



Non-surgical Risk Factors for the Development of Chylothorax in Children after Cardiac Surgery-Does Fluid Matter?

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Received: 6 September 2019 / Accepted: 5 November 2019 / Published online: 12 November 2019
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Abstract

We hypothesize that there are post-operative, non-surgical risk factors that could be modified to prevent the occurrence of chylothorax, and we seek to determine those factors. Retrospective chart review of 285 consecutive patients < 18 years who underwent cardiac surgery from 2015 to 2017 at a single institution pediatric intensive care unit. Data was collected on patient demographics, cardiac lesion, surgical and post-operative characteristics. Primary outcome was development of chylothorax. Of 285 patients, median age was 189 days, median weight was 6.6 kg, 48% were female, and 10% had trisomy 21. 3.5% of patients developed upper extremity DVTs, and 8% developed chylothorax. At 24 h following surgery, a majority were in the 0–10% fluid overload category or had a negative fluid balance (63% and 34%, respectively), and a positive fluid balance was rare at 72 h (16%). In univariate analysis, age, weight, bypass time, DVT, arrhythmia, and trisomy 21 were significantly associated with chylothorax and adjusted for in logistic regression. Presence of an upper extremity DVT (OR 49.8, $p < 0.001$) and trisomy 21 (OR 5.8, $p < 0.001$) remained associated with chylothorax on regression modeling. The presence of an upper extremity DVT and trisomy 21 were associated with the development of chylothorax. Fluid overload was rare in our population. The presence of positive fluid balance, fluid overload, elevated central venous pressure, and early initiation of fat containing feeds were not associated with chylothorax.

Keywords Cardiothoracic surgery · Chylothorax · Post-operative complications · Cardiac intensive care

Introduction

Cardiothoracic surgery is the most common cause of chylothorax, leakage of lymphatic fluid into the pleural space, in children. This complication occurs in 0.25–9% of this

population [1–3]. The development of chylothorax leads to increased resource utilization including prolonged hospital stay and cost, as well as increased morbidity and mortality [3, 4]. Significant morbidities involve the metabolic, immunologic, and hematologic systems due to loss of essential elements within the chylous fluid, including electrolytes, lymphocytes, and proteins such as albumin, globulins, and fibrinogen. Respiratory complications also occur secondary to accumulation of the chyle within the pleural space [5–7].

There are known, unmodifiable perioperative factors associated with chylothorax. Procedures leading to elevated systemic venous pressure, such as cavopulmonary anastomoses, are believed to contribute to chylothorax by elevating central venous pressure (CVP). This elevated CVP causes an increase in hydrostatic pressure within the lymphatic system and thoracic duct, favoring the leakage of chyle to the extra lymphatic spaces [8]. Patients undergoing procedures with high complexity or longer bypass times, such as the Norwood procedure or truncus arteriosus repair, are also more likely to acquire a chylothorax post-operatively. Additionally, younger age has been

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associated with a higher risk of chylothorax development, as neonates and infants have a higher incidence than older children. Lastly, there are certain genetic syndromes that increase the risk of this complication such as Trisomy 21 and Turner syndrome, due to known lymphatic abnormalities [3, 9].

Additional, potentially modifiable factors related to chylothorax development have been postulated. As noted above, elevated CVP is believed to contribute to chylothorax development. While physiologically complex and poorly understood, fluid overload is associated with elevated CVP, and the increased venous wall tension prevents antegrade lymphatic flow at the lymphovenous junction, potentially contributing to the development of chylothorax [10]. Fluid overload, in general, is common after pediatric cardiac surgery and leads to increased morbidity and mortality. Those morbidities include acute kidney injury (AKI), surgical site infection, prolonged mechanical ventilation, and prolonged stay in the pediatric intensive care unit (PICU) [11, 12]. It is known that excess interstitial fluid and diet are the main contributors to lymph volume. However, the association of fluid overload with the development of a chylothorax has not yet been evaluated in this population [10].

Other post-operative factors that may play a role include the initiation of fat containing feeds, which increases lymph production, as well as an arrhythmia or deep vein thrombosis, which increases central venous pressure, limits antegrade lymphatic flow, and thus elevates the hydrostatic pressure within the lymphatic system [10].

We hypothesize that fluid overload is associated with the development of chylothorax in post-operative pediatric cardiac patients. In addition, we seek to evaluate if there are other additional, non-surgical, post-operative risk factors such as time to initiation of fat containing feeds, post-operative arrhythmias, elevated CVP, and the presence of a deep

vein thrombosis (DVT) that could potentially be modified in order to help reduce the occurrence of chylothorax in this cohort of patients.

