J Anesth (2011) 25:799–804
DOI 10.1007/s00540-011-1210-8

ORIGINAL ARTICLE

Acute kidney injury during aortic arch surgery under deep hypothermic circulatory arrest

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Received: 26 March 2011 / Accepted: 4 August 2011 / Published online: 17 August 2011

Abstract
Purpose The aim of this investigation was to describe the renal outcome and to identify risk factors for acute kidney injury (AKI), as defined by the Acute Kidney Injury Network (AKIN), during aortic arch surgery (AAS) under deep hypothermic circulatory arrest (DHCA).
Methods A retrospective and observational study has been performed. One hundred thirty-five patients requiring AAS under DHCA were studied.
Results Seventy-one patients (52.6%) developed AKI during the postoperative period. A logistic regression analysis identified three independent risk factors for AKI: preoperative hypertension (HT), emergency surgery, and duration of DHCA. Renal replacement therapy (RRT) was required in four patients (3.0%). The postoperative mortality rate among the patients with AKI was 2.8%, which was not statistically different from the rate of 1.6% observed in the non-AKI group ($P = 0.62$).
Conclusions A high incidence of AKI during AAS under DHCA was confirmed. Because AKI is highly associated with aortic surgery, novel approaches for protecting the kidneys other than deep hypothermia are needed. The logistic regression model identified HT, emergency surgery, and duration of DHCA as independent risk factors for AKI.

Keywords Acute kidney injury · Aortic arch surgery · Deep hypothermic circulatory arrest · Emergency surgery · Hypertension

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Introduction

The relationship between renal failure and increased postoperative mortality is well recognized [1, 2]. Acute kidney injury (AKI) is a serious and complex situation that develops in a variety of settings ranging from a minimal elevation in serum creatinine to a state requiring renal replacement therapy (RRT). The incidence of postoperative AKI varies according to the definition and type of surgery, but for all causes, AKI is associated with an increased postoperative mortality after aortic arch surgery (AAS) [3]. As a detailed appraisal of AKI is required, the Acute Kidney Injury Network (AKIN) recently proposed uniform standards for diagnosing and classifying AKI [4]. A detailed investigation based on this universal definition of AKI would be valuable for the future management of AKI, and strategies are needed for the treatment of AKI and for renal protection.

Deep hypothermia has proven to be an effective technique for protecting various organs from ischemic damage as a result of circulatory arrest [5], which is required during AAS. Improving the adverse outcomes associated with deep hypothermic circulatory arrest (DHCA), however, has been challenging [3, 6–9]. Although AKI is a common postoperative complication (8.3–48.2%) encountered in patients undergoing AAS under DHCA [3, 6–9], the incidence and risk factors of AKI (as defined by AKIN) during AAS under DHCA need further study.

The aim of this retrospective investigation was to describe the renal outcome and to identify risk factors for AKI during AAS under DHCA.

Materials and methods

Patients

After receiving the approval of our institutional review board, the medical records of patients who underwent AAS between April 2007 and July 2008 were retrospectively reviewed. During this period, 135 patients underwent AAS under DHCA, and these patients comprised the cohort for the present analysis. Patients with a history of preoperative RRT were excluded.

Demographic and preoperative variables included age, sex, body mass index (BMI), serum creatinine level (SCr), previous history of diabetes mellitus (DM) and hypertension (HT: defined as a documented history of HT previously being treated with antihypertensive agents), and surgical status (elective vs. emergency). The duration of cardiopulmonary bypass (CPB), the duration of DHCA, urine volume during surgery and the use of aprotinin, dopamine, and furosemide during surgery were also studied as intraoperative variables. Postoperative variables included the development of AKI (as defined below and shown in Table 1), the introduction of renal replacement therapy (RRT: defined as temporary or permanent dialysis introduced within 48 h after surgery), the postoperative 30-day mortality rate, the postoperative intensive care unit (ICU) stay, and the postoperative hospital stay.

Postoperative AKI

The AKI criteria and classification were defined according to the Acute Kidney Injury Network [4]; this classification is shown in Table 1. The AKI criteria comprised an absolute increase in SCr of more than or equal to 0.3 mg/dl or a percentage increase in the SCr of more than or equal to 50%. We defined the postoperative AKI as the maximal change in SCr within a 48-h postoperative period.

