Journal of Critical Care 40 (2017) 171–177

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Novel urinary biomarkers and the early detection of acute kidney injury after open cardiac surgeries

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1. Introduction

Open heart surgery can be viewed as one of the greatest medical advances of the 20th century. It has been estimated that about 397,000 patient undergone cardiac surgeries in the United States in 2010 and >80% of routine cardiac surgical procedures are performed using cardiopulmonary bypass (CPB) [1]. CPB is complicated by an increased incidence of acute kidney injury (AKI) with incidence rate of (1–30%), which is associated with increased risk of infection, diminished quality of life, delayed discharge and significant morbidity and mortality [2-5]. Despite the deleterious impact of AKI-CPB on outcome, its pathophysiology remains incompletely understood. It is probable that the pathophysiologic changes associated with CPB are accentuated as the duration of CPB increases, which subsequently increases the risk of developing AKI-CPB [6].

Recently, standardized clinical definitions of AKI have been implemented through the use of the RIFLE (Risk, Injury, Failure, Loss, and end stage renal disease (ESRD)), AKIN (Acute Kidney Injury Network) criteria [7,8], and later the Kidney Disease Improving Global Outcomes (KDIGO) work group began by defining AKI by harmonizing the prior RIFLE and AKIN criteria [9]. However, these criteria are still very much dependent on delayed serum creatinine elevations, the current gold standard for the diagnosis of AKI. Furthermore, as a functional marker of glomerular filtration, serum creatinine is not ideally suited to diagnose AKI caused by renal tubular injury, rather than reversible prerenal azotemia [7].

This unfavorable outcome might be tied to the late detection of AKI when the elevation of serum creatinine (SCr) is used where also the change in sCr does not discriminate the time and type of renal insult nor the site and extent of glomerular or tubular injury. Many genes are up-regulated in the damaged kidney with the corresponding protein products appearing in plasma and urine. Some of these are candidate markers for more timely diagnosis of AKI [10].

Therefore, development of new AKI biomarkers has been emphasized to introduce more sensitive and accurate renal biomarkers to clinical use. Early detection of AKI is deemed important to develop therapeutic concepts to treat or at least ameliorate a renal insult. Within the last years various biomarkers reflective of ischaemic tubular injury have been developed to accomplish this task, among them Neutrophil-gelatinase-associated lipocalin (NGAL), Kidney-injury molecule-1 (KIM-1), Interleukin-18 (IL-18), and L-Fatty-acid-binding-protein (L-FABP) [11]. However, most of these novel AKI markers have been derived from animal experiments inducing renal ischemia-reperfusion injury and cardiac surgery with cardiopulmonary bypass (CPB) may be regarded as a prototype clinical scenario of systemic ischaemia-reperfusion injury [12].

NGAL is a glycoprotein consisting of a polypeptide chain of 178 amino acids covalently bound to gelatinase which is synthesized and secreted when acute kidney injury with hypoxic conditions causes a disruption of the endothelial cells of the renal proximal tubules, resulting in increased uNGAL [4]. KIM-1 is a type I transmembrane glycoprotein that is associated with proximal tubule cell injury. Presence of KIM-1 in the urine is highly specific for kidney injury as it's undetected in normal urine. No other organ has been shown to express KIM-1 to a degree that would influence kidney excretion. It has been shown to be much more sensitive than creatinine as a marker for AKI [13].

This study was designed to study the role of urinary NGAL and KIM-1 as biomarkers for early detection of AKI in patients undergoing coronary artery bypass graft (CABG) under CPB, so as to find new tools for early diagnosis and assessment of severity of AKI and to correlate between uNGAL, uKIM-1, complete urine analysis, the other conventional markers of AKI (serum creatinine), and the clinical measurements.

2. Patients and methods

This study was carried out on 45 adult patients, of both sexes Cleveland clinic score of low to intermediate grade (0–5) admitted to Alexandria Main University Hospital, department of cardiothoracic surgery scheduled for elective CABG using CPB.