Materials and Methods

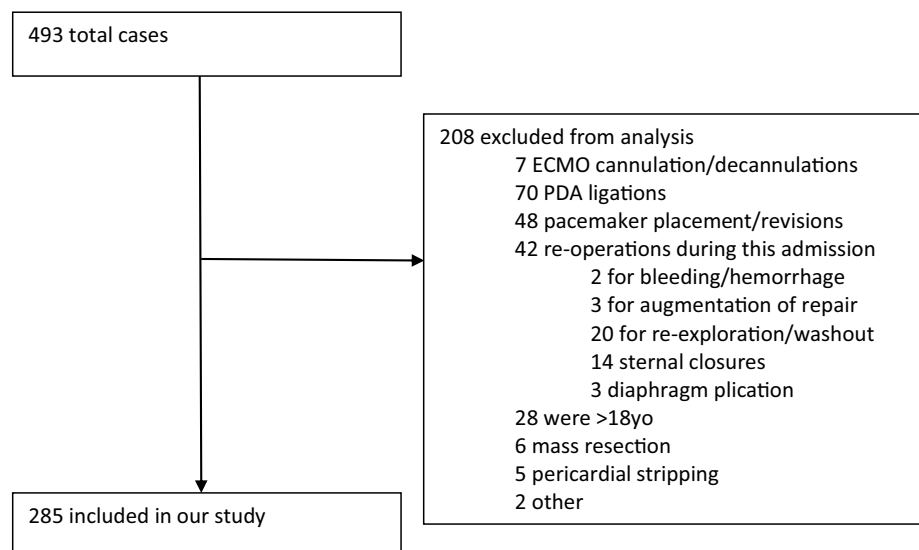
Study Design and Patient Population

In this single institution retrospective chart review, 493 consecutive patient charts from 1 January 2015 to 31 December 2017 were reviewed. Sample size was not calculated, as it was set by the available patient cohort size. Patients were excluded if they underwent surgery for pacemaker placement or revision, ligation of a patent ductus arteriosus, pericardectomy, mass resection, or cannulation/decannulation for extracorporeal support (Fig. 1). The index surgical procedure for each admission was included. 285 patients were included in the analysis.

The charts were reviewed for all patients who met inclusion criteria. At our institution, chylothorax was suspected if there was persistent chest tube output following initiation of feeds that was cloudy or milky in nature. Diagnosis was confirmed when microscopic and biochemical analyses of the fluid revealed a triglyceride level > 110 mg/dL and a white blood cell count $> 1000/\mu\text{L}$ with lymphocyte predominance [6, 13].

Data was collected on patient demographics, cardiac lesion, surgical characteristics including Risk Adjustment for Congenital Heart Surgery (RACHS-1) and the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STAT) scores, as well as post-operative characteristics. Fluid overload was defined as a cumulative balance $> 10\%$ from admission to the intensive care unit at both 24 and 72 h, calculated using the equation: (total

Fig. 1 Study profile



fluid intake-total fluid output) (L)/body weight (kg) × 100. The body weight was based on the patient's weight at ICU admission [11]. Intra-operative fluid management was not considered. This study was reviewed and approved by the Northwell Health Institutional Review Board.

Statistical Analysis

The primary outcome of interest was development of chylothorax. Patient characteristics were reported as count and percent for categorical variables and as median and interquartile range for continuous nonparametric variables. Chi square or Fischer exact test were performed as appropriate for categorical variables, and Mann Whitney U was used for continuous variables. We included all variables with a univariate association ($p < 0.2$) for inclusion in the multivariable model. Logistic regression was performed with backwards selection of significant variables, with only those reaching a p value of < 0.05 retained in the final model. All statistical analyses were performed using JMP Pro 14 (Cary, NC).

Results

Patient Demographics

A total of 285 patients were included for analysis. Patient demographics are shown in Table 1. The median age of our population was 189 days, median weight was 6.6 kg, 48% were female, and 10% of patients had Trisomy 21. The distribution of RACHS-1 and STAT scores as well as other operative variables are shown in the table. Post-operative characteristics are presented in Table 2. A total of 8% of our patients developed chylothorax post-operatively. 3.5% developed upper extremity DVTs, 29% had post-operative arrhythmias, and 54% had acute kidney injury at 24 h. All upper extremity DVTs were in a central vein, including superior vena cava, internal jugular vein, or subclavian vein. At 24 h following surgery, majority of patients were in the 0–10% fluid overload category or had a negative fluid balance (63% and 34%, respectively). A positive fluid balance was rare at 72 h (16%). 2.5% of our patients had $> 10\%$ fluid overload at 24 h. 2% did not survive to discharge (Table 2).

