Low Systemic Oxygen Delivery and BP and Risk of Progression of Early AKI

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Abstract

Background and objectives The optimal hemodynamic management of patients with early AKI is unknown. This study aimed to investigate the association between hemodynamic parameters in early AKI and progression to severe AKI and hospital mortality.

Design, setting, participants, & measurements This study retrospectively analyzed the data of all patients admitted to the adult intensive care unit in a tertiary care center between July 2007 and June 2009 and identified those with stage 1 AKI (AKI I) per the AKI Network classification. In patients in whom hemodynamic monitoring was performed within 12 hours of AKI I, hemodynamic parameters in the first 12 hours of AKI I and on the day of AKI III (if AKI III developed) or 72 hours after AKI I (if AKI III did not develop) were recorded. Risk factors for AKI III and mortality were identified using univariate and multivariate logistic regression analyses.

Results Among 790 patients with AKI I, 210 (median age 70 years; 138 men) had hemodynamic monitoring within 12 hours of AKI I; 85 patients (41.5%) progressed to AKI III and 91 (43%) died in the hospital. AKI progressors had a significantly higher Sequential Organ Failure Assessment score (8.0 versus 9.6; $P<0.001$), lower indexed systemic oxygen delivery (DO_2I) (median 325 versus 405 ml/min per m^2; $P<0.001$), higher central venous pressure (16 versus 13; $P=0.02$), and lower mean arterial blood pressure (MAP) (median 71 versus 74 mmHg; $P=0.01$) in the first 12 hours of AKI I compared with nonprogressors. Multivariate analysis confirmed that raised lactate, central venous pressure, and Sequential Organ Failure Assessment score as well as mechanical ventilation were independently associated with progression to AKI III; higher DO_2I and MAP were independently associated with a lower risk of AKI III but not survival. The associations were independent of sepsis, heart disease, recent cardiac surgery, or chronic hypertension.

Conclusions Higher DO_2I and MAP in early AKI were independently associated with a lower risk of progression.

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Introduction

AKI is common and is associated with significant short- and long-term complications and mortality (1–3). Survivors of AKI are at risk of CKD, even if renal function initially recovers (4–10). In the United Kingdom, the annual cost of AKI to the National Health Service (NHS) is estimated at £1.02 billion, which is more than the expenditure on common cancers combined (11). Strategies to prevent AKI or mitigate its severity have potential to benefit patients as well as the health care system.

Walsh *et al.* showed that even short durations of hypotension during surgery were associated with a higher risk of postoperative AKI (12). In high-risk surgical patients, perioperative hemodynamic monitoring and resuscitation have been shown to protect renal function (13). A Cochrane review including 27 studies in adults undergoing surgery concluded that fluid and/or vasoactive drugs targeted to increase global blood flow reduced mortality and prevented AKI (14). However, most studies were performed in heterogeneous surgical populations without AKI, using different hemodynamic targets and methods of optimization. Experts, including the Kidney Disease Improving Global Outcomes (KDIGO) group, have recommended that physicians consider hemodynamic monitoring in all patients with AKI (15–17). However, there are no evidence-based data on the optimal hemodynamic targets.

Our aim was to investigate the association between hemodynamic indices in the early phase of AKI and the risk of progression to severe AKI and mortality in critically ill patients.

Materials and Methods

Setting

Guy's and St Thomas' NHS Foundation Hospital is a tertiary care center with a 43-bed, level 3 multidisciplinary adult intensive care unit (ICU). The ICU has a fully computerized electronic patient record system in which all data are recorded at the time of

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generation. Serum creatinine is measured daily between 5:00 a.m. and 7:00 a.m.

Patient Selection

We retrospectively analyzed a database containing data on all patients admitted to the ICU between July 2007 and June 2009. We identified those patients with stage 1 AKI (AKI I) according to the creatinine criteria of the AKI Network (AKIN) classification (*i.e.*, rise in serum creatinine by ≥0.3 mg/dl [≥26.4 μmol/L] or by ≥50% from baseline in ≤48 hours) (18). We only used creatinine results obtained during the current hospitalization to diagnose AKI in order to comply with the 48-hour time window, and we defined baseline renal function by the lowest creatinine result.

We screened the electronic medical records of patients identified as having AKI and selected those in whom advanced hemodynamic monitoring had been initiated by the treating clinicians for clinical reasons within 12 hours of the patient meeting the criteria for AKI I. A 12-hour window was chosen for pragmatic reasons. We excluded renal transplant patients, readmitted patients, and patients who left the ICU within 24 hours of AKI I or developed AKI III within 12 hours of AKI I.

Depending on whether patients with AKI I developed AKI III after the 12-hour period, we differentiated between progressors and nonprogressors. AKI III was defined per the AKIN classification (*i.e.*, rise of serum creatinine to >3-fold from baseline or to ≥354 μmol/L with an acute rise of ≥44 μmol/L, or requirement for RRT). Patients who progressed to stage 2 AKI (AKI II) (but not AKI III) and recovered renal function were classified as nonprogressors. Patients with AKI I who died before renal function changed were only included in the mortality analysis, but they were not included in the progression analysis.

