

# High volumes of intravenous fluid during cardiac surgery are associated with increased mortality

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## ABSTRACT

**Introduction:** Positive fluid balance during abdominal surgery has been associated with increased morbidity. We hypothesized that administration of large volumes of intravenous fluids in cardiac surgery is associated with increased mortality.

**Methods:** Retrospective analysis of data on 1358 patients who underwent cardiac surgery from 2001 to 2005 at two major hospitals in Western New York. Patients were divided in to those who received intravenous fluids above the median volume (3.9L) and those who received less than the median volume of intra-operative fluid. Acute Kidney Injury Network criteria based on serum creatinine were used to define Acute Kidney injury.

**Results:** Logistic regression and Cox-proportional models showed increased 90 day mortality (HR -2.8, 95 % CI -1.16-7.01) in those patients who received greater than the median volume of intravenous during cardiac surgery. This was confirmed with propensity score analysis. Furthermore, the marginal effects analysis revealed that after about 4.0 liters of intravenous fluid, the survival probability falls significantly in cardiac surgery patients.

**Conclusions:** Administration of large volumes of intra-operative intravenous fluid is independently associated with an increase in 90 day mortality in cardiac surgery.

**Keywords:** *cardiac surgery, perioperative mortality, outcomes, i fluids, renal dysfunction.*

## INTRODUCTION

Cardiac surgery, primarily coronary-artery bypass grafting (CABG), is commonly performed on a worldwide basis. The unadjusted mortality in the United States has decreased from last decade, however still remains high at 2.2% according to the Society of Thoracic Surgeons. A number of risk factors are associated with increased

surgical mortality: age, female gender, serum creatinine, extra cardiac arteriopathy, chronic airway disease, severe neurological dysfunction, previous cardiac surgery, recent myocardial infarction, left ventricular ejection fraction, chronic congestive cardiac failure (CHF), pulmonary hypertension, active endocarditis, unstable angina, procedure urgency, critical preoperative condition (1). Intra-operative hemodynamic abnormalities, including hypotension during and post cardiac surgery, pulmonary diastolic hypertension have also been shown to be independently associated with increased morbidity and mortality (2, 3). Most of the factors associated with increased mortality

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after cardiac surgeries are non-modifiable. Increased Intravenous Fluid (IVF) in non-cardiac surgery has been shown to be associated with increased morbidity and complications (4). However, controversy still surrounds the type and regimen of fluids to be administered during cardiac surgery. Highly positive intra-operative fluid balance during cardiac surgery has been correlated with increased length of hospital stay and increased rates of Intensive Care Unit (ICU) readmission and blood transfusion (5). We hypothesized that large administration of intravenous fluid during cardiac surgery is associated with increased 90 day mortality.

## METHODS

The study population was drawn from patients who underwent cardiac surgery at 2 tertiary care hospitals affiliated with SUNY at Buffalo: Buffalo Veterans Administration Medical Center (VAMC) and Erie County Medical Center (ECMC). A list of patients who had undergone surgery between January 2001 and January 2006 was generated through the hospital record system. This research protocol was approved by the Buffalo VAMC and SUNY at Buffalo Institutional Review Boards.

Clinical data was collected using a standardized form. Baseline data collection included demographics (age, gender, race, weight, height, BMI, smoking history), co-morbid conditions including congestive heart failure (shortness of breath or weakness with concomitant decreased ejection fraction (< 50%) on two dimensional echocardiography, Anesthesia risk category was determined from American Society of anesthesiologist criteria (ASA). Intra-operative data collection included blood pressure, use of vasopressors, IV fluids and urine output. However dose and type of pressors were

not recorded. Postoperatively serial serum creatinine levels, blood pressure, use of vasopressors, and dialysis requirement were recorded. The total intra-operative IV fluids included Cardiopulmonary bypass (CBP) prime, cardioplegic fluid, crystalloids, colloids and blood transfusions. Urine output was then deducted from above number. Before 2006, ultrafiltration was not being performed during surgery.

