



Markers of cardiogenic shock predict persistent acute kidney injury after out of hospital cardiac arrest

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ABSTRACT

Objective: Ischemia and reperfusion injury (IRI) in cardiac arrest patients after return to spontaneous circulation causes dysfunctions in multiple organs. Kidney injury is generally transient but in some patients persists and contributes both to mortality and increased resource utilisation. Ongoing shock may compound renal injury from IRI, resulting in persistent dysfunction. We tested whether cardiac dysfunction was associated with the development of persistent acute kidney injury (PAKI) in the first 72 h after cardiac arrest.

Methods: We performed an observational retrospective study from January 2013 to April 2017. We included consecutive patients treated after out-of-hospital cardiac arrest at a single academic medical center with renal function measured and immediately and for 48 h post arrest. We also recorded each patient's pre arrest baseline creatinine, demographic and clinical characteristics. Our primary outcome of interest was PAKI, defined as acute kidney injury (AKI) on at least 2 measurements 24 h apart. We compared demographics and outcomes between patients with PAKI and those without, and used logistic regression to identify independent predictors of PAKI.

Results: Of 98 consecutive patients, we excluded 24 for missing data. AKI was present in 75% of subjects on arrival. PAKI developed in 35% of patients. PAKI patients had a longer hospital length of stay (median 21 vs 11 days) and lower hospital survival (47% vs 71%).

Serum lactate levels, dosage of adrenaline during resuscitation and days of dobutamine infusion strongly predicted PAKI.

Conclusions: Among patient who survive cardiac arrest, acute AKI is common and PAKI occurs in more than one third. PAKI is associated both with survival and with length of stay at the hospital. High doses of adrenaline, high serial serum lactate levels, and dose of dobutamine predict PAKI. Evaluation of the trajectory of renal function over the first few days after resuscitation can provide prognostic information about patient recovery.

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Introduction

Whole body ischemia and reperfusion injury causes high mortality and morbidity in survivors of cardiac arrest. In particular, brain injury represents the major cause of death and disability.⁶ However, cardiac arrest also causes acute kidney injury (AKI), which can contribute to both mortality and increased resource utilization.^{7–9} In a recent meta analysis more than 50% of patients developed AKI stage-

1 within 2 days after cardiac arrest.^{5,10} Similar to animal models, AKI in post cardiac arrest patients is mediated by inflammation and T cell-mediated injury.¹¹ Although AKI is transient in most patients, some develop persistent AKI.

The development of AKI is influenced both by preexisting renal disease and post-resuscitation hypoperfusion.^{8,12} Renal dysfunction is associated with outcome after resuscitation. However, prior studies have not clearly defined the role of AKI after cardiac arrest, because of lack of baseline measures or renal function and clear definitions for AKI.

In order to understand the relative contributions of these factors to post-cardiac arrest AKI, we sought to evaluate the predictors of persistent AKI in resuscitated cardiac arrest patients treated with

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therapeutic normothermia for 24 h after return to spontaneous circulation. In this cohort, we prospectively collected echocardiographic data on heart function, along with serial measurements of renal function and acidosis. We tested the specific hypothesis that cardiac dysfunction after cardiac arrest was associated with development of persistent AKI (PAKI) in the first 72 h after cardiac arrest.

Methods

Study design and population

We studied consecutive unconscious (GCS < 9) adult patients resuscitated after out of hospital cardiac arrest and admitted to the intensive care unit (ICU) of a single center from January 2013 to April 2017. Our university institutional review board approved this study and waived the need for informed consent because the study was minimal risk. We excluded patients for age less than 18 years, pregnancy, or pre-existing end-stage renal disease according to KDOQI guidelines.¹ In order to determine AKI, we also excluded patients with death within 72 h (could not measure PAKI) or uncertain baseline of serum creatinine (SCr) data within 120 days of cardiac arrest (could not quantify AKI).

Study definitions and data collection

We defined cardiac arrest as the abrupt loss heart function with no pulse. We categorized initial ECG rhythm as ventricular fibrillation (VF), ventricular tachycardia pulseless (VT), pulseless electrical activity (PEA) or asystole. Time to achieve return to spontaneous circulation was defined as the total time from witnessed collapse until return of pulses. We determined the baseline serum creatinine from pre-arrest medical records, and used the most recent measures within 120 days before CA. We collected SCr values, lactate levels and serum bicarbonate (HCO₃⁻) at the admission to the emergency department and at 6, 12, 24, 48 and 72 h after admission. We calculated glomerular filtration rate using the modification of diet in renal disease (MDRD) study equation.