Data Collection

We recorded information on demographics, comorbidities, diagnoses, and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment (SOFA) scores (19,20) on admission to the ICU. We also recorded information on SOFA scores, 24-hour urine output, cumulative fluid balance, type of organ support, and presence of sepsis on the day of AKI I. Sepsis was defined per consensus criteria (21). We collected the following data within the first 12 hours of AKI I: first available indexed cardiac output (CI) and contemporaneous arterial oxygen saturation (SO_2), hemoglobin (Hb), arterial lactate, central venous pressure (CVP), and mean arterial blood pressure (MAP). Indexed systemic oxygen delivery (DO_2I) was calculated as $DO_2I = 1.34 \times Hb \times SO_2 \times CI$. We calculated mean MAP and mean urine output during the first 12 hours of AKI I.

The same data were collected again on the day of AKI III (in progressors) or 72 hours after the diagnosis of AKI I (in nonprogressors). The 72-hour time point was chosen because the mean duration between AKI I and AKI III was 2.6 days (SD 3.4), and 85% of progressors met the criteria for AKI III at 72 hours after AKI I. The main outcomes were development of AKI III and hospital mortality.

Statistical Analyses

Continuous variables were summarized as the mean (SD) or the median (interquartile range [IQR]) as appropriate. Categorical variables were described as the frequency (percentage). Comparisons between progressors and nonprogressors as well as hospital survivors and nonsurvivors were made using unpaired *t* tests or Mann–Whitney tests when the characteristics were summarized using a continuous scale. Categorical data were compared using a chi-squared or Fisher's exact test.

The associations between hemodynamic indices and odds of AKI progression and hospital mortality were evaluated by logistic regression analysis using a forward stepwise procedure. The variables considered for inclusion in the multivariate models were based on clinical judgement and a *P* value <0.10 in univariate analysis. Odds ratios and *P* values for nonsignificant variables were calculated by adding them, one at a time, to a model including all those identified as significant.

To assess the stability of the model identified using stepwise procedures, a bootstrapping approach was utilized. One thousand bootstrap samples of equal size to the study data set were randomly drawn, with replacement from the data set and a stepwise procedure implemented within each sample. The percentage of samples in which each variable was entered into the model was recorded.

Logistic regression models were used to explore associations between trends in hemodynamic indices after the initial 12-hour period of AKI I and outcome (progression to AKI III and mortality). Univariable models were used to show the unadjusted associations. Multivariable models provided estimates of associations adjusted for hemodynamic indices and any other variables found to be associated with progression or death in the above-described stepwise models. Variables that were highly correlated were not included in the multivariable analysis to avoid any issues of colinearity. The assumptions of the logistic regression models were verified by assessing the log-linearity of the relationship between the two outcomes and each of the covariates entered into the models using the Box–Tidwell test. Overall goodness of fit was assessed using the Hosmer–Lemeshow test. There was no evidence to reject the assumptions of log-linearity or adequate fit of the models (all *P* values >0.05).

In sensitivity analyses, we stratified the models by presence of sepsis, heart disease, preexisting hypertension, and admission after cardiac surgery to investigate any potential interactions. All tests were two sided and $P<0.05$ was considered statistically significant. Analyses were conducted using Stata12MP software.

Ethics

This study had institutional approval. The need for individual informed consent was waived because this was a retrospective analysis of data collected prospectively for routine care with no breach of privacy or anonymity (UK National Research Ethics Service).

Results

There were 2118 patients who were admitted to the ICU; 790 patients (37%) met the criteria for AKI I. Sixty-nine patients were excluded (Figure 1). Among the remaining

