Fluid Accumulation After Neonatal Congenital Cardiac Surgery; Clinical Implications and Outcomes

Running/short title: Fluid accumulation outcomes in neonates

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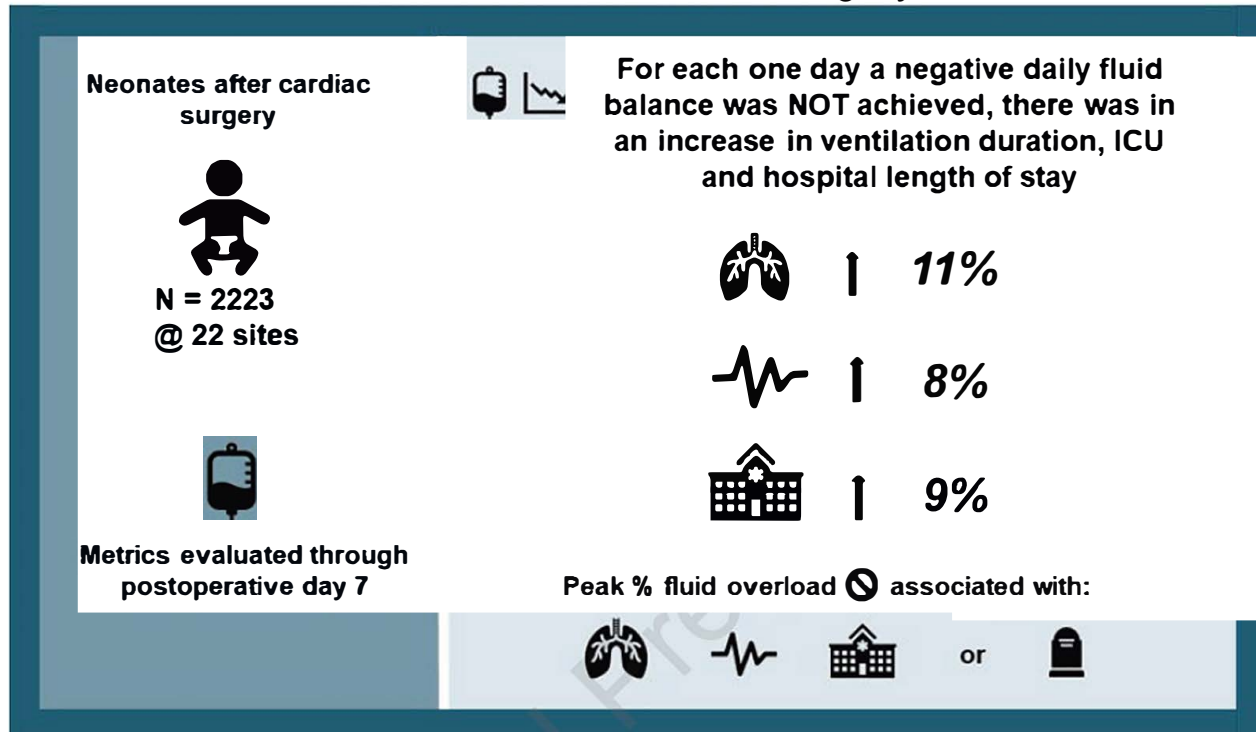
ABSTRACT

BACKGROUND: To determine the association between fluid balance metrics and mortality and other postoperative outcomes after neonatal cardiac surgery in a contemporary multi-center cohort.

METHODS: Observational cohort study across 22 hospitals in neonates ($\leq$30 days) undergoing cardiac surgery. We explored overall % fluid overload, postoperative day 1 % fluid overload, peak % fluid overload, and time to first negative daily fluid balance. The primary outcome was in-hospital mortality. Secondary outcomes included postoperative duration of mechanical ventilation, and intensive care unit (ICU) and hospital length of stay. Multivariable logistic or negative binomial regression was used to determine independent associations between fluid overload variables and each outcome.