## Definitions

Acute kidney injury was defined using the Acute Kidney Network (AKIN) criteria: increase in serum creatinine of  $\geq 0.3$  mg/dl (25  $\mu$ mol/l) or an increase of 50-200% from baseline (6). We did not use urine output criteria in defining AKI.

Race was categorized as Caucasian, African American, or other based on what patient noted in his medical record.

Type of surgery was defined as elective or emergency as per surgical attending note. Hypotension was defined as Systolic Blood pressure less than 90 for more than 15 minutes during the surgery.

ASA was determined from preoperative anesthesia records and stratified into 5 categories. ASA 1 was defined as a healthy individual; ASA 2-patient with mild systemic disease; ASA 3-patient with severe systemic disease; ASA 4-patient with severe systemic disease with constant threat to life; ASA 5-moribund patient who is not expected to survive without surgery. The incidence of all cause mortality was recorded 90 day period from the date of surgery.

## Statistical analysis

Patients were divided into those who received above median intra-operative IVF (> 3.9 liters) and those intra-operative IVF was at or below median ( $\leq 3.9$  liters). The reason to use median to estimate the risk is based on logistic regression analysis showing increasing risk with increasing

IVF especially after 4 liters. Descriptive statistics and/or frequency distributions was obtained for age, gender, body mass index (BMI), preoperative use of angiotensin converting enzyme inhibitors (ACEI) and NSAIDS, preoperative presence of cardiac failure, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, gastrointestinal disorder diseases, liver disease and neurological disease, intra-operative vasopressors and hypotension, and postoperative hypotension, vasopressors use and development of acute kidney injury for all patients. The comparison of continuous variables for patients in the above-median and below-median intra-operative IVF groups was performed using Wilcoxon rank sum test and the comparison of proportions was done using the Chi-square test or the Fisher exact test.

We used logistic regression and Cox proportional models to determine the effect of intra-operative IVF on mortality. For both logistic regression and Cox proportional methods, we constructed several models. First, intra-operative IVF was included as a continuous variable in a stepwise selection model along with other factors. Next we included intra-operative IVF as a dichotomous variable using median value as the separation point as described above, in a stepwise selection along with other variables. Further, we matched the below-median and above-median groups using propensity score. The propensity score was calculated from a stepwise selection logistic model that included all pre-operative variables. The matching was done using the nearest neighbor algorithm with a caliper of 0.01. A final logistic model of mortality was based on the matched sample that included only those variables that were not balanced and the dichotomous indicator for above or below median. We were also interested in identifying the marginal effect of IVF on mortality from the logistic regres-

sion model. The marginal effect of a predictor is defined as the partial derivative of the event probability with respect to the predictor of interest. A more direct measure is the change in predicted probability for a unit change in the predictor from one level to another and can be directly computed by estimating  $p_{xi} - p_{xj}$ , the difference in event probabilities at levels  $i$  and  $j$  of the predictor, here a unit change in IVF (measured in liters). Note that the marginal effect is not constant and depends on the level of the predictor variable. We calculated the predicted probability for unit change in IVF at different values of IVF and plotted them for various combinations of other binary predictors. Finally we also derived KM curves for cumulative probability of survival for different values of IVF. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test. SAS 9.1.3 was used to estimate the KM survival function and the Cox models.

## RESULTS

Thirteen hundred and fifty eight patients over the age of 18 years who underwent cardiac surgery at two major hospitals in Western New York between 01/1/2001 to 12/31/2005 were the subjects of study. The mean age of patients was 65.9 (+ 11.4) years. The majority of the patients were Caucasians (**86%**) and were male (79.2%). The mean BMI was 29.3 (**± 5.9**). 33.7% had diabetes, 80% had hypertension, 20% had CHF and 18% had COPD. The mean baseline serum creatinine was 0.96 ( $\pm 0.21$ ) mg/dl and the majority of the surgery was CABG alone (**87%**) and done electively (**91%**) with cardiopulmonary bypass pump (69%). The mean use of IV fluids during surgery was **3910 ml ( $\pm 2121$ )**. 44.6% developed hypotension during operation and 13% developed hypotension after opera-

tion. The mean length of hospital stay of all patients was **8 ( $\pm$  10.4)** days.