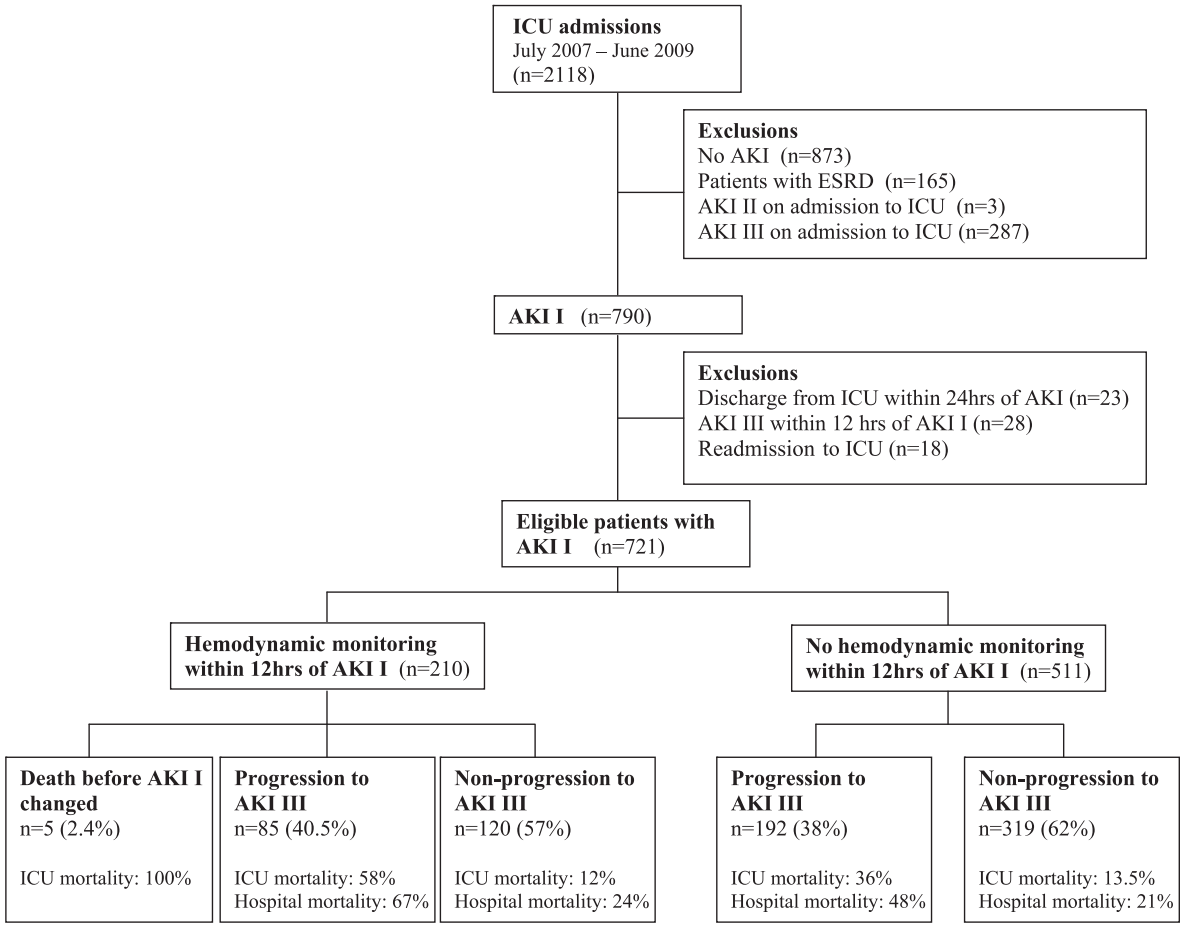

Figure 1. | **Flow of patients.** AKI I, stage 1 AKI; AKI II, stage 2 AKI; AKI III, stage 3 AKI; ICU, intensive care unit.

721 patients, hemodynamic monitoring using a pulse-induced contour or lithium dilution cardiac output technique was initiated by the clinical team in 210 patients within 12 hours of AKI I. The median age of this cohort was 70 years (IQR, 57–77), 68% of patients were men, and 44% had underlying cardiac disease (coronary artery disease [CAD] and/or congestive cardiac failure [CCF]) (Table 1). The median number of days between ICU admission and AKI I was 1 (IQR, 0–22). ICU mortality and hospital mortality were 32.4% and 43.3%, respectively (Table 1). Eighty-five patients (41%) developed AKI III.

For comparison, early hemodynamic monitoring was not initiated in 511 patients with AKI I. Their outcome was significantly better than that of patients with early hemodynamic monitoring (ICU mortality: 22% versus 32%, P=0.001; hospital mortality: 32% versus 43%, P=0.004) but they were less sick on admission to the ICU (Table 1). In this group, 192 patients (38%) developed AKI III; of these patients, 69 (36%) died in the ICU and 92 (48%) died in the hospital.

Progression to AKI III

Among patients with early hemodynamic monitoring within 12 hours of AKI I, 85 patients (41.5%) developed AKI III; 78 (92%) of these patients received RRT. The mean time from diagnosis of AKI I to AKI III was 2.6 days (SD 3.35). Progressors had a significantly higher prevalence of heart disease compared with 120 patients with AKI I who did not progress to AKI III (58% versus 34%; P=0.001) (Table 2). There was no difference in age, sex, or severity of illness on admission to the ICU. In the first 12 hours of AKI I, progressors had a significantly higher SOFA score and CVP and significantly lower CI, DO_2I, urine output, and MAP compared with nonprogressors. ICU and hospital mortality were significantly higher in progressors (Figure 1, Table 2). The clinical characteristics of patients in the lower quartiles of DO_2I or MAP were not significantly different from those with higher values (Supplemental Tables 1 and 2).

Mortality

Sixty-eight patients with AKI I (32%) died in the ICU and 91 (43%) died in the hospital (Table 1). Hospital nonsurvivors were older, had a significantly higher SOFA score and total cumulative fluid balance, and needed vasopressor treatment more often on the day of AKI I compared with hospital survivors (Table 2). Hemodynamic indices in the first 12 hours of AKI I were not significantly different (Table 2).