RESULTS: The cohort included 2223 patients. In-hospital mortali y was 3.9% (n=87). Overall median peak % fluid overload was 4.9%, (interquartile range 0.4-10 5%). Peak % fluid overload and postoperative day 1 % fluid overload were not associated with primary or secondary outcomes. Hospital resource utilization increased on each successive day of not achieving a first negative daily fluid balance and was characterized by longer duration of mechanical ventilation (incidence rate ratio 1.11, 95% confidence interval 1.08-1.14, ICU length of stay (incidence rate ratio 1.08, 95% confidence interval 1.03-1.12), and hospital length of stay (incidence rate ratio 1.09, 95% confidence interval 1.05-1.13).

CONCLUSIONS: Time to first negative daily fluid balance, but not % fluid overload is associated with improved postoperative outcomes in neonates after cardiac surgery. Specific treatments to achieve an early negative fluid balance may decrease postoperative care durations.

Fluid Balance Metrics Associated with Adverse Outcomes in Neonates After Cardiac Surgery

Neonates after cardiac surgery

N = 2223
@ 22 sites

Metrics evaluated through postoperative day 7

For each one day a negative daily fluid balance was NOT achieved, there was in an increase in ventilation duration, ICU and hospital length of stay

11%

8%

9%

Peak % fluid overload 🚫 associated with:

or

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Abbreviations

AKI: acute kidney injury

ICU: intensive care unit

FO: fluid overload

ICU: intensive care unit

IQR: interquartile range

LOS: length of stay

NEPHRON: The NEonatal and Pediatric Heart Renal Outcomes Network

PC4: Pediatric Cardiac Critical Care Consortium

POD: postoperative day

STAT: The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

VIS: vasoactive inotropic score

Our current understanding of the clinical importance of fluid overload (FO) after *neonatal* cardiac surgery, is mainly derived from three retrospective single center cohort studies. [1–3] Wilder et al. (n=436 following cardiopulmonary bypass) first showed that FO >16% on POD 3 was independently associated with a poor composite outcome (death, need for renal replacement therapy, extracorporeal life support within 30 post-operative days) and that these patients were slower to diurese. [3] Mah et al. (n=117 after cardiopulmonary bypass) next showed for each 1% increase in FO there was a 5.8% greater odds of in-hospital mortality regardless of acute kidney injury (AKI) status. [1] Recently, Piggot et al. (n=99 after cardiac surgery, age 6 to 29 days) showed by unadjusted analysis that FO >15% was associated with longer hospital LOS, ventilation duration, and mortality. [2]

While each of these studies suggest that FO after neonatal cardiac surgery is detrimental, the generalizability of the results remains in question due to the small sample sizes, lack of detailed epidemiologic data, inconsistent fluid balance metrics, and different outcomes measured. Multicenter efforts are thus needed to determine which metrics of FO are currently associated with clinically important outcomes in neonates after cardiac surgery.

Accordingly, the NEonatal and Pediatric Heart Renal Outcomes Network (NEPHRON) was developed, in part, to investigat the impact of FO on neonatal cardiac surgery clinical outcomes. [4] We used the NEPHRON data infrastructure to describe FO epidemiology and its association with in-hospital mortality, duration of mechanical ventilation, and ICU and hospital LOS. We hypothesized that FO is common after neonatal cardiac surgery and that peak %FO and longer time to first negative daily fluid balance are independently associated with worse clinical outcomes.

MATERIAL AND METHODS

The analysis included data from the previously described NEPHRON module, which collected data relevant to fluid balance and AKI in neonates (≤ 30 days) undergoing cardiac surgery across 22 hospitals contributing to the Pediatric Cardiac Critical Care Consortium (PC4) between September 2015 to January 2018. [4,5] Audits of PC4 centers occur on a regular schedule, demonstrating a major

discrepancy rate of 0.6%. [6] We excluded patients with a major cardiovascular reoperation less than 7 days after index operation, intraoperative extracorporeal support or initiation within 24 hours, preoperative serum creatinine >1.5 mg/dL, preoperative renal replacement therapy, or missing data elements required to calculate %FO. The University of Michigan Institutional Review Board provides oversight on all PC4 analyses. The IRB reviewed this study protocol and waived need for written informed consent.