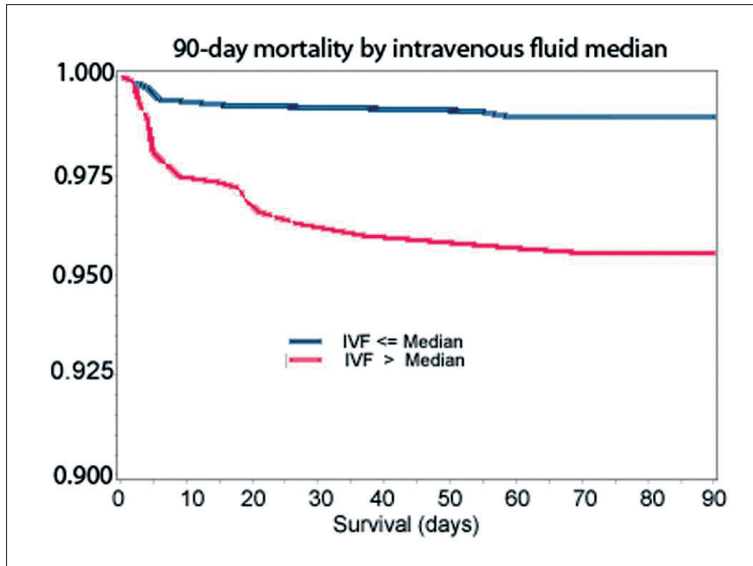
The distribution of demographic variables, co-morbidities, intra- and post-operative risk factors across the 2 groups of IVF administration are shown on *Table 1*. Factors associated with increased intra-operative IVF administration were: male gender, caucasian race, ASA risk of 4/5, combined surgery, higher preoperative serum creatinine level, CHF, COPD, hypotension during surgery, use of intra-operative vasopressors, on-pump surgery, and non elective surgery. Thirty seven patients died within 90 days of surgery. The mortality among patients who received greater than the median amount of IVF was 5.12/10,000 patient-year compared to 1.15 in patients who received less than the median volume of IVF. Univariate analysis showed that administration of greater than median volume of intra-operative IVF was significantly associated with higher 90 days mortality ( $p=0.002$ ) (*Figure 1*). In addition,

univariate analysis also showed that higher age, CHF, anesthesia risk category 4 and 5, intra- or post-operative hypotension and higher baseline serum creatinine were significantly associated with 90 days mortality. Several adjusted Cox proportional hazard models and logistic models were built and the effect of demographic variables, anesthesia risk category 4/5, intra-operative risk factors and postoperative risk factors were included. After including the effect of all significant variables administration of greater than the median amount of IVF intra-operatively remained an independent risk factor for the 90 days mortality after cardiac surgery (*Table 2*). The unmatched models of mortality with IVF as a continuous variable and as a binary variable indicate that high levels of IVF increased the risk of mortality. For every liter of IVF given during surgery the odds of death increased by 27%. Similarly for patients who receive above median IVF the odds of mortality were 3.6 times