Anesthesia

Patients underwent general endotracheal anesthesia, and propofol, sodium thiopental, sevoflurane, midazolam, fentanyl, and vecuronium bromide were given to maintain anesthesia. The patients routinely received aprotinin dosed as a load of 2.5×10^6 kallikrein inhibition units in CPB prime solution until the marketing suspension of aprotinin in November 2007. Pharmacological cardiovascular support was titrated to maintain a mean arterial pressure of >60 mmHg.

Surgery

Arterial cannulation was typically performed in the ascending aorta. The transapical aortic cannulation was primarily performed for an acute type A (DeBakey type I or II) dissection. Venous cannulations were bicaval. During DHCA, retrograde cerebral perfusion (RCP) was performed via a snared superior vena cava cannula, or antegrade selective cerebral perfusion (ASCP) was performed via the brachiocephalic trunk, left common carotid artery, and left subclavian artery. DHCA was initiated after confirming no cerebral activity on the electroencephalogram with a tympanic membrane temperature <20°C and a rectal and bladder temperature <25°C. An arterial blood gas analysis was performed every 30 min. During CPB, the following metabolic goals were maintained: pH 7.35–pH 7.45, $PaO_2 > 100$ mmHg, $PaCO_2$ 30–40 mmHg, and a hematocrit level >20%. RCP was continuously performed at a flow rate of 200–250 ml/min. ASCP was continuously performed at a perfusion pressure of 100–120 mmHg and a flow rate of 10 ml/kg/min. After aortic arch repair, the aortic graft was cannulated and proximally cross-clamped. After the termination of RCP, antegrade arterial perfusion and patient rewarming were initiated.

Table 1 Classification/staging system for acute kidney injury proposed by the Acute Kidney Injury Network [4]

Stage	Serum creatinine criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 150–200% (1.5- to 2-fold) from baseline
2	Increase in serum creatinine to more than 200–300% (>2- to 3-fold) from baseline
3	Increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dl)

Individuals who receive renal replacement therapy (RRT) within 48 h after surgery are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT

Table 2 Detailed information for emergency surgery cases

Diagnosis	Acute kidney injury (AKI) group (n = 16)	Non-AKI group (n = 5)	P value
Acute aortic dissection (DeBakey type I)	11	4	0.08
Acute aortic dissection (DeBakey type II)	2	1	0.62
Ruptured aortic arch aneurysm	3	0	0.09

Table 3 Demographic, preoperative, intraoperative, and postoperative variables according to AKI definition

	AKI group (n = 71)	Non-AKI group (n = 64)	P value
Age	71.5 ± 10.0	70.7 ± 11.2	0.2
Sex [male (%)]	51 (71.8)	40 (62.5)	0.25
BMI (kg/m^2)	23.9 ± 3.7	23.6 ± 2.9	0.68
Surgical status [emergency (%)]	16 (22.5)	5 (7.8)	0.016*
HT (%)	49 (69.0)	33 (51.6)	0.038*
DM (%)	1 (1.4)	2 (3.1)	0.5
Duration of CPB (min)	216.3 ± 36.9	211.0 ± 42.0	0.43
Duration of DHCA (min)	75.7 ± 22.4	67.5 ± 24.6	0.043*
Aprotinin used during surgery (%)	27 (38.0)	30 (46.9)	0.3
Dopamine used during surgery (%)	51 (71.8)	46 (71.9)	0.46
Furosemide used during surgery (%)	16 (22.5)	8 (12.5)	0.53
Urine volume during surgery (mL)	1356 ± 678	1462 ± 731	0.38
RRT (%)	4 (5.6)	0 (0.0)	0.05
Mortality (%)	2 (2.8)	1 (1.6)	0.62
Postoperative ICU stay (days)	9.4 ± 11.9	8.5 ± 7.7	0.59
Postoperative hospital stay (days)	14.7 ± 15.0	13.4 ± 9.5	0.56

Numbers are given as mean ± SD

AKI acute kidney injury during the first postoperative 48 h, *BMI* body mass index, *HT* previous history of hypertension, *DM* previous history of diabetes mellitus, *CPB* cardiopulmonary bypass, *DHCA* deep hypothermic circulatory arrest, *RRT* renal replacement therapy within 48 h after surgery, *ICU* intensive care unit

* Statistical significance ($P < 0.05$) between AKI group and non-AKI group

Data analysis

Records of the demographic and perioperative variables were reviewed. A statistical analysis was then performed using JMP 7 (SAS Institute Japan). Potential associations between demographic, preoperative, intraoperative, and postoperative variables and AKI were first tested using univariate procedures. The variables identified by the univariate analyses were then analyzed using a multivariate procedure with a forward stepwise logistic regression (P value of entry <0.05). Collinearity diagnostics were evaluated for all variables. The odds ratios (OR) and their 95% confidence intervals (CI) were calculated. All P values were two-tailed, and a P value of <0.05 was considered statistically significant.

