors for VTE (e.g. inherited thrombophilia) were not routinely assessed. The small sample size affects our statistical power to identify or rank contributors to thrombotic risk in this study.

Table 2
Independent multivariate predictors of VTE in long gap esophageal atresia patients.

Variable	Odds ratio	95% CI	*P*
Age at Foker I (months)	1.00	0.90–1.11	.72
Number of paralysis days	1.01	0.96–1.05	.39
More than 2 episodes of paralysis	12.5	2.8–56.3	<.001*
Number of CVC or PICC lines	1.22	0.77–1.94	.23
Length of stay in ICU (weeks)	1.05	0.98–1.14	.17

CVC, central venous catheter; PICC, peripheral inserted central catheter; ICU, intensive care unit; CI, confidence interval.
* Statistically significant independent predictor of VTE.

4. Future studies and conclusion

Our study identifies a specific cohort of pediatric patients who display a higher incidence of VTEs relative to patients admitted to pediatric tertiary care facilities and critically ill children with CVCs. We conclude that exposure to prothrombotic factors during the Foker process, including CVC and altered mobility may contribute to this increased VTE incidence. Further prospective studies are necessary to determine the effects of modifying prothrombotic factors as well as to develop specific guidelines for thromboprophylaxis for this select group of patients.

At our institution, these data have initiated multidisciplinary and multiunit discussions regarding thromboprophylaxis and development of a consensus-driven approach. Pediatric patients with multiple risk factors should be considered for prophylaxis. We have initiated risk-stratified thromboprophylaxis for LGEA patients at our institution and since its initiation, no symptomatic VTEs have been identified. We will continue to monitor the effectiveness and safety of this approach.

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