**Table 1** - Frequency distribution and Univariate Statistics of Variables by IVF administrat

Variable	IVF < Median (%)	IVF > Median (%)	P <sup>§</sup>
Age*	65.4 (+ 11.9)	66.4 (+ 12.0)	0.1
Female	174 (25.5 %)	109 (89.0)	0.008
White	574 (84.0)	600 (89.0)	< .0001
Body Mass Index*	29.31 (+ 5.99)	29.31 (+ 6.21)	0.9
Diabetes	157 (28.34 %)	141 (32.87 %)	< .0001
Hypertension	417 (75.27 %)	351 (81.82 %)	0.0001
CHF	80 (14.44 %)	75 (17.48 %)	< .0001
COPD	75 (13.54 %)	85 (19.81 %)	0.001
Serum Creatinine at Baseline*	0.94 (+ 0.19)	0.94 (+ 0.21)	< .0001
Anesthesia Risk Category $\geq$ 4	129 (23.29 %)	140 (32.63 %)	< .0001
Elective/Urgent Surgery	519 (93.68 %)	391 (91.14 %)	0.002
Surgery Type - CABG	510 (92.06 %)	380 (88.58 %)	< .0001
On Pump Surgery	342 (61.84 %)	295 (68.93 %)	< .0001
Intra-operative Hypotension	204 (36.82 %)	198 (46.15 %)	< .0001
Intra-operative IVF use*	3701 (+ 1996)	3960 (+ 2302)	0.0001
Post-operative Hypotension	56 (10.11 %)	56 (13.05 %)	0.004

\*Value expressed in Mean (+ SD); §p-value calculated by CMH Test for fixed variables and by Kruskal-Wallis Test for continuous variables. IVF - Intravenous fluids. Note: Conversion factors for units: serum creatinine in mg/dL to mol/L,  $\times$  88.4



**Figure 1**  
Univariate analysis showing risk of mortality and IVF.

**Table 2 - Analysis of Maximum Likelihood Estimates.**

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiS	Hazard Ratio	95 % Confidence Limits	
IVF ≥ Median	0.96	0.42	5.01	0.025	2.61	1.12	6.06
Anesthesia Risk Category ≥4	1.26	0.35	12.31	0.0004	3.53	1.74	7.14
Post-operative Hypotension	1.51	0.34	18.89	< .0001	4.56	2.30	9.06
Intra-operative Hypotension	0.71	0.40	3.18	0.075	2.05	0.93	4.52
Change in Peak creatinine*	0.76	0.13	34.44	< .0001	2.15	1.66	2.78
On/OffPump	-0.88	0.36	6.03	0.014	0.41	0.20	0.83

**Table 3 - Odds Ratio Estimates (Multivariate Analysis).**

Effect	Point Estimate	95 % Wald Confidence Limits	
IVF ≥ median Vs < Median	3.61	1.54	8.43
Intra-operative Hypotension	3.27	1.49	7.17
AKI	2.61	1.28	5.30
Off -Pump	0.42	0.21	0.87

IVF = Intravenous fluids. AKI = Acute Kidney Injury.

**Table 4** - Odds ratio estimates based on propensity score matched patients

Effect	Point Estimate	95% Wald Confidence Limits
Age	1.04	1.0 1.09
IVF $\geq$ than Median	2.85	1.16 7.01
Intra-operative Hypotension	3.25	1.35 7.82
ASA risk	2.74	1.20 6.25
AKI	2.69	1.08 6.69
Off -Pump	0.37	0.16 0.88

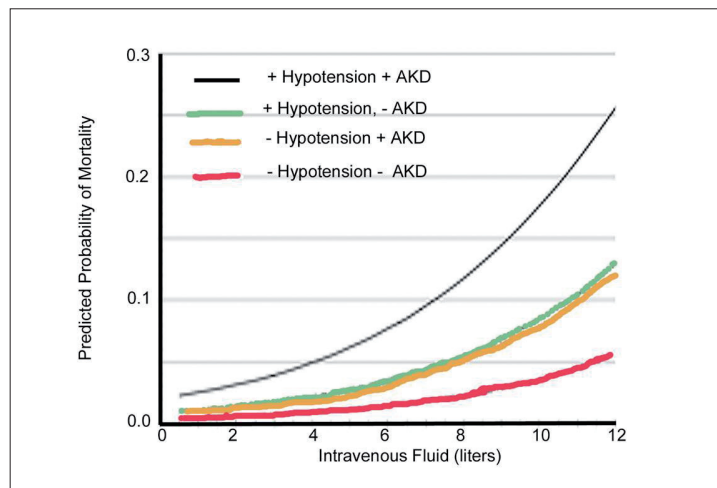
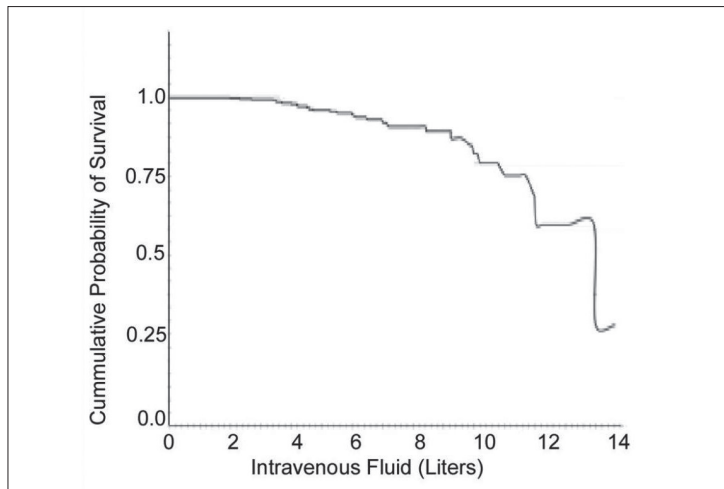
IVF = Intravenous fluid. AKI = Acute Kidney Injury. ASA = American Society of Anesthesiologists.