DATA COLLECTION

Prematurity was defined as < 37 weeks gestation. AKI was classified using the modified neonatal Kidney Diseases: Improving Global Outcomes criteria during postoperative days (POD) 1-6. [4,7] Severe AKI was defined as stage 2 or 3. Prophylactic peritoneal dialysis was defined as active peritoneal dialysis within the first 24 postoperative hours not for FO or AKI and was not assigned stage 3 AKI. The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) categories were used to classify surgical complexity. [8] Vasoactive Inotropic Score (VIS) was assigned during the first two postoperative hours. [9] PC4 registry-defined postoperative complications are listed in Supplemental Table 1. Additional clinical data included: pre-operative and daily serum creatinine level, net daily fluid balance, birth weight and da ly weights.

ASSESSMENT OF FLUID ACCUMULATION

We measured fluid intake and output daily from 7AM to 7AM except for POD 0 which began at time of postoperative admission until the following 7AM, at which point POD 1 began. For fluid balance metrics, POD reflects the previous day's fluid totals, such that fluid balance on POD 1 reflects changes during POD 0, and so on. The following formula was applied daily through POD 6: Total fluid in (Liters) – Total fluid out (Liters). Fluid balance in the operating room was not included due to inconsistent reporting. Daily weights were not used to calculate fluid balance because they are not routinely measured

at all hospitals and were missing in ~70% of subjects on POD 1 and 2. The %FO was calculated as follows: [10]

$$\% \text{ Fluid overload } = \frac{Total\ fluid\ in\ (L) - Total\ fluid\ out\ (L)}{preoperative\ weight} * 100$$

Peak %FO determination began at time of postoperative ICU admission through POD 6, death, or ICU transfer/discharge. The POD 1 %FO begins at postoperative admission up to POD 1. Peak FO% as a categorical variable was characterized based on discrete groupings commonly accepted as cut-offs for assessing fluid overload in critical illness (<10%, 10 to <20%, 20 to 30%, or >30%). [1,11] Days to first negative daily fluid balance was defined as the first full POD on which the daily output exceeded the daily input.

STATISTICAL ANALYSIS

The primary outcome was in-hospital mortality. Secondary outcomes included postoperative duration of mechanical ventilation and postoperative ICU and hospital LOS. Descriptive analyses were performed using parametric and/or non-parametric statistics, as appropriate. We determined univariate associations between patient and operative characteristics and peak %FO. Multivariable regression models were used to evaluate the association between peak %FO with the primary and secondary outcomes; a logistic model was used for mortality and negative binomial regression was used for duration of mechanical ventilation, ICU and hospital LOS. The primary analyses included peak %FO as a categorical variable and time to first negative daily fluid balance. Several measures of FO are highly correlated – peak FO%, peak POD1 FO%, and categorical measures of fluid overload - so we could not include all of these variables in a single model. We performed separate analyses where we evaluated peak %FO and POD 1 %FO, as continuous variables, in place of %FO. Since 23 patients were transferred out of the ICU prior to achieving a negative daily fluid balance before POD 6, analysis on time to first

negative fluid balance excluded these patients. Each model included other clinical variables known to be associated with the outcomes of interest: weight-for-age z-score, prematurity, chromosomal abnormalities, pre-operative mechanical ventilation, peri-operative mechanical circulatory support, STS preoperative risk factors, STAT score, early postoperative VIS, postoperative chest tube output, any post-op complication, and any post-operative infection. We accounted for clustering within hospitals by including a hospital-specific random effect term in the model, and obtained robust (sandwich) estimators for variance for confidence interval construction and inference. We performed bootstrap resampling (1000 samples) to obtain bias-corrected 95% confidence intervals for the estimates in the multivariable model. For all comparisons a p-value of <0.05 was considered to be statistically significant. Analysis was performed using SAS v9.4 (SAS Institute) and Stata Version 15 (StataCorp, College Station, TX).