Patients with history of previous cardiac surgery, pre-existing renal impairment or with history of recent perioperative exposure to

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[1] Contribution: The senior author who lead the team of work.
[2] Contribution: Clinical diagnosis of the patients of acute renal injury.
[3] Contribution: Performing the laboratory investigations to detect the biomarkers.
[4] Contribution: The senior anesthetist who anaesthetize the patients and monitor them throughout the operation, collect the samples and write the manuscript.
[5] Contribution: The second anesthetist who help in anaesthesia, collect the samples, monitor and follow up the patients and write the manuscript.

http://dx.doi.org/10.1016/j.jcrc.2017.03.029
0883-9441/

Table 1
Demographic, preoperative and surgical related data.

	Non-AKI (n = 34)	AKI (n = 11)	Significance (p value)
Demographic data			
Sex			0.064
Male, n (%)	30 (88.2%)	7 (63.6%)	
Female, n (%)	4 (11.8%)	4 (36.4)	
Age (years)	55.6 ± 7.9	60.5 ± 6.6	0.206
Preoperative assessment by Cleveland clinic score			
0, n	6	0	0.001*
1, n	6	0	
2, n	16	2	
3, n	4	3	
4, n	2	6	
Mean ± SD	1.7 ± 1.0	3.4 ± 0.8	
Surgical related data			
Duration of anaesthesia (hr)	3.9 ± 0.7	4.2 ± 0.8	0.143
Duration of surgery (hr)	3.0 ± 0.7	3.4 ± 0.9	0.129
CPB time (min)	74.2 ± 16.7	90.5 ± 16.2	0.010*
Aortic cross-clamp (min)	48.2 ± 14.8	60.9 ± 8.1	0.017*
Blood requirement (units)	1.6 ± 0.7	3.0 ± 0.6	0.001*
Weaning of ventilator (hr)	4.1 ± 1.0	3.9 ± 1.1	0.605
Chest tube drainage (ml/day)	518.8 ± 123.6	653.6 ± 79.2	0.002*
Adrenaline			
Dose (μg/kg/min)	0.07 ± 0.02	0.09 ± 0.01	0.101
Duration (hr)	6.27 ± 1.24	6.29 ± 1.8	0.983
Dopamine			
Dose (μg/kg/min)	4.53 ± 2.03	4.66 ± 0.81	0.699
Duration (hr)	8.0 ± 2.79	15.64 ± 3.32	0.001*
POAF	6 (17.6%)	5 (45.5%)	0.062!
Neurological complications	7 (20.6%)	4 (36.4%)	0.213

* Statistically significant at p ≤ 0.05.

nephrotoxic drugs, extremes of age (<18 or >75 years), off pump cardiac surgery, ejection fraction of <35%, emergency CABG or combined cardiac surgery, or neoplasms as they increase NGAL levels were excluded from the study. After approval of the local Medical Ethics committee of the Faculty of Medicine and taking a written informed consent, patients were screened for complete urine analysis, conventional renal function tests and novel urinary markers by blinded investigators.

After formal pre-anaesthetic assessment of every patients as regard cardiac, coagulation profile, renal function, and pulmonary systems all preoperative cardiac medications was continued until the morning of surgery with the exception of drugs which have renal effects like ACE inhibitors drugs. On arrival to the operating room, peripheral and central venous cannulation and radial artery cannulation was done under local anaesthesia and IV sedation in the form of 2 mg midazolam and 4 mg morphine sulphate after applying standard monitoring to the patient.

Induction and maintenance of anaesthesia was standardized in all patients in the form of midazolam (0.05 mg/kg), fentanyl (5 μg/kg), sevoflurane (6–7%), and rocuronium (0.9 mg/kg) to facilitate tracheal intubation. The lungs was ventilated at normocapnia (monitored by end tidal CO_2 at 35 mmHg) with sevoflurane (1–2%) in an air-oxygen mixture. Additional bolus doses of fentanyl and rocuronium was injected if necessary. CPB was managed to maintain mean arterial pressure (MAP) between 50 and 80 mmHg with tepid hypothermia (32°–34 °C) and keeping haematocrit above 20% with the addition of fresh packed RBCs as needed.