Multivariate Analyses

Multivariate analysis confirmed that underlying heart disease (CAD and/or CCF), SOFA score, CVP, arterial lactate,

Table 1. Characteristics of patients with AKI I with and without hemodynamic monitoring within 12 hours of AKI I

Indices	Patients with Hemodynamic Data within 12 h of AKI I (*n*=210)	Patients without Hemodynamic Data within 12 h of AKI I (*n*=511)	*P* Value
Age (yr)	70 (57–77)	65 (51–75)	0.002
Men	142 (67.6)	329 (65.5)	0.59
Comorbidities			
Diabetes mellitus	40 (19.1)	96 (18.8)	0.94
Chronic hypertension	81 (38.6)	178 (34.8)	0.34
CAD/CCF	92 (43.8)	210 (41.1)	0.50
CKD	25 (12.2)	72 (14.1)	0.43
COPD	27 (12.9)	61 (11.9)	0.73
Chronic liver disease	12 (5.7)	31 (6.1)	0.56
Malignancy	28 (13.3)	73 (14.3)	0.74
Neurologic disease	23 (11.0)	46 (9.0)	0.42
Postsurgical admission	72 (34.3)	171 (33.5)	0.83
Admission diagnosis			
Cardiac	54 (25.7)	106 (20.7)	0.14
Respiratory	34 (16.2)	109 (21.3)	0.12
Sepsis	38 (18.1)	69 (13.5)	0.12
Post cardiac surgery	42 (20)	42 (8.2)	<0.001
Post noncardiac surgery	30 (14.3)	129 (25.2)	0.001
Gastrointestinal	8 (3.8)	41 (8.0)	0.04
Other	4 (1.9)	15 (2.9)	0.61
Source of admission			
Accident and emergency department	13.3	19.6	0.14
Operating room	31.9	31.7	
Ward	40	33.1	
Transfer from other hospital	14.3	15.6	
Severity of illness on admission to the ICU			
APACHE II score	18 (14–22)	17 (14–21)	0.04
SOFA score, mean (SD)	7.12 (2.76)	6.2 (3.1)	0.002
Severity of illness on the day of AKI I			
Sepsis	125 (60)	261 (51.1)	0.04
SOFA score, mean (SD)	8.7 (2.7)	7.4 (3.2)	<0.001
Arterial lactate (mmol/L)	1.8 (1.3–2.6)	[a]	
CVP (cm H_2O)	14 (10–18)	[a]	
Treatment with vasopressors	187 (89.1)	347 (67.9)	<0.001
Treatment with mechanical ventilation	191 (91.0)	373 (73)	<0.001
MAP in first 12 h of AKI I (mmHg), mean (SD)	73.7 (7.9)	73.0 (6.9)	0.24
Hemoglobin in first 12 h of AKI I (g/dl)	9.9 (8.7–11.6)	9.9 (8.8–11.7)	0.98
Outcome			
Days spent in ICU	12 (6–23)	8 (5–20)	0.01
ICU mortality	32.4	22.1	0.004
Hospital mortality	43.3	31.5	0.002
Progression to AKI III	85 (41.5)	192 (37.6)	0.47

Data are presented as the median (interquartile range), *n* (%), or percentage, unless otherwise indicated. AKI I, stage 1 AKI; CAD, coronary artery disease; CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CVP, central venous pressure; MAP, mean arterial blood pressure; AKI III, stage 3 AKI.
[a]Data not available for all patients.

and mechanical ventilation on the day of AKI I were independent risk factors for AKI III (Table 3). Higher DO_2I and higher MAP in the first 12 hours of AKI I were associated with a lower risk of AKI III. There was a clear relationship between DO_2I and MAP categories and risk of progression to AKI III (Figures 2 and 3). Across the bootstrap samples, CAD/CCF and arterial lactate were the most consistently identified predictors and entered into 80% of the models; DO_2I and MAP were significant in two-thirds. SOFA scores, lower urine output, and vasopressor therapy on the day of AKI I were independently associated with hospital mortality (Table 3).

Stratification for AKI Risk Factors

There were 125 patients (60%) with sepsis on the day of AKI I; 35% of these patients progressed to AKI III compared with 51% of patients without sepsis (*P*=0.03).