higher than those for patients at or below median (Table 3). Sensitivity analysis was done for intra-operative IVF administration based on BMI and weight and no difference was noted.

The propensity score model could match only 494 patients from each group. The outcome model after matching also established increased risk of mortality with administration of higher volume of IVF although the odds were reduced to 2.86 (CI 1.16-7.01) (Table 4).

The predicted probability increased at every level of IVF. The marginal effects further

**Figure 2**  
Survival Probability Vs IVF.



**Figure 3**  
Predicted Effect of IVF for Different Intra-operative Hypotension and AKI.

demonstrate that change in the probability for unit change in IVF also increases at every level of IVF. Finally the survival curves indicate that after about 4.0 liters of IVF, the survival probability falls and drastically changes above 9 liters (*Figure 2*). Mortality was further increased with presence of intraoperative hypotension and later development of AKI (*Figure 3*).

## DISCUSSION

We found that administration of greater than the median amount of IV fluid during cardiac surgery was associated with a greater than three-fold increase in mortality. In univariate analysis, preoperative variables that were significantly associated with mortality included increasing age, combined valve surgery and CABG compared to CABG alone, ASA category 4/5 compared to 2/3, intra- and post-operative hypotension, CHF, and change in serum creatinine and more than median IVF. Adjusting for these factors in logistic and Cox models confirmed the association of greater than the median amount of intravenous fluid with increased mortality. Furthermore, propensity score analyses confirmed the results (HR 2.86).

Currently, the practice of giving IV fluids is often dictated by a non evidence based approach, taking account of pre-operative deficit, maintenance requirements, and extrapolated third space losses (7). There is a perception that patients who are undergoing cardiac surgery require liberal fluid replacement, there are no evidence based guidelines on how much fluid to give. Moreover evidence suggests that extracellular volume is well maintained after surgery due to the neuro endocrine responses (8). There may be a tendency to use more IVF during cardiac surgery especially in patients who develop hypotension. Intra-

operative hypotension is an independent predictor of death in cardiac surgery patients. We adjusted our analysis with intraoperative hypotension in the model, the effect of IVF remain significant on mortality (*Figure 3*). Although data is lacking on the association of IVF amount and mortality in cardiac surgery patients, Toraman et.al showed that increased intra-operative fluid balance in cardiac surgery is associated with increased length of hospital stay (5). The study did not show significant increase in mortality with increased IVF. However, this study only examined patients who had more than 500 cc of positive fluid balance. In addition, studies of patients undergoing colorectal and abdominal surgeries randomized to restrictive and standard fluid IV fluid administration showed an increase in postoperative morbidity and longer hospital stay in the latter group (9, 10). Increasing weight, indicative of water and salt retention, has been shown to correspond with increased mortality while achieving a negative balance within the first 72 hours of ICU admission has been postulated as an independent predictor of survival (11). Indeed, sepsis trials have shown an association between volume overload and adverse clinical outcomes (12-15). Recently, Bouchard et al showed that fluid accumulation (defined by increase of more than 10% weight from baseline) among 618 critically ill patients with AKI was associated with higher odds of death (16). In our study, we showed that a patient who receives higher than median IVF during cardiac surgery had significantly higher 90 day mortality. However the use of median is only an arbitrary number as there is no data in the literature to show what the optimum IVF is. Now a day, ultrafiltration is being employed during surgery, the effect of which on mortality is not studied so far. We did not use ultrafiltration during surgery in our patients.