To estimate ventricular dysfunction, we recorded the total duration of utilization of vasoactive drugs during the ICU stay, and we performed a transthoracic echocardiogram 3 to 6 h after CA. The wall motion score index (WMSI) is a semi-quantitative analysis of regional cardiac systolic function. Raters assign a score (1–5) for systolic wall cardiac motion to each single segment of the ventricle. Global WMSI is defined as the sum of all segmental scores divided by the number of segments rated (simple mean).

WMSI score: score 1 = normo-kinetic or hyperkinetic score 2 = hypo-kinetic score 3 = akinetic score 4 = dyskinetic score 5 = aneurysm

We defined AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as the increase in SCr by ≥ 0.3 mg/dl (26.5 μ mol/l) from baseline within 48 h or the increase in SCr to ≥ 1.5 times baseline, or urine output less than 0.5 ml/kg/h for 6 h. Staging of AKI is in Table 1.¹³

Table 1
KDIGO staging of AKI

Stage	Serum creatinine	Urine output
1	≥ 0.3 mg/dl (26.5 μ mol/l) or 1.5–1.9 times baseline	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥ 12 h
3	3 times baseline or increase serum Creatinine ≥ 4.0 mg/dl (≥ 353.6 μ mol/l) or Initial RRT or in Patients < 18 Years duress of GFR < 35 ml/min per 1.73 m ²	anuria ≥ 12 h

We determined the presence of AKI at each measurement time relative to the SCr baseline value: ED arrival, 6, 12, 24, 48 and 72 h after ROSC. Persistent AKI is characterized by renal dysfunction without recovery within 3 days. We considered as PAKI the presence of at least 2 sCr values that satisfy the KDIGO guidelines for AKI during the observation period.^{2,3} Peak creatinine value was identified as the highest value during the observation period. Baseline chronic renal dysfunction was defined as baseline SCr > 1.1 mg/dl.

Study data analysis

We compared patients with the presence of persistent AKI (PAKI) or not (NPAKI) during the first 72 h after return to spontaneous circulation using descriptive statistics. We made univariate comparisons between PAKI and NPAKI groups using Chi-square test or Fisher exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. We used a Generalised Linear Model for the binary family with a logit linkage to test the independent association of WMSI, duration of vasoactive support, and repeatedly measured lactate levels with PAKI, when adjusted for other variables. We censored repeated measures data occurring after development of PAKI so it was not included in our models. We tested for collinearity between variables before modelling, and did not include strongly collinear variables in the same model. We only included variables in our adjusted model if they had a strong univariate association with PAKI ($p < 0.05$ on univariable tests). (Table 4) We performed all statistical analysis using STATA version 15 (StataCorp, 4905 Lakeway Drive College Station, Texas 77,845 USA).

Results

Patient profile

We studied 98 consecutive comatose patients (GCS < 9) patients successfully resuscitated after out of hospital cardiac arrest and threatened with therapeutic normothermia (TN) from January 2013 to April 2017. Only 74 patients were included in the analysis, because 24 had no SCr in their records within 120 days of arrest or did not survive for 72 h. (Fig. 1)

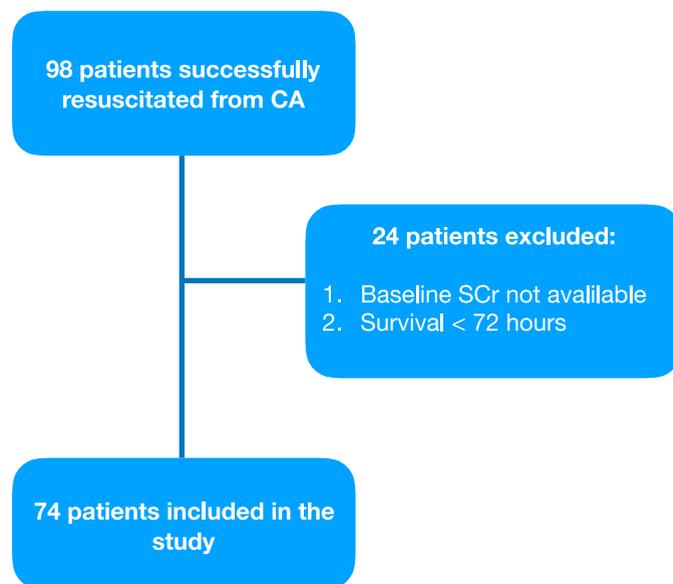


Fig. 1. Flowchart of the study: sCr serum creatinine, CA cardiac arrest.