Univariate Analysis and Logistic Regression

Our univariate analysis is shown in Table 3. Notably, patient age, weight, bypass time, the presence of an upper extremity DVT, the presence of an arrhythmia, and Trisomy 21 were significant ($p < 0.05$). Other variables of interest are shown in Table 3. Importantly, potentially modifiable factors including fluid balance (positive or negative), time to initiation of fat containing feeds, and central venous

Table 1 Demographics

Variable	Incidence
Age (days), median (IQR)	189 (73.5, 1508.5)
Weight (kg), median (IQR)	6.56 (4.2, 15)
STAT score, n (%)	
1	140 (49)
2	63 (22)
3	31 (11)
4	44 (15)
5	5 (2)
RACHS-1 score, n (%)	
1	48 (17)
2	135 (47)
3	79 (28)
4	15 (5)
5	0 (0)
6	5 (2)
Sex, n (%)	
Male	148 (52)
Female	137 (48)
Surgeon 1, n (%)	169 (59)
Surgeon 2, n (%)	116 (41)
Bypass time (min), median (IQR)	69 (43, 97)
Cross clamp time (min), median (IQR)	36 (17, 62)
Re-operation, n (%)	67 (23)
Any syndrome, n (%)	64 (22)
Trisomy 21, n (%)	29 (10)

pressure, were not significant. Development of DVT and upper extremity DVT were not associated with negative fluid status, or $> 10\%$ negative fluid balance, at 24 or 72 h (24 h $p = 0.38$ and 0.84 , 72 h $p = 0.22$ and 0.07 respectively).

Variables with a univariate association ($p < 0.2$) were adjusted for in our logistic regression analysis. The presence of an upper extremity DVT (OR 49.8 CI 11.3, 219; $p < 0.001$) and Trisomy 21 (OR 5.8, CI 1.9, 16.4; $p < 0.001$) were the only variables that remained significantly associated with the development of a chylothorax (Table 4) with an AUC of 0.73.

Given fluid overload was the initial variable of interest, additional models were performed, with fluid overload at 24 h and over 10% fluid overload after 24 h retained regardless of p value. These models did not differ from our primary model, with only upper extremity DVT and Trisomy 21 associated with chylothorax development, and fluid status, including positive fluid balance, negative fluid balance, or degree of fluid overload, remaining non-contributory. Time to fat containing feeds was significant on univariate analysis, however, a more rapid time to initiation was associated with a lower odds of chylothorax development. This seemed

Table 2 Post-operative characteristics

Variable	Incidence
Chylothorax, <i>n</i> (%)	24 (8.4)
DVT, upper extremity, <i>n</i> (%)	10 (3.5)
Maximum lactate (mmol/L), median (IQR)	2.2 (1.5, 3.5)
Time to initiation of feeds (h), median (IQR)	24.5 (9, 50)
Positive fluid balance at 24 h, <i>n</i> (%)	191 (67)
> 10% Fluid overload in first 24 h, <i>n</i> (%)	7 (2.5)
Positive fluid balance at 72 h, <i>n</i> (%)	47 (17)
> 10% fluid overload in first 72 h, <i>n</i> (%)	6 (2)
Fluid overload category in first 24 h, <i>n</i> (%)	
0 (<0% fluid overload)	98 (34)
1 (0–10% fluid overload)	180 (63)
2 (> 10–20% fluid overload)	6 (2)
3 (> 20% fluid overload)	1 (0.4)
ECMO, <i>n</i> (%)	6 (2)
Delayed sternal closure, <i>n</i> (%)	22 (8)
Vasoactive infusion score, median (IQR)	8 (5, 12)
Vent free days, median (IQR)	28 (26, 28)
Presence of an arrhythmia, <i>n</i> (%)	82 (29)
Reintubation, <i>n</i> (%)	23 (8)
Central venous pressure 24 h, median (IQR)	10 (7, 12.5)
Central venous pressure 72 h, median (IQR)	10 (7, 13)
Acute kidney injury 24 h, <i>n</i> (%)	154 (54)
KDIGO Stage 24 h, <i>n</i> (%)	
0	131 (46)
1	98 (34)
2	47 (16)
3	9 (3)
Acute kidney injury 72 h, <i>n</i> (%)	56 (20)
Mortality, <i>n</i> (%)	6 (2)

improbable and therefore was not included in the regression model.

