# The association between fluid overload and adverse outcomes following pediatric cardiac surgery

PhD thesis

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Budapest
2017

## Introduction

Fluid overload (FO) during and after pediatric cardiac surgery is common. Intraoperative FO is associated with factors such as the lower tolerability and reserve capacity in children, excessive exogenous fluid used for the cardiopulmonary bypass (CPB) priming, cardioplegia, medication administration and hypotension management. Children undergoing cardiac surgery often arrive in the operating room already overloaded due to a degree of heart failure, complex congenital abnormalities and diminished baseline renal function. Recently, FO has been shown to be associated with poor outcomes, including increased mortality, acute kidney injury (AKI), acute lung injury, sepsis and low cardiac output syndrome (LCOS). The assessment of the severity of FO suggests that a cutoff value of 10% is associated with increased mortality in children. Furthermore, intraoperative CPB and surgical stress cause ischemia, reperfusion injury and systemic inflammatory response, and these processes also augment edema formation and damaged microcirculation.

## Objectives

We hypothesized that AKI and/or LCOS might be exacerbated by FO, and if so, exploration of risk factors for FO is crucial in reducing acute and long-term adverse outcomes. The aim of this study was to investigate the relationship of fluid overload and adverse outcomes in a large and heterogeneous cohort of pediatric patients undergoing open-heart surgery in a single center. As a novel approach, we also aimed to explore the risk factors of developing early FO. Our primary objectives were:

- To assess the etiology of FO by defining its occurrence and degree
- To uncover the relationship between demographic and patient specific variables and the occurrence of FO
- To determine the effect of FO on the occurrence of postoperative adverse outcomes
- To ascertain the risk factors leading to postoperative FO as an adverse outcome
- To study the occurrence and degree of AKI of different age groups and its relationship with perioperative FO

## Methods

Institutional Review Board approval (IRB 189/2008) was given for the retrospective use of the selected data collated from a prospectively collected database of consecutive pediatric patients undergoing cardiac surgery who were admitted to our cardiac intensive care unit (ICU) at Gottsegen Hungarian Institute of Cardiology in Budapest, Hungary between January 1, 2004 and December 31, 2008, including waiving the requirement for informed consent from the parents. During the study period, 1665 cardiac surgeries were performed. Only patients undergoing open-heart surgery and under 18 years old were considered for the study. 1216 patients (80%) were on CPB during surgery. 145 patients were excluded in the case of preoperative renal replacement therapy (RRT) administration, and where the fluid balance for the study period could not be calculated due to missing data. Only the first operation was considered for the present analysis. The surgical and medical management of the patients, and institutional policies were identical during the study period.

The fluid intake and output were recorded perioperatively up to 72 hours after surgery. The urine

output was recorded and analyzed as ml/kg/hr. The daily fluid balance was calculated from the difference in the intake (crystalloids, colloids, parenteral nutrition, oral intake and transfusion) and the output (recorded fluid loss included any fluid removed by a drain or chest tube, urine or stool, and blood for testing or lost from bleeding). The fluid intake and output were recorded hourly, and the daily data were analyzed as ml/kg. As a general guideline, patients were treated with dextrose containing (D5) 0,45% normal saline as much as 750 $ml/m^2$ and 1000 $ml/m^2$ body surface area on DOS and POD1, respectively.

Using the patient's fluid balance in ml/kg, the percent FO was calculated for each patient by the following formula: (total fluid intake - total fluid output) [L]/body weight [kg] *100. The body weight was based on the patient's weight at hospital admission or the most recent available patient weight measured in the ICU. The cumulative FO (cFO) was calculated by summarizing the respective %FO of the postoperative days.

RRT was defined as the implementation of either peritoneal dialysis or hemodialysis for indications including metabolic/electrolyte imbalance, ascites,

pulmonary edema and excess fluid removal as per the attending physician's preference. Furosemide was used as 1 mg/kg bolus administration without an institutional protocol.

LCOS during the study period was defined using clinical signs (tachycardia, hepatomegaly, cardiac arrest) with a base excess lower than -4 mmol/l or a lactate level above 2 mmol/l in two consecutive arterial blood samples or urine output lower than 1ml/kg/hr or a maximum VIS higher than 20 or the need for mechanical circulatory support.

Prolonged mechanical ventilation (PMV) was defined as longer than 72 hours as 75% of our patients were extubated by POD2 and previous studies showed a median duration of 3 days.

Vasoactive inotropic score (VIS) was calculated as: dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100x epinephrine (μg/kg/min) + 10x milrinone (μg/kg/min) + 10,000x vasopressin (U/kg/min) + 100x norepinephrine (μg/kg/min).