Weaning from CPB and reperfusion of the heart was performed according to the patient's general condition and cross-clamp time. There was no fixed postoperative treatment regimen for either pharmaceutical or mechanical support. Weaning and extubation from the ventilator was done after haemodynamic (defined as a MAP of 60–90 mmHg, heart rate (HR) between 60 and 90 bpm, a central venous pressure (CVP) between 10 and 15 mmHg) and ventilatory stability. Analgesia was given in the form of morphine sulphate infusion (2–3 mg/h) in the first 48 h and paracetamol 1 g/6h.

Measurements included assessment of the AKIN stages after ICU admission and every 6 h for the first 72 h postoperative; urinary examination for NGAL, KIM-1 (after induction, 2, 6, 12, and 24 h after termination of CPB), and urinary sediment microscopic examination [14] (preoperative, 2, 12, 24, and 48 h after termination of CPB); haematological measurements (sCr, and blood urea) just before anaesthesia and every day for 3 days after the end of surgery; and clinical measurements including (duration of anaesthesia and surgery, CPB and aortic cross clamping times, total amount of packed RBCs given during surgery, weaning from the ventilator postoperatively, and intra and postoperative complications).

2.1. Statistical analysis

Data were analyzed by using SPSS[R] software (Statistical package for social science for personal computers) using "t" test, ANOVA test and chi-square X^2 test, data were expressed as mean ± SD and $P < 0.05$ considered significant.

3. Results

In this study 11 (24.4%) out of 45 patients developed AKI diagnosed by AKIN criteria of serum creatinine rise without finding any patient requiring renal replacement therapy.

Demographics and surgical core data in the different groups are presented in Table 1.The demographic results didn't show any significant difference between both groups as regard age or gender with more females in AKI group (36.4% vs 11.8% in non-AKI group) in the AKI group. On comparing the CCS between the two groups it was found to be higher in the AKI patients. On assessing the AKIN stages in both groups it was significantly higher in the AKI group than the non-AKI group (starting from 24 h after surgery till third postoperative day) either due to increased serum creatinine in some patients or decreased urine output in others.

As regard the CPB time and aortic cross-clamp time were significantly higher in the AKI group with mean values of (90.5 ± 16.2 vs 74.2 ± 16.2 min) and (60.9 ± 8.1 vs 48.2 ± 14.8 min) respectively. It was noticed that the amount of postoperative bleeding and perioperative

Table 2
Haematological measurements of biomarkers for acute kidney injury.

Parameter		preoperative	24 h after surgery	48 h after surgery	72 h after surgery
Serum creatinine (mg/dl)	AKI	1.15 ± 0.33	1.20 ± 0.22	1.49 ± 0.41	1.60 ± 1.03
	Non-AKI	1.01 ± 0.23	0.99 ± 0.24	1.04 ± 0.29	1.11 ± 0.49
	P	0.216	0.066	0.004*	0.036*
Estimated GFR (ml/min)	AKI	117.32 ± 22.38	98.76 ± 20.19	71.46 ± 18.1	52.48 ± 15.59
	Non-AKI	125.63 ± 23.03	134.94 ± 27.67	121.9 ± 24.2	121.6 ± 26.02
	P	0.174	0.001*	0.001*	0.001*
Urea (mg/dl)	AKI	39.2 ± 9.7	34.1 ± 8.1	36.7 ± 10.7	45.9 ± 20.5
	Non-AKI	36.4 ± 7.8	31.7 ± 7.2	34.3 ± 7.9	40.4 ± 15.7
	P	0.745	0.056	0.001*	0.001*

Data are given as Mean ± SD.
* Statistically significant at p ≤ 0.05.