Discussion

This is one of few studies to evaluate modifiable risk factors for the development of chylothorax, and to our knowledge, no study has specifically evaluated the role of fluid status or the initiation of feeds on the development of chylothorax. Contrary to our hypothesis, we did not find any modifiable post-operative risk factors that contributed to our primary outcome. Neither a positive fluid balance nor fluid overload were associated with an increased incidence of chylothorax in our population. In addition to fluid status, early initiation of feeds, and central venous pressure were not associated with chylothorax development.

It has been demonstrated that the etiology of chylothorax is often due to a stretch tear of the thoracic duct during

surgery. However, there are variations in lymphatic pathways by which injury to small lymphatic vessels during any procedure may occur, leading to chyle leakage. Lymphatic dysplasia, which occurs in certain syndromes, predisposes to chylous effusion as well. Thus, the increased association of chylothorax in children with Trisomy 21 identified in our population is consistent with what has been previously reported [11, 14].

Chylothorax can also occur due to obstruction of the superior vena cava without injury to the lymphatic vessels, which was experimentally shown by Blalock et al. [15]. This has been supported by several studies documenting the association of a higher incidence of chylothorax in those with the presence of thrombosis in the upper venous system [16–18]. Our study was consistent with the finding of increased risk of chylothorax with upper extremity DVT. We also evaluated lower extremity DVTs, and found no association with chylothorax development. This finding may help guide decision making on the location of central venous line placement.

When evaluating for elevation in CVP, we were surprised that there was no association. Mechanistically, this would be physiologically consistent with a thrombosis in the upper body venous system. Since the thoracic duct drains into the left subclavian vein at its junction with the internal jugular vein, upper vein thrombosis leads to increased venous pressure, resulting in elevated hydrostatic pressure within the lymphatics and subsequent leakage from the lymphatic system into the pleural space. A consistently elevated CVP could potentially cause a similar elevation in hydrostatic lymphatic pressure. Despite the physiologic similarity, CVP was not associated with chylothorax in our patient population. In addition, central venous line location was not specifically evaluated in our patients.

In univariate analysis, the presence of an arrhythmia was associated with the development of chylothorax, but this did not remain significant on logistic regression. This has not previously been shown in the literature, but elevated venous pressures due to loss of atrioventricular synchrony is well described and could be expected to cause lymphatic leakage in a manner similar to that of a DVT [19]. Additional analysis on a larger patient cohort may be warranted to explore this potential association. In addition, a distinction between the various types of arrhythmias present in the post-operative period and their association with the development of chylothorax could be evaluated.

Our study is limited in the rare occurrence of > 10% fluid overload in our population. Given the low frequency of fluid overload, it is possible that we missed an association that would become apparent with more fluid overloaded patients. However, we found no association with chylothorax in those with a positive fluid balance at 24 or 72 h post-operatively. This is in the setting of a well-known increase in morbidity

Table 3 Univariate analysis

Variable	Chylothorax (<i>n</i> =24)	No chylothorax (<i>n</i> =260)	<i>p</i> value
Age (days), median (IQR)	115 (67, 183)	212 (74, 1628)	0.03
Weight (kg), median (IQR)	4.7 (4, 6)	6.7 (4, 17)	0.02
Bypass time (min), median (IQR)	93 (57, 131)	67 (42, 95)	0.03
Cross clamp time (min), median (IQR)	67 (21, 94)	34 (16, 57)	<0.01
DVT, upper extremity			
Yes, <i>n</i> (%)	7 (70.0)	3 (30.0)	<0.01
No, <i>n</i> (%)	17 (6.2)	258 (93.8)	
Arrhythmia			
Yes, <i>n</i> (%)	12 (14.6)	70 (85.4)	0.03
No, <i>n</i> (%)	12 (5.9)	191 (94.1)	
Acute kidney injury 24 h			
Yes, <i>n</i> (%)	7 (4.6)	147 (95.4)	0.02
No, <i>n</i> (%)	17 (13.0)	114 (87.0)	
Trisomy 21			0.02
Yes, <i>n</i> (%)	6 (20.7)	23 (79.3)	
No, <i>n</i> (%)	18 (7.0)	238 (93.0)	
Positive fluid balance 24 h			0.65
Yes, <i>n</i> (%)	15 (7.9)	176 (92.1)	
No, <i>n</i> (%)	9 (9.6)	85 (90.4)	
> 10% fluid overload 24 h			0.46
Yes, <i>n</i> (%)	1 (14.3)	6 (85.7)	
No, <i>n</i> (%)	23 (8.3)	255 (91.7)	
Positive fluid balance 72 h			
Yes, <i>n</i> (%)	6 (12.8)	41 (87.2)	0.25
No, <i>n</i> (%)	18 (7.6)	220 (92.4)	
> 10% fluid overload 72 h			
Yes, <i>n</i> (%)	1 (16.7)	5 (83.3)	0.41
No, <i>n</i> (%)	23 (8.2)	256 (91.8)	
Time to feeds (h), median (IQR)	49 (25, 68)	24 (8, 48)	0.01
Central venous pressure 24 h (mmHg), median (IQR)	10 (5, 12)	10 (7, 13)	0.59
Central venous pressure 72 h (mmHg), median (IQR)	9 (5, 14)	10 (7, 13)	0.59

