



# Blood Pressure and Blood Pressure Deficits as Predictors of Acute Kidney Injury in Vasopressor Dependent Patients Post **Cardiovascular Surgery**

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#### Abstract

BACKGROUND: Acute kidney injury (AKI) is a common and serious post-operative complication following cardiovascular surgery

AIM: The aim of the study was to evaluate the value of blood pressure and blood pressure deficits as predictors of AKI in post cardiovascular surgery vasopressors' dependent patients.

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METHODS: A prospective observational, single center study, conducted on 100 patients requiring vasopressor support for more than 4 h after cardiovascular surgery. All included patients were subjected to the measurements of three or more systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) readings from the ward charts before surgery and the mean of these measures was calculated, was recorded and

pre-operative systolic perfusion pressure (SPP), diastolic perfusion pressure (DPP), and mean perfusion pressure (MPP) were calculated. A vasopressor-associated average values for hemodynamic pressure-related parameters (SAP, DAP, MAP, CVP, SPP, DPP, and MPP) were calculated on the 1<sup>st</sup> 24 h after admission. The percent deficit in post-operative average parameters in relation to pre-operative parameters was determined as % parameter deficit.

RESULTS: The pre-operative SAP, DAP, MAP, SPP, DPP, and MPP were significantly higher in the non-AKI compared to AKI patients while pre-operative central venous pressure (CVP) was significantly higher in AKI patients. The post-operative DAP, MAP, DPP, and MPP were also higher in non-AKI and the post-operative CVP was lower in non-AKI compared to AKI patients.

CONCLUSIONS: This study concluded that the relative decrease in the perfusion pressures could be significant predictors of AKI after cardiovascular surgery in vasopressor dependent patients. The higher pre- or post-operative CVP or its relative decrease after cardiac surgery was seen also to be associated with higher incidence of AKI.

# Introduction

Blood pressure (BP) is an important factor in determination of renal perfusion. Hence, achieving optimal BP in vasopressor-dependent patients is considered important to prevent the development of acute kidney injury (AKI). The international consensus guidelines recommend to adjust BP depending on the premorbid BP [1].

AKI is a common complication in patients after cardiovascular surgery that is associated with increased morbidity, mortality, and length of ICU stay [2], [3].

An observational cohort study investigated mean deficits between premorbid and actual mean perfusion pressure (MPP) in vasopressor-dependent patients in the intensive care unit (ICU) ("relative hypotension") and demonstrated an association with AKI development [4].

Accordingly, we investigated the impact of the differences between pre- and post-operative hemodynamic parameters on AKI development in vasopressor-dependent patients who had undergone cardiovascular surgery.

# Patients and Methods

This was a prospective observational cohort study that recruited vasopressor dependent patients after elective or emergent cardiovascular surgery in Cairo University Hospitals over the period from December 2016 to March 2018. Vasopressor dependency was defined as the requirement of vasopressor support for more than 4 h post-operative.

We excluded patients below 18 years old age, patients required intra-aortic balloon pump (IABP) support, patients on regular dialysis and those who were readmitted to the ICU during the same hospitalization from the study.

Following full medical history and examination assessment, hemodynamic assessment included heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), temperature (TEMP), respiratory rate (RR), central venous pressure (CVP), and urine output (UOP). Mean arterial pressure (MAP) was estimated as MAP = DAP + [(SAP-DAP)/3]. Systolic perfusion

pressure (SPP), diastolic perfusion pressure (DPP), and mean perfusion pressure (MPP) were calculated as (SAP-CVP), (DAP-CVP), and (MAP-CVP), respectively.

All these hemodynamic parameters were assessed during the pre-operative and post-operative periods. The average of 24 h duration was considered. The percent deficit in post-operative average parameters in relation to pre-operative parameters was determined as % parameter deficit. For example, we calculated %DPP deficit as [(achieved post-operative DPP- pre-operative DPP)/ pre-operative DPP] × 100.

Complete blood count (CBC), prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR), partial thromboplastin time (PTT), arterial blood gases analysis (ABG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), total proteins, and albumin, sodium, and potassium levels. Routine labs were withdrawn on post-operative ICU admission.

We evaluated the severity using the APACHE II [5] and EuroSCORE [6].

Our outcome of interest was the occurrence of AKI according to the Kidney Disease: Improving global outcomes (KDIGO) creatinine and urine output criteria for staging and definition of AKI [7].

The study protocol was approved by the institutional review board at Cairo University.