Table 2
Descriptive statistics, demographic and co-morbidities

	Tot	PAKI	NPAKI	p-value
Number (%)	74 (100)	26 (35.1)	48 (64.9)	
Age median (IQR), y	63.5 (54–71)	65 (59–72)	61 (50–70)	0.09
Male gender, n (%)	56 (77)	19 (73)	37(77)	0.71
Presenting cardiac rhythms, n (%)				
VF/VT	53 (71.6)	17 (65.4)	36 (75)	0.38
Pea/Asystole	21 (28.4)	9 (34.6)	12 (25)	0.38
Resuscitation details				
Median (IQR)				
Adrenaline (mg)	0 (0–1.)	1 (0.2)	0 (0–1)	0.001
Time to ROSC (mins)	18 (13–24)	21.5 (16–29)	15.5 (11–20.5)	0.004
Baseline co-morbidities, n (%)				
Chronic renal failure	2 (2.7)	2 (7.2)	0 (0)	0.05
Hypertension	40 (54)	17 (65)	23 (48)	0.15
Coronary disease	17 (23)	8 (31)	9 (19)	0.24
Liver disease	5 (7)	3 (11)	2 (4)	0.22
Chronic heart failure	7 (9)	4 (15)	3 (6)	0.2
Diabetes	6 (8)	2 (8)	4 (8)	0.9

Baseline demographic data are summarized in Table 2. Most subjects were male, median age was greater than 63 years old, and the most frequent cause of cardiac arrest was ventricular fibrillation (VF) (72%) due to a myocardial infarction (MI) (69%). PAKI developed in 26 (35%) subjects during the observation period. No subjects required RRT by 72 h after cardiac arrest. None of the patients excluded for death prior to 72 h required RRT. Subjects with PAKI compared to subjects without PAKI had a longer hospital length of stay (median 21 days vs 11; $p < 0.05$) and lower hospital survival (47% vs 71%; $p < 0.05$).

Subjects with PAKI received more adrenaline ($p < 0.001$) and had longer duration of arrest prior to return of pulses ($p < 0.004$) compared to those without PAKI.

Serum bicarbonate ($p = 0.028$) and base excess ($p = 0.022$) measured in the ED were lower in the PAKI group. Among the subjects with PAKI, only two (7%) suffered chronic renal dysfunction prior to arrest.

We calculated the illness severity indices with APACHE II score at the beginning of ICU admission. PAKI group had higher values than NPAKI (median 22 vs 29). Illness severity indices, renal function, acid base balance and hemodynamics are shown in Table 3. Value of sCr measured over time after ROSC was significantly greater in the PAKI

Table 3
Illness severity indices and renal function

	Tot	PAKI	NPAKI	p-value
Number (%)	74 (100)	26 (35.1)	48 (64.9)	
Apache II	25 (22–27)	28 (25–31)	22 (19–23)	
Acid base balance				
HCO ₃	20.8 (18.8–22)	19 (18–20.8)	19.5 (21.2–22)	0.028
BE	-5.2 (8–3)	-7.9 (-10.4–4.3)	-4.4 (-7–3)	0.022
Hemodynamic h, mean				
Noradrenaline	18.8	24.9	15.5	0.08
Dobutamine	9.4	20.4	3.5	0.003
WMSI median (IQR)	13(1.13–1.57)	1.2(1.13–1.52)	1.4(1.19–1.97)	0.46
Renal function				
Delta sCr, median (IQR)				
Delta sCr 6	0.18 (0.05–0.3)	0.43 (0.26–0.51)	0.95 (-0.005–0.2)	<0.0001
Delta sCr 12	0.9 (-0.05–0.23)	0.31 (0.14–0.15)	0.005 (-0.75–0.16)	<0.0001
Delta sCr 24	0 (-13–0.18)	0.2 (0.05–0.44)	-0.8 (-0.17–0.01)	<0.0001
Delta sCr 48	0.02 (-0.08–0.18)	0.24 (0.05–0.43)	0 (0.16–0.04)	<0.0001
Delta sCr 72	0.02 (-0.06–0.16)	0.14 (0.02–0.45)	0 (-0.08–0.07)	<0.001
Peak sCr, d (%)	1 (75)	5–6 (67)	1 (75)	0.01
Survival, n (%)	46 (62)	12 (46)	34 (71)	0.037
Day of stay, median (IQR)	12.5 (7–21)	20.5 (6–67)	11 (8–17)	<0.05