Table 4 Final multivariate model

Variable	OR (95% CI)	<i>p</i> value
DVT, upper extremity	31.24 (6.13, 159.28)	<0.01
Trisomy 21	3.59 (1.15, 11.18)	0.04
Bypass time	0.99 (0.98, 1.01)	0.41
Cross clamp time	1.02 (0.99, 1.04)	0.16
Arrhythmia	1.38 (0.48, 3.98)	0.56
Age	1.00 (0.998, 1.001)	0.77
Weight	0.97 (0.79, 1.19)	0.77

and mortality associated with > 10% fluid overload in pediatric patients following cardiac surgery. Additionally, a positive fluid balance on the day of surgery regardless of the percentage of overload has been associated with the

development of acute kidney injury and low cardiac output syndrome [11, 20].

An additional concern is the propensity for DVT development in profoundly fluid deficient patients, predisposing to chylothorax. In our cohort, four patients (1.4%) had a > 10% negative fluid balance at 24 h and 75 patients (26%) had a > 10% negative balance at 72 h. We looked at the association of negative fluid balance, as well as a > 10% negative fluid balance, with development of DVT, and found no association at 24 or 72 h. Similarly, negative fluid balance was not associated with chylothorax development.

We also had a lower number of patients in the RACHS 4–6 categories, which carry a higher risk of chylothorax development, compared to those in categories 1–3, potentially making our findings less generalizable to some intensive care units.

Retrospective data collection is limited by missing data not captured in the documentation reviewed. There is a lack of clinical standardization and documentation for some of the data points we have captured, which is a limitation of our study design. We also did not capture central venous line size or location, which may play a role in central venous pressure or DVT development, and might contribute to our primary outcome. Our data suggests that if line location plays a role, it is likely due to DVT formation and not pressure phenomenon, as DVT but not CVP was associated with chylothorax development. Additionally, the side that the upper extremity DVT was located on was not accounted for, and a left sided thrombosis could potentially be associated with a higher incidence of chylothorax development compared to a right sided thrombosis due to direct obstruction of the thoracic duct. Lastly, this is a single center study, and a larger cohort might enable us to draw additional conclusions regarding our outcome of interest.

The harmful effects of excess fluid administration and fluid overload is a quickly growing area of research and education leading to significant change in practice across many disciplines. Specific to pediatrics, and even further individualized to pediatric cardiac surgical patients, fluid overload has been shown to be associated with an increase in acute kidney injury, prolonged mechanical ventilation, PICU length of stay, and mortality [21–23]. It is therefore crucial as providers to continue to improve our fluid management practices and be aware of these adverse effects.

It is interesting that in a population where fluid overload is historically common, we found very few patients with fluid overload, or even a positive fluid balance, despite complex congenital cardiac surgery. This may be secondary to a decreased incidence and severity of the systemic inflammatory response after pediatric congenital heart surgery due to advances in myocardial protection and bypass techniques. In addition, there may be a paradigm shift in the amount of fluid given in the post-operative period due to the increasing knowledge by providers of the adverse outcomes associated with fluid overload [12, 24, 25]. Future studies may seek to explore these findings.

Conclusions

The presence of an upper extremity DVT and trisomy 21 were associated with the development of chylothorax. Fluid overload was rare in our population. The presence of positive fluid balance, fluid overload, elevated central venous pressure and early initiation of fat containing feeds were not associated with chylothorax.

Funding No funding was received for this study.

Compliance with Ethical Standards

Conflicts of interest All authors declare that they have no conflicts of interest.

Ethical Approval This study was approved by the Institutional Review Board of Feinstein Institute at Northwell Health.

Informed Consent Informed consent was waived as it did not contain human participants.

Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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