Table 2. Univariate analysis: Comparison between AKI progressors and nonprogressors and hospital survivors and nonsurvivors

Indices	Did Not Progress to AKI III (*n*=120)	Progressed to AKI III (*n*=85)	*P* Value	Hospital Survivors (*n*=119)	Hospital Nonsurvivors (*n*=91)	*P* Value
Median age (yr)	69.5	71	0.11	69	72	0.01
Men	75 (65.2)	57 (69.5)	0.53	76 (66.7)	60 (68.2)	0.82
Postsurgical admission	34 (28.3)	31 (36.5)	0.22	37 (31.1)	28 (30.8)	0.96
Comorbidities						
CAD	41 (34.2)	45 (52.9)	0.01	47 (39.5)	41 (45.1)	0.42
CHF	0	4 (4.7)	0.02	1 (0.8)	3 (3.3)	0.32
Diabetes	21 (17.5)	17 (20)	0.65	22 (18.5)	18 (19.9)	0.91
CKD	12 (10)	13 (15.3)	0.25	12 (10.1)	15 (16.5)	0.17
COPD	14 (11.7)	12 (14.1)	0.60	16 (13.5)	10 (11.0)	0.59
Chronic liver disease	6 (5.0)	5 (5.9)	0.78	4 (3.4)	8 (8.8)	0.13
Malignancy	15 (12.5)	12 (14.1)	0.60	14 (11.8)	14 (15.4)	0.44
Chronic hypertension	46 (38.3)	33 (38.8)	0.94	46 (38.7)	35 (38.5)	0.98
Severity of illness on admission to the ICU						
APACHE II score	17 (13–21)	18 (15–22)	0.09	17 (14–21)	19 (14–22)	0.05
SOFA score, mean (SD)	6.9 (2.7)	7.5 (2.9)	0.14	6.95 (2.69)	7.34 (2.86)	0.32
Severity of illness on the day of AKI I						
Presence of sepsis	79 (66.4)	43 (50.6)	0.02	70 (59.3)	55 (60.4)	0.87
SOFA score, mean (SD)	8.0 (2.5)	9.6 (2.8)	<0.001	8.1 (2.4)	9.5 (2.9)	<0.001
Need for mechanical ventilation	103 (85.8)	84 (98.8)	<0.001	104 (87.4)	87 (95.6)	0.05
Parameters in first 12 h of AKI I						
Hemoglobin (g/dl)	9.6 (9.0–10.5)	9.6 (8.5–10.5)	0.64	9.7 (9.1–10.5)	9.3 (8.5–10.5)	0.09
Arterial SO_2	0.95 (0.94–0.96)	0.95 (0.94–0.96)	0.81	0.95 (0.94–0.96)	0.95 (0.94–0.96)	0.49
Cardiac index (L/min per m^2)	3.32 (2.52–4.2)	2.63 (2.11–3.33)	<0.001	3.29 (2.47–4.19)	2.94 (2.19–3.79)	0.05
DO_2I (ml/min per m^2)	405 (302–514)	325 (266–401)	<0.001	390 (308–518)	364 (268–443)	0.05
CVP (cm H_2O)	13 (10–17)	16 (11–19)	0.02	14 (10–18)	15 (10–19)	0.56
MAP (mmHg)	74 (70–79)	71 (68–77)	0.01	73 (69–79)	72 (67–77)	0.06
MAP <65 mmHg for >1 h	55 (45.8)	52 (61.2)	0.03	58 (48.7)	51 (56.0)	0.29
Cumulative fluid balance (ml)	2379 (935–4221)	2363 (974–3197)	0.99	1844 (589–3698)	2536 (1445–4133)	0.01
Urinary output (ml/h)	66 (46–104)	54 (32–79)	0.002	66 (45–103)	54 (27–79)	<0.001
Arterial lactate (mmol/L)	1.6 (1.1–2.3)	2 (1.5–3)	<0.001	1.6 (1.1–2.5)	1.9 (1.4–2.8)	0.06
On vasopressor therapy	100 (83.3)	82 (96.5)	0.003	99 (83.2)	88 (96.7)	0.002
ICU mortality	14 (11.7)	49 (57.6)	<0.001	—	—	—
Hospital mortality	29 (24.2)	57 (67.1)	<0.001	—	—	—

Data are presented as the median (interquartile range), *n* (%), or percentage, unless otherwise indicated. CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AKI I, stage 1 AKI; SO_2, oxygen saturation; DO_2I, indexed systemic oxygen delivery; CVP, central venous pressure; MAP, mean arterial blood pressure; AKI III, stage 3 AKI.

Patients with sepsis had a significantly higher CI (3.3 versus 2.74; $P<0.001$) and higher DO_2I (397 versus 333; $P=0.001$) on the day of AKI I than patients without sepsis, but there was no difference in mean MAP and number of vasopressors.