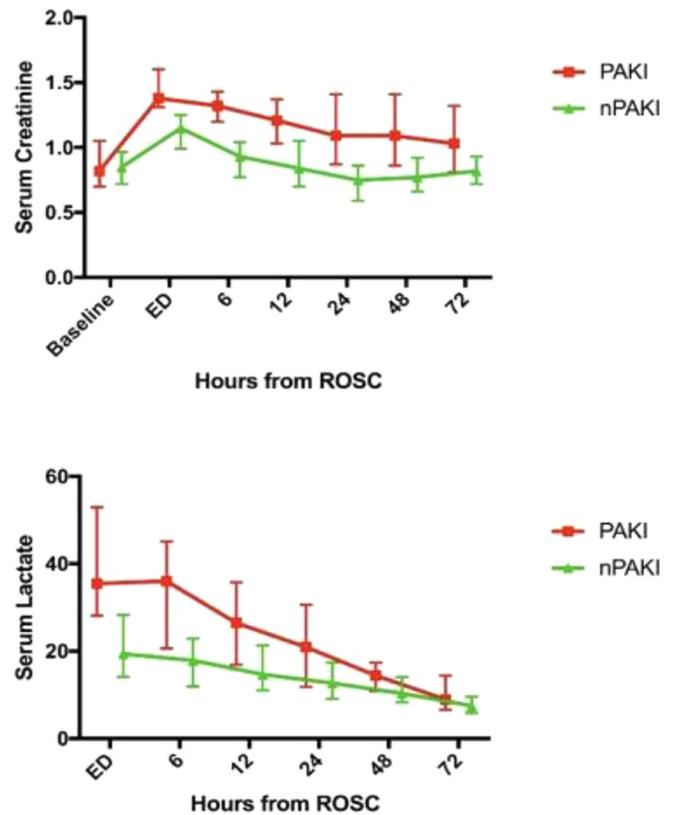


Fig. 2. Trends of median serum Creatinine and Serum Lactates in PAKI and nPAKI group during the first 72 h after ROSC.

group ($p = 0.0001$). Serum lactate levels were strongly associated with PAKI, with significant differences between PAKI and NPAKI subjects at earlier time points and declining over time. (Fig. 2) Subjects with PAKI had longer durations of treatment with dobutamine for post arrest myocardial dysfunction (PAMD).¹⁴ Total WMSI did not differ between groups.

Predictors of persistent AKI

In multivariate analysis high serum lactate, days of usage of dobutamine, cumulative dosage of adrenaline during CPR, days of

Table 4
Multivariate analysis on risk factors to development of persistent AKI

Multivariate linear regression model	Odds	Conf. interval	p-value
Adrenaline	7.19	4.00–13	<0.001
Dobutamine	1.04	1.03–1.06	<0.001
Serum lactate	1.06	1.03–1.08	<0.001

stay in hospital and survival were independently associated with persistent AKI. (Table 3).

Discussion

Impairment of renal function is reversible after cardiac arrest in most patients, but persisting AKI is associated with a poor outcome.¹⁵ In this study, we confirmed that the incidence of AKI is variable and often resolves within two days after admission,⁵ and that persistent AKI was related to survival and days of stay in the hospital. None of our patients received renal replacement therapy during the first 72 h, because they did not reach the life threatening KDIGO criteria for dialysis during this time. We determined that clinicians can recognize patients at risk for persistent AKI by higher early serum lactate values, the cumulative dose of adrenaline used during resuscitation, and the dosage of dobutamine required to maintain cardiac contractility.