#### Statistical methods

Data were prospectively collected and coded before analysis using the Statistical Package of the Social Science (SPSS version 22). A variable was considered normally distributed if the Shapiro-Wilk's test had a p > 0.05 [8], [9] and z-value of skewness and kurtosis between -1.96 and +1.96 [10]. Our variables were non-normally distributed. Continuous variables were accordingly expressed as median (25th-75th) percentiles [Median  $(Q_1 - Q_2)$ ]. Categorical variables were expressed as frequency and proportion. When two groups were studied, non-parametric test (Mann-Whitney U test) was used for comparison between two groups as regard quantitative variables. Chi-square test  $(x^2)$  was used for comparison between two groups regarding qualitative data. Exact test was used instead when the expected frequency is <5. Univariate binary regression analysis was done to evaluate the predictive value of different hemodynamic parameters in predicting AKI. Results were considered statistically significant if  $p \le 0.05$ .

### Results

We initially enrolled 135 vasopressor dependent patients underwent cardiovascular surgery at Cairo

University Hospitals, during the period from December 2016 to March 2018, subsequently 35 patients were excluded as 13 patients discharged from operation room (OR) on IABP, 15 patients were on regular hemodialysis, and 7 patients were readmitted in ICU. The remaining 100 patients represented in our study sample.

The study sample was subsequently divided into two groups according to the development of AKI including 31 patients in the AKI group and 69 in the non-AKI group.

The demographic data, comorbidities, type of operation, severity scores, ICU length of stay (ICU-LOS), and in-hospital mortality of our study sample including both groups are seen in Table 1.

Table 1: The demographic data, comorbidities, type of operation, severity scores, ICU-LOS, and in-hospital mortality of the study sample

Parameter		Total sample	AKI	Non-AKI	p value		
		N=100	N = 31	N = 69			
Age [Median (Q1-Q3)]		59 (52-66)	62 (51-68)	59 (53-65)	0.739		
Male gender [No (%)]		67 (67%)	18 (58%)	49 (71%)	0.148		
Diabetes Mellitus [No (%)]		62 (62%)	17 (44.7%)	14 (22.6%)	0.018		
Hypertension [No (%)]		55 (55%)	19 (34.5%)	12 (26.7%)	0.265		
Type of	CABG	47 (47%)	11 (34.5%)	36 (52.2%)	0.137		
operation	Valve replacement	25 (25%)	9 (29%)	16 (23.2%)			
[No (%)]	Mixed	17 (17%)	7 (22.5%)	10 (14.5%)			
	Aortic dissection	6 (6%)	2 (6.5%)	4 (5.8%)			
	Others	5 (5%)	2 (6.5%)	3 (4.3%)			
APACHE II score		9 (7-11)	11 (8-12)	8 (7-9)	<0.001		
EuroSCORE		4 (2-5)	5 (4-7)	3 (2-5)	<0.001		
ICU-LOS (days)		5 (4-7)	6 (4-12)	5 (4-6)	0.061		
In-hospital mortality [No (%)]		18 (18%)	14 (45.2%)	4 (5.8%)	<0.001		

ICU-LOS: ICU length of stay; AKI: Acute kidney injury; CABG: Coronary artery bypass graft surgery; APACHE II: Acute physiology and chronic health evaluation score.

The baseline serum creatinine of the study population was 1.1 (0.97–1.32) mg%. Thirty-one patients (31%) developed AKI while eleven patients (11%) needed renal replacement therapy (RRT). Median baseline serum creatinine level was not statistically significant in patients who developed AKI compared to those who did not develop AKI (1.14 [0.9–1.5] vs. 1.1 [1–1.3] mg%, p = 0.712).

The pre-operative SAP, DAP, MAP, SPP, DPP, and MPP were significantly higher in the non-AKI compared to AKI patients while pre-operative CVP was significantly higher in AKI patients (Table 2). The postoperative DAP, MAP, DPP, and MPP were also higher in non-AKI and the post-operative CVP was lower in non-AKI compared to AKI patients (Table 2).