The mechanisms by which increased administration of intravenous fluid may result in increased mortality are unclear. Two main factors that may contribute are: 1) development of congestive heart failure; and 2) hemodilution.

Hemodilution has been linked to decreased oxygen delivery, increased lactate production and increased risk of AKI and mortality (17-19). Indeed, Lassnigg et. al showed a significant increase in mortality in the group of patients with the most pronounced fall in postoperative serum creatinine ( $\geq 0.3$  mg/dl) (20). Patients who had less than a 0.3 mg/dl drop in serum creatinine had better outcomes compared to those who had a decrease greater than 0.3 mg/dl. Cardiopulmonary bypass (CPB) may cause systemic inflammatory response syndrome (SIRS) (21, 22), leading to third space fluid loss. Contact of blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia, operative trauma, and non-pulsatile blood flow, are possible causes of SIRS in this situation (1, 23). This inflammatory response and increased vascular permeability in conjunction with massive intravenous fluid administration leads to extravascular fluid accumulation and pulmonary edema and prolongs the stay in the hospital (24). In one study interstitial fluid volume increased by an average of 14% during coronary artery bypass graft surgery (25). During cardiac surgery, the patient is exposed to the administration of a considerable amount of intravenous fluids. Such fluids include the preoperative period, intra-operative period including CPB pump prime, the fluids used for cardioplegia and fluids given to deal with hypotensive episodes and in the postoperative period (26, 27). This increased fluid overload burdens a heart which often is weakened by the original pathology for which surgery is being done. Often it leads

to fluid overload which may participate in the pathogenesis of postoperative hypoxemia, myocardial edema and organ edema leading to a delay in recovery. Myocardial edema has been implicated as the cause of an increase in left ventricle stiffness and a decrease in the LV volume (28). This can lead to vicious cycle of hypotension and administration of more IVF further exacerbating the edema.

Our study has several strengths. We included all patients who had undergone cardiac surgery in 2 different academic medical centers in with different demographics and clinical condition, increasing the generalizability of our results. Furthermore we used propensity score analysis adjust for confounding by indication. There are important limitations to our study. We did not distinguish whether IVF was crystalloid or colloid, or CBP prime. We did not account for the variability of IVF administration based on surgeon or the anesthesiologist. Since this being a retrospective study we do not have a data on why increased IVF were used in some patients and what intraoperative techniques were used to determine it. Our results could be confounded by other factors such as renal dysfunction events. However adjusting for AKI in our study, effect of increased IVF on mortality remains significant. Since this is a retrospective study, even with various logistic models, we cannot truly evaluate the effect of intravenous fluid on mortality as we could in prospective randomized trial. Although propensity score model can adjust for confounding by indication, it may not eliminate residual unobserved factors.

### **Limitations**

In the median number of 3.9 liters is arbitrary cut off and cannot be established. However, marginal effects analyses further confirm that above 4.0 liters of IVF, the survival probability falls and drastically chang-



es above 9 liters. Since this is a retrospective study, even with various logistic models, we cannot truly evaluate the effect of intravenous fluid on mortality as we could in prospective randomized trials. Further studies are needed to confirm these results.

## CONCLUSIONS

We have shown an association between administering increasing volumes of intravenous fluid during cardiac surgery and increased risk of mortality at 90 days. We suggest a more judicious and conservative approach to intra-operative intravascular volume expansion for all patients.

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