Patients with CAD and/or CCF had significantly lower CI (median 2.59 [IQR, 2.2–3.3] versus 3.32 [2.6–4.1]; $P<0.001$] and DO_2I (median 329 [IQR, 265–408] versus 401 [IQR, 296–508]; $P<0.001$) compared with patients without heart disease. There was no difference in mean

Table 3. Multivariate analysis: Risk factors for progression to AKI III and hospital mortality

Indices	Progression to AKI III			Hospital Mortality		
	Odds Ratio (95% Confidence Interval)	*P* Value	Percent Retained in Bootstrap Analysis	Odds Ratio (95% Confidence Interval)	*P* Value	Percent Retained in Bootstrap Analysis
Mechanical ventilation	22.6 (2.37 to 215.0)	0.01	28	0.75 (0.56 to 2.18)	0.60	5
CAD/CCF	3.32 (1.61 to 6.84)	0.001	79	1.21 (0.66 to 2.12)	0.53	13
Arterial lactate within 12 h of AKI I (per 1 mmol/L)	1.53 (1.14 to 2.06)	0.004	81	1.19 (0.97 to 1.46)	0.10	26
SOFA score on the day of AKI I	1.18 (1.03 to 1.37)	0.02	47	1.17 (1.04 to 1.32)	0.01	54
CVP (per 2 cm H_2O)	1.09 (1.02 to 1.16)	0.01	54	0.99 (0.94 to 1.04)	0.79	5
DO_2I (per 50 ml /min per m^2)	0.87 (0.77 to 0.98)	0.03	63	0.96 (0.86 to 1.06)	0.40	9
MAP 12 h (per 5 mmHg)	0.76 (0.59 to 0.98)	0.03	65	1.02 (0.83 to 1.26)	0.83	8
Vasopressor use	1.49 (0.36 to 6.22)	0.59	5	3.92 (1.08 to 14.2)	0.04	30
Urine output on the day of AKI I (per 100 ml)	0.46 (0.20 to 1.07)	0.07	39	0.99 (0.98 to 0.99)	0.004	71
Fluid balance on the day of AKI I (per 1000 ml)	1.00 (0.89 to 1.13)	0.99	8	1.07 (0.96 to 1.20)	0.22	26
APACHE II score on admission to the ICU	1.04 (0.97 to 1.10)	0.28	25	1.05 (0.99 to 1.11)	0.08	34

Multivariate analysis of risk factors identified in univariate analysis using forward stepwise logistic regression. AKI III, stage 3 AKI; CAD, coronary artery disease; CCF, congestive cardiac failure; AKI I, stage 1 AKI; SOFA, Sequential Organ Failure Assessment; CVP, central venous pressure; DO_2I, indexed systemic oxygen delivery; MAP, mean arterial blood pressure; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

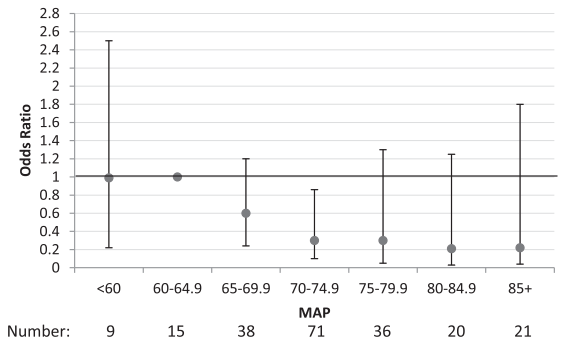

Figure 2. | Association between MAP and risk of progression to AKI III. The figure demonstrates odds ratios and 95% confidence intervals per multivariate analysis (reference: MAP category = 60–64.9 mmHg). Number indicates the number of patients included per category. AKI III, stage 3 AKI; MAP, mean arterial pressure in first 12 hours after diagnosis of AKI I (in mmHg).

MAP in the first 12 hours of AKI I in patients with and without heart disease (73 [SD 7.3] versus 74 [8.3], respectively; *P*=0.22) and there was no statistically significant difference in the proportion of patients on vasopressor support (91.3% of patients with heart disease versus 87.3% of patients without heart disease; *P*=0.36).

Multivariate analysis confirmed that the effects of MAP and DO_2I on the risk of progression and mortality were independent of whether patients had sepsis on the day of AKI I or had heart disease (Table 3). There was no statistically significant difference in the risk of AKI III between patients with AKI I with and without preexisting hypertension or after cardiac surgery (Supplemental Table 3).

Trends in Hemodynamic Parameters 12–72 Hours after Diagnosis of AKI I

Beyond the initial 12-hour period of AKI I, a rise in DO_2I, Hb, or SO_2 had no effect on the risk of AKI III or mortality (Table 4). An increase in MAP was associated with a significantly lower risk of AKI III, and a rise in cumulative

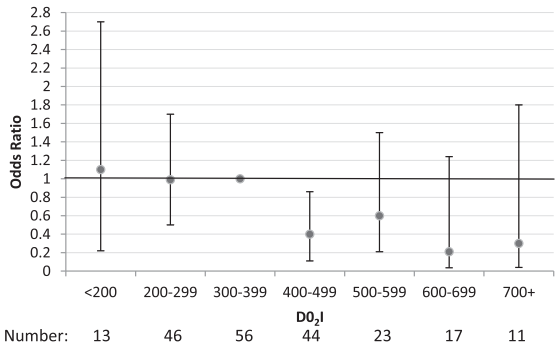

Figure 3. | Association between DO_2I and risk of progression to AKI III. The figure demonstrates odds ratios and 95% confidence intervals per multivariate analysis (reference: DO_2I category = 300–399 ml/min per m^2). Number indicates the number of patients included per category. AKI III, stage 3 AKI; DO_2I, indexed systemic oxygen delivery (in ml/min per m^2).

fluid balance >1 L/d was independently associated with a higher risk.