Table 2: The	pre- and	post-operative	hemodynamic	parameters
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Parameter		AKI	Non-AKI	P-Value	Odds ratio
SAP	Pre-operative	128 (116-132)	134 (130-142)	0.001	0.937
(median Q1-Q3)	Post-operative	119 (114-130)	122 (118-128)	0.359	0.984
mmHg					
DAP	Pre-operative	78 (66-80)	79 (71-82)	0.025	0.926
(median Q1-Q3)	Post-operative	63 (58-67)	65 (61-69)	0.025	0.897
mmHg					
MAP	Pre-operative	95 (83-98)	98 (91-101)	0.004	0.924
(median Q1-Q3)	Post-operative	82 (77-85)	85 (80-88)	0.045	0.910
mmHg					
CVP	Pre-operative	10 (8-11)	5 (3-7)	<0.001	2.066
(median Q1-Q3)	Post-operative	9 (7-11)	7 (6-9)	0.002	1.375
mmHg					
SPP	Pre-operative	120 (108-129)	128 (123-135)	<0.001	0.910
(median Q1-Q3)	Post-operative	107 (105-122)	115 (108-120)	0.130	0.962
mmHg					
DPP	Pre-operative	69 (57-70)	72 (66-78)	<0.001	0.843
(median Q1-Q3)	Post-operative	55 (49-57)	58 (54-62)	< 0.001	0.851
mmHg					
MPP	Pre-operative	86 (73-88)	91 (85-96)	<0.001	0.858
(median Q1-Q3)	Post-operative	72 (68-78)	78 (72-80)	< 0.001	0.867
mmHg					

SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; MAP: Mean arterial pressure; CVP: Central venous pressure; SPP: Systolic perfusion pressure; DPP: Diastolic perfusion pressure; MPP: Mean perfusion pressure Our data showed that % SAP, % DAP deficits, and % MAP deficits did not differ between the two groups. The SAP and DAP declined by 5.4 (11.2–4.8) and 16.9 (22–13.5) % in non-AKI patients compared to 2.7 (5.6–1.7) and 17.5 (23.1–13.7) % in AKI patients, p = 0.324 and 0.391, odds ratio = 1.161 and 0.968 for both, respectively. The MAP declined by 12.1 (16.7–9)% and 13.8 (16–10)% for non-AKI and AKI patients, respectively (p = 0.841, odds ratio = 1.008), Figure 1.



Figure 1: The percent decline of SAP, DAP, and MAP in relation to AKI. (a) Percent decline of SAP, (b) percent decline of DAP, (c) percent decline of MAP

Contrary to this, CVP increase postoperatively was higher in patients who developed AKI. It increased by 50 (0-100) % in AKI versus 0 (-30-9) % in non-AKI, p < 0.001, odds ratio = 0.965), Figure 2.

The post-operative decrease of SPP, DPP, and MPP was associated by higher incidence of AKI. The SPP decreased by 7.3 (13.5–4) % in AKI patients compared to 2.8 (6.2–0) % in non-AKI patients, p < 0.001, odds ratio = 1.213), the DPP and MPP decreased by 20.3 (22.5–15.7) % and 14 (19.8–11.1) % in AKI versus 19.7 (26–16.8) % and 12.5 (15.6–9.1) % in non-AKI (p = 0.042 and 0.031, odds ratio = 0.989 and 1.055, respectively), Figure 3.

#### Discussion

Acute kidney injury (AKI) is one of the major and serious complications of cardiovascular surgery and is accompanied by increased morbidity and mortality and increased ICU length of stay [11], [12]. However, patients requiring renal replacement therapy have higher mortality rate that may exceeds 60% [13]. Treatment strategies targeting optimal BP in vasopressor-dependent patients is an important determinant in preventing AKI development [1].



Figure 2: The percent decline of CVP in relation to AKI

Target BP for vasopressors dose titration in post cardiac surgery patients is still controversial. In septic shock, the surviving sepsis campaign settled a target MAP of 65 mmHg [14]. However, some clinicians



Figure 3: The percent decline of SPP, DPP, and MPP in relation to AKI. (a) Percent decline of SPP, (b) percent decline of DPP, (c) percent decline of MPP

acknowledge that targeting a standard MAP may not be suitable for all patients [15], [16]. International consensus guidelines recommend to adjust BP targets according to patients' pre-morbid BP [1]. This is based on the supposition that in critically ill patients, autoregulation might be impaired due to comorbidities [17] and critical illness [18], [19]. This raised the importance of using the hemodynamic deficits that compare the postmorbid to the premorbid conditions. There are limited studies investigating the benefits of adjusting BP targets according to pre-operative levels in the clinical setting.

We investigated accordingly, differences between pre-operative and achieved hemodynamic parameter levels (CVP, SAP, DAP, MAP, SPP, MPP, and DPP) to evaluate the relationship between pressure deficits and development of AKI in a prospective observational cohort study that recruited 100 patients with vasopressor-dependent post cardiovascular surgery at Cairo University Hospitals. We specifically, focused on patients whose pre-operative CVP could be estimated accurately, to enable a more precise estimate of perfusion pressures. We used the kidney disease: Improving global outcomes (KDIGO) for staging and definition of AKI [7].