Presence of AKI can be divided into two distinct time periods: an initial increase of sCr at admission, and a later rise over 24–48 h in the subset of patients with PAKI. As reported in other studies before, the time to achieve ROSC is greater in PAKI group and the persistence AKI might be the reflection of prolonged cardiac arrest.¹⁶ In our study, AKI at admission to the ED is present in 75% of patients. Other studies reported the immediate rise of serum creatinine after cardiac arrest, but the mechanism is unknown.¹⁷ The muscular creatinine release during CPR and the lack of creatinine clearance during the no-flow and low-flow period are potential mechanisms.¹⁸

The peak of SCr level in PAKI group was 48 to 72 h after cardiac arrest. Direct ischemic damage to the kidney during cardiac arrest could result in impaired filtration and accumulation of creatinine over this time period. In our study we found that patients who developed PAKI received greater cumulative epinephrine doses. Even though not much is known about the effects of epinephrine on regional renal blood flow¹⁹ vasoconstriction could lead to intrarenal haemodynamic changes.²⁰ Neumayr et al. recently considered in a

large study how cumulative dose of epinephrine exposure lead to develop an acute kidney injury in children after cardiac arrest.²¹

We did not find a direct relationship between cardiac impairment, which can be rapidly estimated with WMSI^{22,23} and PAKI. We confirmed previous studies reporting that haemodynamic instability is frequent after cardiac arrest.^{24,25} However, the WMSI data did not confirm that the presence of cardiogenic shock is independently associated with increase of serum creatinine after cardiac arrest.¹² We measured WMSI only in the initial 6 h from return to spontaneous circulation, and it is possible that later decreases in cardiac contractility contributed to PAKI.

Indirect indices of cardiac output include early lactate clearance and lower requirements for dobutamine. These measures of tissue perfusion are related to better survival²⁶ and functional recovery.²⁷ Thus, our finding that lactate and dobutamine dose are related to PAKI indirectly suggest that adequacy of tissue perfusion is a factor in renal injury.²⁸

We acknowledge several limitation of the study. This is a single center retrospective observational study in a tertiary care center, which may limit generalizability. Data about the cardiac arrest and acute kidney injury were collected from clinical and electronic laboratory findings which have variable reliability.

Some patients in this series had diagnostic coronary angiography. Kidney function may have been influenced by the infusion of contrast material. However, a recent meta analysis suggests that contrast induced AKI is a related to severity of illness and hemodynamic instability rather than to the contrast itself.⁴

WMSI is a valid tool for evaluation of early cardiac dysfunction in patients post MI²⁹ but may not be valid in cardiac arrest patients. Serial echocardiograms and WMSI scores beyond the first 6 h after cardiac arrest also might reveal relationships with outcomes.

Our patients were all treated with therapeutic normothermia at 36 °C for 24 h and then gradually re-warmed until reaching 37 °C for 48 h more. Other temperature management strategies might produce different results. However, in a recent meta analysis, target cooling temperature was not associated with the odds of AKI.³⁰

The list of abbreviation is available on Table 5.

Conclusions

Among patient who survive cardiac arrest, acute AKI is common (> 75%) and persistent AKI occurs in more than one third of patients. Persistent AKI is associated both with survival and with length of stay at the hospital. High doses of adrenaline, high serial serum lactate levels, and dose of dobutamine predict persistent AKI. Evaluation of the trajectory of renal function over the first few days after resuscitation can provide prognostic information about patient recovery.

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Table 5
Legend in the order of their appearance

CA	Cardiac Arrest
ROSC	Return to Spontaneous Circulation
AKI	Acute kidney injury
PAKI	Persistent Acute kidney Injury
OHCA	Out of Hospital Cardiac Arrest
GCS	Pittsburgh-Glasgow Coma Scale
EKG	Cardiogram
VF	Ventricular Fibrillation
MI	Myocardial Infarction
VT	Ventricular Tachycardia
PEA	Pulsless Electrical Activity
RRT	Renal Replacement Therapy
MDRD	Modification of Diet in Renal Disease
WMSI	Wall Motion Score Index
PAMD	Post arrest Myocardial Dysfunction
CPR	Cardiopulmonary Resuscitation
KDIGO	Kidney Disease Improving Global Outcomes
APACHE	Acute Physiology And Chronic Health Evaluation
ED	Emergency Department
SCr	Serum Creatinine
TN	Normothermia treatment
ICU	Intensive Care Unit

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