Discussion

This retrospective single-center study shows that higher systemic oxygen delivery and higher MAP in the initial 12 hours of AKI I was associated with a significantly lower risk of AKI III. Once AKI was established (*i.e.*, 12 hours after AKI I), a rise in DO_2I was not associated with a lower risk of AKI III, progressive fluid accumulation was associated with progression.

Kidneys receive approximately 20% of the cardiac output, and renal oxygen extraction is low (approximately 10%–15%), yet kidneys are very susceptible to tissue hypoxia. Multiple factors contribute to the development of AKI, including regional variations in perfusion and oxygen consumption, impaired autoregulation, endothelial injury, microvascular thrombosis, inflammation, and arteriovenous shunting (22–26). Hypotension, low cardiac output, and volume depletion are deleterious for kidney function, but the optimal hemodynamic targets for patients with early AKI are unknown. In surgical patients, preemptive strategies of hemodynamic optimization have been shown to prevent postoperative AKI (13). The benefit is believed to relate to an increase in oxygen delivery to tissues and prevention of "oxygen debt" (27). A meta-analysis of studies in critically ill patients confirmed significantly better outcomes if goal-directed therapy (GDT) was instituted before the onset of organ failure, but there was no improvement if GDT was initiated later (28).

In clinical practice, fluids, vasopressors, and inotropes are commonly used to raise MAP and CI and to influence renal blood flow, but the role of GDT in early AKI is unknown. Our data show that patients with a higher MAP in the first 12 hours of AKI I had a lower risk of developing AKI III. For every 5-mmHg higher MAP within this early period of AKI, there was a 21% lower risk of AKI III. Redfors *et al.* showed similar results in patients with noradrenaline (NE)-dependent vasoplegia and AKI (29). When sequentially increasing the NE infusion rate to target a MAP of 60, 75, and 90 mmHg, restoration of MAP from 60 to 75 mmHg improved renal DO_2, GFR, and renal oxygenation, but there was no significant difference between MAP 75 and 90 mmHg. An observational study in 217 critically ill patients suggested that a MAP of 72–82 mmHg may be necessary to avoid AKI in patients with septic shock and early renal impairment (30). A Finnish study showed that patients with sepsis who developed AKI within 5 days of ICU admission had a significantly lower MAP (74 mmHg) compared with patients with sepsis without AKI (MAP 79 mmHg) (31). Finally, a recent prospective observational study in 264 patients after cardiac surgery concluded that GDT for 8 hours from admission to the ICU was associated with a significantly lower incidence of AKI (32). However, other studies in humans failed to show a benefit with strategies to increase MAP. Bourgoin *et al.* reported that raising MAP to >70 mmHg in

Table 4. Association between changes in parameters during the 12- to 72-hour period after AKI I and outcome

Variable	Change during 12- to 72-h Period after Diagnosis of AKI I	Risk of Progression to AKI III		Risk of Hospital Mortality	
		Odds Ratio (95% Confidence Interval)	*P* Value	Odds Ratio (95% Confidence Interval)	*P* Value
Hemoglobin	per 1 g/dl	2.38 (0.74 to 7.68)	0.15	1.30 (0.51 to 3.17)	0.58
SO_2	per 0.05	6.63 (0.36 to 120.7)	0.22	2.69 (0.27 to 26.38)	0.40
DO_2I	per 50 ml/min per m^2	0.99 (0.40 to 2.52)	1.00	0.81 (0.74 to 4.59)	0.59
MAP 12 h	per 5 mmHg	0.38 (0.15 to 0.96)	0.04	0.51 (0.43 to 2.20)	0.08
CVP	per 2 cmH_2O	1.98 (0.74 to 5.30)	0.18	1.88 (0.08 to 2.85)	0.14
Cumulative fluid balance	per 1 L/d	6.09 (2.39 to 15.52)	<0.001	1.41 (0.49 to 2.58)	0.38
Arterial lactate	per 1 mmol/L	4.44 (0.70 to 28.12)	0.11	1.16 (1.01 to 1.34)	0.06

Odds ratios were adjusted for all variables shown in the table and others. All models were adjusted for initial hemodynamic indices. Estimates of risk of progression were additionally adjusted for SOFA score on day of AKI I, lactate levels, mechanical ventilation and history of cardiac disease. Estimates of risk of mortality were adjusted for SOFA score on admission to the ICU, use of vasopressors and urine output on day of AKI I. AKI I, stage 1 AKI; SO_2, oxygen saturation; DO_2I, indexed systemic oxygen delivery; MAP, mean arterial blood pressure; CVP, central venous pressure; AKI III, stage 3 AKI; SOFA, Sequential Organ Failure Assessment.