RESULTS

A total of 2223 patients met inclusion after 64 patients were excluded (Supplemental Figure 1). Table 1 shows patient characteristics and postoperative outcomes. In-hospital mortality was 3.9% (n=87). In-hospital mortality counts across fluid balance categories <10%, 10 to <20%, 20 to <30%, and >30% was 49, 17, 6, and 6 respectively. Mortality counts by time to initial negative daily fluid balance from POD 1-6 respectively was 24, 27, 10, 11, 1 and 1. Four mortalities occurred in patients that never achieved a negative daily fluid balance during the study period.

The median duration of mechanical ventilation was 72 hours, (interquartile range ((IQR)), 40.3-143.3), ICU LOS was 8 days (IQR 5-15.70), and hospital LOS was 16 days (IQR 10-31). Severe AKI (Stage 2 and 3) occurred in 23% of the patients. A urinary catheter was present for 40% of patient ICU days (POD 1-6). Prophylactic peritoneal dialysis was utilized in 8.4% (n=187) of the cohort, passive peritoneal drainage without dialysis in 14.8% (n=330), and PD for FO/AKI in <1% (n=12).

FLUID OVERLOAD AND TIME TO NEGATIVE DAILY FLUID BALANCE

Aggregate median peak %FO was 4.9% (IQR 0.4%, 10.5%), and most commonly occurred on POD 1 (44%, n=981). The cohort distribution of peak %FO is shown in Figure 1. The median POD1 %FO was 1.2% (IQR -2.4% to 4.7%). Exposure to cardiopulmonary bypass did not impact magnitude of peak %FO, or time to initial negative daily fluid balance, but POD 1 %FO was higher in those who received cardiopulmonary bypass (p=0.022) (Supplemental Tables 2 and 3).

Across sites, median peak %FO ranged from 0.1% to 12% (Figure 2). Daily median % FO also varied by site (Figure 3).

Ninety-six percent achieved a negative daily fluid balance, which first occurred on median POD2 (IQR 1,2), and ranged between POD 1-3 across sites.

PREDICTORS OF MORTALITY

In multivariable regression, no association was found between the peak %FO as a continuous (not shown) and categorical variable, or time to first negative daily fluid balance and mortality (Table 2). Additional analyses exploring POD 1 %FO expressed as continuous variables also demonstrated no association with mortality. Additional factors associated with mortality are shown in Supplemental Table 4.

FLUID BALANCE PREDICTORS OF SECONDARY OUTCOMES

Regression analyses showed that peak %FO and POD 1 %FO were not associated with any of the secondary outcomes. Analysis using peak % FO as a continuous variable were also not significant. Time to initial negative daily fluid balance was associated with duration of mechanical ventilation, and ICU and hospital LOS. Each day the first negative daily fluid balance was not achieved, there was an increased likelihood of duration of mechanical ventilation (IRR 1.11, 95% CI: 1.08-1.14), ICU LOS (IRR 1.08, 95% CI 1.03-1.12), and hospital LOS (IRR 1.09, 95% CI 1.05-1.13) (Table 2).

COMMENT

This study represents the first large multicenter study identifying associations between FO metrics and outcomes after neonatal cardiac surgery. Contrary to our hypothesis and previous reports in neonates after cardiac surgery, [1–3] we observed no association between peak %FO, or POD 1 %FO and our primary and secondary outcomes. Importantly, shorter time to initial negative daily fluid balance was associated with improved outcomes including shorter mechanical ventilation and ICU and hospital LOS.

Our analysis adds *clinical focus* to management of postoperative fluid accumulation by showing that input/output based peak %FO and POD 1 %FO are not independently associated with mortality or duration of critical illness. Instead, our findings suggest that *the first negative daily fluid balance is a clinically important milestone*. Wilder et al. also showed adverse outcomes were associated with longer time to negative fluid balance. [3] We postulate that time to net negative fluid balance encapsulates many complex recovery processes such as restoration of endothelial integrity, fluid mobilization, and improving cardiac output. The inability to achieve a negative daily fluid balance may be an important trigger to prompt investigation for residual lesions occult complications, and other factors that preclude the hemodynamic resilience necessary for tissue fluid mobilization after neonatal cardiac surgery. Additionally, we utilized the highly granular data contained in the PC4 registry to control for covariables associated with our primary and secondary outcomes that were not adjusted for in the previous three neonatal reports. (Supplemental Table 4).