For continuous variables, the p-values are based on a Mann-Whitney U test comparing patients with and without adverse outcomes. The adjusted risk of FO and

mortality, LCOS and PMV were calculated using multivariable logistic regression. Model selection and fitting was based on Akaike Information Criterion using backward stepwise selection method. Deaths prior to the investigated cFO day were excluded. A separate multivariable model was constructed for the analysis of the predictors for cFO > 5%, and also a linear regression model for cFO at the second postoperative day. For survival analysis, Kaplan-Meier log-rank pairwise comparison was used.

## Results

Of the 1520 patients, 90 patients (5.9%) died, 370 patients (25.4%) had postoperative LCOS, and 102 patients (6.7%) required RRT. Twenty-two patients (1.3%) died on the day of surgery (DOS), 21 patients (1.3%) died on the first postoperative day (POD1), and 6 patients (0.4%) died on the second postoperative day (POD2), thus 54% of all deaths occurred during the study period. Patients requiring RRT on the day of surgery (n=75) had higher intraoperative fluid balances (ml/kg, 20.3 ± 25.3 vs. 24.16 ± 41.1, p=0.004). 121 patients (7.3%) reached Kidney Disease Improving Global

Outcomes (KDIGO) Stage I, 29 (1.7%) reached Stage II and 114 (6.8%) reached Stage III. Of the 153 patients with cFO greater than 5% at the end of POD2, 30 patients (20%) were newborns, 35 (23%) underwent acute or urgent operation, 20 (13%) had univentricular physiology; 9 (6%) underwent arterial switch, 10 (7%) modified Blalock-Taussig Shunt and 10 patients (7%) underwent Norwood procedure.

We found that during the first 72 hours of the postoperative period, 1367 patients (89.9%) had a cFO below 5%, 120 patients (7.8%) had a cFO between 5% and 10%, and 33 patients (2.1%) had a cFO above 10%. Patients with >5% cFO were younger, had lower body weight and underwent more complex surgeries with higher occurrence of cyanotic lesions, longer CPB and aortic cross-clamp times.

The non-survivors had higher fluid balances and cFOs on DOS and POD1 compared with the patients without complications. After adjusting for confounding variables, cFO by DOS remained an independent predictor of mortality, as for every % of FO by the end of DOS the risk of mortality increased by 14%. As the strongest predictor, the occurrence of LCOS increased

the risk for mortality by 14 times. Mean survival time for patients with <5%, >5% and >10% cFO on POD2 was 67.7 (95%CI: 62.1-73.4), 39.9 (95%CI: 35.6-44.3, p=0.03) and 35.6 days (95%CI: 23.2-48.1, p<0.001), respectively.

In the whole population, the KDIGO Stage III (OR: 18.8, 95% CI: 9.6-36.6, p<0.001), the AKIN Stage III (OR: 38.3, 95% CI: 20.6-70.9, p<0.001) and pRIFLE Failure group (OR: 13.6, 95% CI: 7-26.3, p<0.001) were associated with increased mortality. The AUCs for mortality were similar (AUC: 0.81) with the KDIGO and AKIN systems in the whole population, while AKIN proved to be more reliable in the neonate (AUC: 0.83), pRIFLE in the infant (AUC: 0.81) and KDIGO in the >1 year old (AUC: 0.81) age groups. Overall, 6.2% of the patients required RRT, for which the highest AUC-ROC curve was 0.89 in infant patients categorized by the pRIFLE system. ROC analysis using AKIN and KDIGO categories without the inclusion of RRT criteria showed weaker prediction value than pRIFLE.

Patients requiring RRT had higher intraoperative, DOS, POD1 and lower POD2 fluid balances and cFO compared to those without complications.

Patients with LCOS had higher intraoperative, DOS and lower POD2 fluid balances and cFO compared to those without complications. After adjusting for confounding variables, cFO by DOS remained an independent predictor of LCOS, as for every % of FO by the end of DOS the risk of LCOS increased by 15%. As the strongest predictor, the need for RRT increased the risk for LCOS by 5 times.

Patients requiring prolonged mechanical ventilation had higher fluid balance and cFO on DOS compared to those without complications. After adjusting for confounding variables, cFO by POD2 remained an independent predictor of PMV, as for every % of FO by the end of POD2 the risk of PMV increased by 1,2%. As the strongest predictor, the occurrence of LCOS increased the risk for PMV by 7 times.

The non-survivors had a lower UO on the DOS and POD1 compared with the patients without complications and patients with LCOS had a higher UO on POD1 and POD2 compared to those without complications. Patients requiring RRT had lower urine output on all three postoperative days compared with the patients without complications.