patients with shock did not improve urine output or serum creatinine (33). Similarly, in a study in 10 patients with septic shock, targeting the dose of NE to MAPs of 65, 75, and 85 mmHg, did not affect urine output (34). Legrand *et al.* evaluated the association between systemic hemodynamics in ICU patients with sepsis within 24 hours of ICU admission and new or persistent AKI (35). They found that patients with AKI had a lower diastolic arterial blood pressure and higher CVP in the first 24 hours of ICU admission, but there was no significant difference in MAP or cardiac output. Finally, a recent randomized controlled trial (RCT) comparing a target MAP of 80–85 mmHg versus 65–70 mmHg in patients with septic shock showed no difference in mortality (36). However, patients with chronic hypertension randomized to a higher MAP needed RRT less often.

There are no clear recommendations on the target MAP and the role of GDT in patients with early AKI. We found that both a higher MAP and a higher DO_2I in the first 12 hours of AKI I were independently associated with less AKI III. Importantly, a rise in DO_2I after AKI had already been present for ≥12 hours was not associated with better outcomes. This is in line with previous GDT studies, which showed no benefit if hemodynamic optimization was applied after organ failure had already occurred (37). However, our data also showed that a rise in MAP by ≥5 mmHg after the 12-hour window was independently associated with a lower risk of AKI III. Clearly, more research is necessary to identify whether a "golden window" of time exists during which kidney function can be influenced.

The recent KDIGO AKI guideline concluded that "the choice of target MAP range of 65–90 mmHg as a component of resuscitation needs further study" and that "research is required to determine the specific components of GDT that accrue benefit for patients at risk for AKI" (17). Our data support these recommendations. It is possible that subgroups of patients with particular illnesses or specific comorbidities benefit more than others and that timing of hemodynamic optimization also matters.

Our study also highlights the importance of fluid overload in AKI. An increase of cumulative fluid balance by >1 L/d after AKI had developed was associated with an odds ratio of AKI III of 6.09 and a 95% confidence interval of 2.39 to 15.52. Previous studies have shown similar associations between fluid accumulation and harm (38–42), and, almost 10 years ago, an RCT in patients with acute lung injury confirmed that a conservative strategy of fluid management improved lung function without causing severe AKI (43). Importantly, we did not determine whether fluid accumulation was attributable to fluid administration or reduced urine production.

We acknowledge some limitations. First, our main database only contains 24-hour urine data but not hourly urine outputs. We therefore only used serum creatinine criteria to define AKI and acknowledge that we may have missed patients with AKI. Second, our results are based on a retrospective analysis of a heterogenous patient population with different comorbidities admitted to a single center. The data were obtained during routine clinical practice and the decision to initiate hemodynamic monitoring was made by the medical team caring for the patient without a standardized protocol. Third, we performed a retrospective observational study and cannot prove a causal relationship between DO_2I, MAP, and outcome. Fourth, we recorded the first available CI and DO_2I and contemporaneous parameters and acknowledge that the timing varied between patients and that the values may have differed from global DO_2I during the 12-hour period. Fifth, our analysis showed that CI and DO_2I were highly correlated, and only DO_2I was included in the multivariate analysis to avoid any issues of colinearity. Sixth, we calculated DO_2I but did not measure renal oxygenation. In addition, we recorded the number of vasopressors but not the actual doses, and we have no data on cardiac function prehospitalization. Seventh, we were unable to determine the exact etiology of AKI and the causes of death. Finally, we used a stepwise procedure to identify factors independently associated with progression to AKI III and death, followed by a bootstrapping approach to verify the stability of the model. We acknowledge that stepwise procedures may not result in the optimal model for predicting outcome, and significant factors may have been missed. Although the majority of factors identified as predictors of progression were retained in at least 60% of the bootstrap samples, there was some variability. Ideally, a larger multicenter sample is needed to produce a more robust model. We also did not adjust the statistical models for progression to AKI III but acknowledge that mortality may be affected by progression. Our aim was to investigate the effect of hemodynamic indices in the early phase of AKI, at which point progression would not be known.

Despite these limitations, our data support the call for more research to determine the role of hemodynamic monitoring in early AKI. Better understanding of the factors contributing to severe AKI and/or death may provide opportunities to intervene. In our opinion, a prospective RCT is warranted.

A higher DO_2I and MAP within the first 12 hours of AKI I was associated with a lower risk of AKI III. The effects were independent of preexisting heart disease, hypertension, recent cardiac surgery, or presence of sepsis, but patients who progressed to AKI III were sicker on the day of AKI I.

Once AKI was established, a rise in DO_2I was not associated with less progression to AKI III and fluid accumulation was associated with progression. Uncertainty about best hemodynamic management of early AKI and variation in clinical practice prompts the need for an adequately powered intervention study.

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Disclosures

None.

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