As mortality rates decline, the patterns of causes of mortality may also shift which may impact why we did not see an association between FO and mortality. In-hospital neonatal post cardiac surgery mortality across all participating PC4 centers has decreased from 9.1% in 2013 to 6.5% in 2018 when our data collection concluded (https://pc4.arbormetrix.com). By comparison, Wilder reported a 3% 30 day mortality (2006-2010), Mah reported a 7.7% in-hospital mortality (2010-2012), and Piggot 8.4% 30 day mortality (2010-2013). [1–3] Importantly, of these studies, only Mah et al. used mortality as a single endpoint.[1]

Another novel finding was that the degree and prevalence of peak %FO was lower in our cohort compared to the previous neonatal studies following cardiac surgery. Compared to our results, the prevalence of peak FO >10% in Mah's study was 2x greater (65% versus 26%) [1] and the prevalence of FO >15% in Piggot's report was nearly 4x greater (27% vs 7.5%). [2] Furthermore, when compared with the three prior reports of neonates after cardiac surgery, the peak % FO was lower at 18 of the 22 NEPHRON sites. These findings suggest that our multi-center study provides a more contemporary and generalized estimate of FO. We surmise increased clinical focus on FO prevention, driven by recent neonatal and pediatric literature, may have contributed to less FO than previously reported in the three aforementioned neonatal studies. [1–3,12–15]

In our study, because ~ 70% of weights on POD 1 and 2 were not performed, we calculated peak %FO based on daily fluid intake and output, similar to Mah and Piggot [1,2], but Wilder used daily weights. [3] Comparison of these two methods for measuring %FO with respect to accuracy and differential impact on outcomes warrants further investigation.

While the aim of this paper was to determine which metrics of FO are associated with mortality and secondary outcomes, we also appreciated variation in peak % FO (0.1% to 12%) and time to first negative daily fluid balance (median 1 to 3 days) across sites (Figure 2). This variation across sites suggests that FO and time to negative fluid balance are potentially modifiable. Given that we have now established that time to negative fluid balance is indeed a clinically relevant target in neonates following cardiac surgery, it becomes important to focus research and quality improvement endeavors on improving our understanding of risk factors and clinical decisions that influence this metric, including perioperative use of diuretics and prophylactic peritoneal dialysis. [15] The variation in peak %FO across sites may be attributed to differences in perioperative fluid management and removal practices. Use of diuretics, peritoneal dialysis and modified ultrafiltration were all associated with a lower peak %FO (Supplemental Table 3). We hypothesize that application of these therapies, particularly in cohorts perceived as higher risk for FO (i.e, cardiopulmonary bypass, severe AKI, open sternum, STAT 5 surgery) might explain the very small difference in peak %FO compared to lower risk patients (Supplemental Table 3). In fact, the

overall peak %FO was no different in those with and without cardiopulmonary bypass, and both groups had the same median time (2 days) to achieving first negative daily fluid balance.

We recognize several inherent limitations of a retrospective cohort design, which does not allow causal inference and carries an intrinsic risk of confounding. Similar to all prior reports in neonates after cardiac surgery, our study does not account for operating room fluid balance accrual, including bleeding and blood product resuscitation. Thus all these studies most precisely measure fluid accumulation that occurs exclusively in the ICU. We do not presume that the fluid balance status upon arrival to the ICU is equal across sites or surgeries, or that fluid mitigation practices are uniform within or across hospitals. While all NEPHRON abstractors completed training sessions dedicated to NEPHRON variables in addition to the unique training required to abstract data for PC4, institutional inconsistencies in data recording and abstraction are possible. Although we controlled for center clustering effects, we did not control for site specific practices. Notably, fluid balance was measured only once a day at time of shift change, and we did not separate the influence of urine output, chest tube output, or peritoneal drainage, nor did we analyze the influence of fluid restriction on net fluid balance. Because our study period was limited to POD 6, we cannot make conclusions related to chronic fluid overload and the impact on outcomes. Calculation of fluid balance was based on daily inputs and outputs, rather than daily weights, which may not account for insensible losses. [11,16]