In the present study, 31% of the included patients developed AKI. Other studies showed an incidence of AKI to range from 43.6% [20] to 47% [21] in post cardiac surgery patients. These differences between other studies and ours may be related to differences in study design, patients' profile, and diagnostic criteria. These incidences of AKI are consistent with those of studies reporting the epidemiology of AKI in patients undergoing cardiovascular surgery [22], [23].

We reported higher mortality in AKI patients. Many other investigators concluded also this association between AKI and mortality [24], [25]. Contrary to these results Saito *et al.*, 2016 [21] revealed no relationship between development of AKI and mortality. These contradictory findings may be related to the different definitions and staging of AKI used in different studies. When considering more severe AKI that required renal replacement therapy, it was associated with higher mortality in most studies [13].

In the present study, the patients who developed AKI had significantly higher pre-operative CVP and lower pre-operative SPP, DPP, and MPP. This was also seen in another study that recruited similar cohort of patients [21]. Previous studies demonstrated an association between greater pre-operative MAP and a shift of the kidney's autoregulation range to the right [26]. These results imply that the perfusion pressures strongly affect the autoregulation of the renal blood flow. Similarly, our results and that of Saito *et al.*, 2016 showed that the higher post-operative CVP and lower post-operative DAP, MAP, CVP, DPP, and MPP are associated with higher incidence of AKI [21].

We found also that the more increase in CVP (% CVP deficit) and percent increase in the deficits of SPP, DPP, and MPP postoperatively compared to pre-operative measurements are associated with the development of AKI. This rise the consideration that decreasing CVP or renal venous pressure and increasing diastolic blood flow may be important targets in the future for hemodynamic adjustment in post cardiac surgery patients. We could not assess a causal relationship between hemodynamic parameter deficits and AKI progression. The possible role and importance of the CVP in the development of AKI have previously been demonstrated both in patients with acute or chronic cardiovascular disease [27], [28] and in critically ill patients with sepsis [26] suggesting the contribution of the venous congestion in the pathophysiology of AKI.

A retrospective case series reported a significant association between organ-ischemia (spinal cord hypoperfusion) and relative hypotension (MAP of 80% of pre-operative baseline) and elevated CVP in the postoperative period [29]. Animal experiments showed that the premise that renal perfusion pressure is equal to MAP may not be valid after aggressive fluid resuscitation [30]. In an experimental study of pigs with septic shock, the difference in CVP among AKI and control group was statistically significant [30]. These data indicate that systemic venous pressure might be an important determinant of the net renal perfusion pressure.

These observations and the findings of our study are consistent with accumulating evidence, suggesting an association between CVP and impaired renal function. A retrospective study of 137 septic surgical ICU patients reported an association between higher CVP and AKI within the 1<sup>st</sup> 24 h of ICU admission, but not between MAP and AKI [26]. Increased CVP (but not MAP) has also been associated with worsening and/or impaired renal function and increased mortality in patients with a broad spectrum of cardiovascular diseases [27], [28].

In critically ill patients with shock, absolute BP values may be misleading [31]. Absolute hypotension (SBP of 90 mmHg, or MAP of 60–70 mmHg) has been one of the necessary criteria to identify shock in major randomized controlled trials [32], [33], such criteria may lead to under-treating patients with relative hypotension.

In an observational study involving 51 patients requiring vasopressors [4], the incidence of AKI development was greater among patients with higher MPP deficits. Another study included patients with septic shock investigated the effect of change from premorbid values with AKI development concluded that the median MAP deficit is similar for patients with or without severe AKI; however, median MPP deficit was higher in patients with severe AKI [34]. In a case-control study in noncritically ill patients, patients who developed AKI had relative hypotension than control patients [35].

Our study is limited by the relatively small sample size. Being a single center study is considered

another limitation. Multicenter studies might be needed to validate the impact of blood pressure deficits on prediction of AKI. We did not evaluate the hemodynamics invasively. The measurement of cardiac output and other hemodynamic parameters may add to the tools that may be used to tailor the blood pressures postoperatively. Our target was, however, to use simple tools that are routinely used during the patients' course.

We concluded that the relative decrease in the perfusion pressures could be significant predictors of AKI after cardiovascular surgery in vasopressor dependent patients. The higher pre- or post-operative CVP or its relative decrease after cardiac surgery was seen also to be associated with higher incidence of AKI.

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