Independent risk factors of cFO greater than 5% by the end of POD2 include maximum SCr level, blood loss on DOS, maximum VIS point and the occurrence of LCOS, while higher body weight showed a protective association. Every point increase in the maximum VIS, every μmol/l elevation in the maximum SCr level and every 1 ml/kg blood loss on DOS increased our patient's risk for >5% cFO by 1.3%, 1.2% and 1.4%, respectively. As the strongest predictor, the occurrence of LCOS increased the risk for >5% FO by 3 times.

After multivariable linear regression analysis, risk factors of cFO by the end of POD2 include preoperative inotrope administration, intraoperative red blood cell use (ml/kg), blood loss on DOS (ml/kg), maximum VIS point, maximum SCr level, delayed chest closure, occurrence of LCOS and the need for RRT. The final model was statistically significant ($F=21.164$, adjusted $R^2=0.347$, $p<0.001$). There was no first order linear auto-correlation in the final model ($d=1.967$). There was no multicollinearity present in the final model (highest VIF=3).

## Conclusions

Based on our results, we show that early postoperative FO was independently associated with adverse outcomes. While a positive postoperative fluid balance on the day of surgery was associated with higher risks of mortality and adverse outcomes, this association decreased on POD1, and no relationships were observed with mortality on POD2. Early positive FO on DOS was also associated with higher risk of LCOS, while cumulative FO by the end of POD2 was associated with higher risk of PMV. After analyzing the potential predictors of FO, we found higher risk in the case of higher maximum creatinine levels and inotrope requirements, early postoperative blood loss and the occurrence of LCOS.

Several risk factors of FO overlap with predictors of other adverse outcomes, pointing at possible additive effects. Preoperative poor status requiring inotrope administration possibly carries an existing volume load that poses a difficult assessment later. Intraoperative RBC use and early postoperative blood loss are markers of operational complexity and surgical success. High postoperative SCr values correlate with kidney

dysfunction and high postoperative inotropic requirement and delayed chest closure are possibly surrogate markers of LCOS and hemodynamic instability leading to diminished urine output and FO. Identification of high-risk patients for FO by calculation of fluid balance has its limitations and here we present additional markers available to use as early as POD1. Early intervention in the management of FO appears to be the key factor for reducing mortality and morbidity, although the correct timing of RRT initiation is still unclear because of the lack of clinical definitions and thresholds and unconfirmed biomarker values. A detailed analysis of the fluid balance, UO and cumulative FO has also confirmed the renal angina phenomenon in the pediatric cardiac population, i.e., a large proportion of the patients (most likely those with a pRIFLE Risk category) are unable to fulfill the higher demand for fluid excretion in the intraoperative and early postoperative period. This inability may be due to both pre-renal and renal causes. These patients will have a positive fluid balance, which will be eliminated at the end of the second postoperative day. This may be exacerbated in cases where normal creatinine and poor UO is ascribed to pre-renal factors

including volume depletion, and it is treated with additional fluids. In these cases, the renal injury may have already occurred and not been recognized, leading to an imbalance in fluids that is then recognized and dealt with on POD1 and POD2.

Our results showed increased sensitivity of the pRIFLE system in detecting AKI particularly in neonates and infants where there was limited data in the original KDIGO assessment. It suggests that pRIFLE alone in young infants was superior to other assessments of AKI. The difference between the methods applied in the categorization yielded a significant number of patients undetected by both SCr systems as compared to eCrCl. However, the higher fluid balances in these patients, by diluting SeCr may have led to a potential overstatement of the CrCl decrease. This amounts to the consideration earlier established regarding the bedside ease of use, that the application of only one type of clinically measured factor would be desired. The pediatric-validated pRIFLE classification system is particularly useful in this particular patient population. Our results indicate that postoperative fluid overload is more important than positive intraoperative fluid balance as a possible risk

factor in the development of AKI.

Using an exceptionally large cohort of pediatric patients undergoing cardiac surgery, we found that FO was independently associated with an increased risk for mortality, low cardiac output syndrome and prolonged mechanical ventilation, after adjustment for covariates such as age, weight, acute operation, RACHS-1 score, CPB time, intraoperative RBC use, RRT, delayed chest closure, maximum VIS score, early postoperative blood loss and postoperative infection. Our data also indicate that the degree of fluid overload that is dangerous appears to be lower than 10%. Our study adds to the growing body of evidence regarding risk factors of postoperative FO and aims to help in the early identification of high-risk patients. Avoidance of aggressive fluid therapy and early intervention with fluid removal or institution of RRT appear to be the key therapeutic concepts. Furthermore, the uncertain methodology of assessing fluid balance, the lack of a universal definition for FO and the need to better evaluate pre-operative fluid status in the pediatric cardiac population calls for further studies on this subject.

# Bibliography of the candidate's publications

## Publications related to the PhD thesis


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## Further publications


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