CONCLUSIONS

Time to first negative daily fluid balance, but not %FO is associated with improved postoperative outcomes in neonates after cardiac surgery. Specific treatments to achieve an early negative fluid balance may decrease duration of ventilation, and LOS in the ICU and hospital. Further investigation into time to first negative fluid balance thresholds associated with deleterious outcomes and therapies to achieve negative fluid balance is warranted.

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Table 1. Demographic, clinical, and outcome characteristics

Variable	All Patients
Age, days (IQR)	7 (5-11)
Male, n (%)	1349 (61%)
Underweight, kg, median (IQR)	346 (16%)
Preterm, yes, n (%)	285 (13%)
Chromosomal syndrome, yes, n (%)	380 (17%)
STAT category, n (%)	
1-3	671 (30%)
4-5	1544 (69%)
Not classified	3 (<1%)
Cardiopulmonary bypass , n (%)	1652 (74%)
Cardiopulmonary bypass time (min), median (IQR)	131 (91-166)
Open Sternum, n (%)	701 (32%)
Cardiac arrest first 24h postop, n (%)	17 (<1%)
Duration of ventilation (hr), median (IQR)	72.4 (40.3-143.3)
ICU LOS days, median (IQR)	8.1 (5-15.7)
Hospital LOS days, median (IQR)	16 (10-31)
CRRT (y), n (%)	12 (<1%)
In-hospital mortality, n (%)	87 (3.9%)

[a] Peak % fluid overload up to POD 6
[b] Peak % fluid overload up to POD 1
CI=confidence interval; CRRT=continuou ren l replacement therapy; FO=fluid overload; ICU=intensive care unit; IRR=incidence rate ratios; IQR=interqu rtile range; LOS=length of stay; POD=postoperative day; STAT=Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery risk of mortality

Table 2: Multivariable fluid balance predictors of mortality and secondary outcomes

	Mortality[a,b]	Duration of Ventilation[b]	ICU LOS[b]	Hospital LOS[b]
	OR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Categorical Peak %FO				
<10 vs 10 to <20	0.96 (0.54, 1.70)	0.86 (0.73, 1.02)	1.00 (0.90, 1.11)	0.92 (0.81, 1.04)
<10 vs 20 to <30	1.36 (0.57, 3.23)	0.92 (0.71, 1.20)	1.02 (0.88, 1.18)	0.88 (0.76, 1.01)
<10 vs >30	2.57 (0.65, 10.16)	1.02 (0.74, 1.39)	1.01 (0.77, 1.32)	0.81 (0.61, 1.09)
Time to initial negative daily fluid balance[c]	1.07 (0.87, 1.39)	**1.11 (1.08, 1.14)**	**1.08 (1.03, 1.12)**	**1.09 (1.05, 1.13)**

[a]Adjusted for stage 3 acute kidney injury
[b]Adjusted for weight-for-age z-score, prematurity, chromosomal abnormalities, pre-operative mechanical ventilation, pre-operative mechanical circulatory support, STS preoperative risk factors, STAT score, early postoperative vasoactive-infusion score, postoperative chest tube output, any post-op complication, and any post-operative infection.
[c]Patients who did not achieve a negative fluid balance were assigned the median of 2 days
CI=confidence interval; FO=fluid overload; ICU=intensive care unit; LOS=length of stay; IRR=incidence rate ratio; OR=odds ratio

FIGURE LEGENDS

Figure 1. Cohort distribution of peak % fluid overload.

Figure 2. Median peak % fluid overload by center.

Figure 3. Median % fluid overload by center and postoperative day.

Peak % Fluid Overload