Results

The mean age of the 135 patients [91 men (67.4%), 44 women (32.6%)] was 71.1 years (range, 37–91 years). Comorbidities included a history of DM (2.2%) and HT (60.7%). Twenty-one (15.6%) of these operations were performed in an emergency setting. The detailed results for the emergency surgeries are shown in Table 2. Median durations of CPB and DHCA were 214 and 72 min, respectively. Fifty-seven patients (42.2%) received aprotinin until its marketing suspension in November 2007. No association between aprotinin use and AKI was detected (Table 3). Perioperative serum creatinine levels are shown in Table 4.

During the first postoperative 48 h, 71 patients (52.6%) developed AKI. Significant differences between the AKI group and the non-AKI group were detected for the following variables: HT, emergency surgery, and duration of DHCA (Table 3). A logistic regression analysis identified HT, emergency surgery, and duration of DHCA as independent risk factors for AKI (Table 5).

RRT was required within 48 h after surgery in four patients. The 30-day postoperative mortality rate in the AKI group was 2.8%, and this rate was not statistically

Table 4 Perioperative serum creatinine levels (mg/dl)

	AKI (n = 71)	Non-AKI (n = 64)	P value
Pre-op	1.14 ± 0.96	0.84 ± 0.21	0.87
POD1	1.42 ± 0.73	0.92 ± 0.24	0.002*
POD2	1.39 ± 0.81	0.86 ± 0.24	0.001*

Numbers are given as mean ± SD

Pre-op preoperative day, *POD* postoperative day

* Statistical significance ($P < 0.05$) between AKI group and non-AKI group

Table 5 Multivariate Analysis for AKI

	Odds ratio	95% confidence interval	P value
HT	2.36	1.13–5.09	0.024
Emergency surgery	5.05	1.73–17.3	0.005
Duration of DHCA	1.02	1.00–1.03	0.016

HT previous history of hypertension, *DHCA* deep hypothermic circulatory arrest

different from the rate of 1.6% observed in the non-AKI group.

Discussion

AKI is a common postoperative complication (8.3–48.2%) encountered among patients undergoing AAS [3, 6–9] and has been identified as a risk factor for postoperative mortality [3, 10]. There are two possible mechanisms for the development of AKI during AAS. First, ischemic injury of the kidney arising from DHCA may lead to AKI [11, 12]. Another possible mechanism of AKI is the atheroembolic burden during cardiac surgery [13]. However, the incidence and outcome of AKI during AAS in previous investigations have not been consistent (Table 6), probably because of the lack of a standardized definition and classification for AKI [3, 6–9]. This lack of standardization has likely hindered the improvement of perioperative patient management as well as the surgical outcome of AAS.

The AKIN group has proposed refinements of the former criteria [4]. In particular, the AKIN group intended to increase the sensitivity of the former criteria by recommending that a smaller change in the serum creatinine level be sufficient to define the development of AKI. Also, a time constraint of 48 h for the diagnosis of AKI was proposed. The present study is the first to determine the risk factors for AKI during AAS under DHCA based on the latest universal definition proposed by AKIN.

In the present study, the incidence of AKI was 52.6%, and this value was higher than those in previous studies (Table 6). The previous discrepancies in the incidence of AKI may have been caused by differences in its definition. Indeed, the incidence of postoperative RRT in our study (3.0%) was similar to those in previous reports, although the incidence of AKI was higher [3, 6–9]. Another possible explanation was false-positive labeling as AKI with the less rigorous criteria of the proposed AKI criteria brought these discrepancies [4].

Although several reports have documented the independent association between AKI and mortality in aortic surgery [3, 14, 15], no significant difference in mortality was observed in the present study, probably because the mortality rate was low and the number of patients might not be large enough to detect a difference in mortality.

The logistic regression model identified HT, emergency surgery, and duration of DHCA as independent risk factors for AKI (Table 3).

HT is prevalent among patients with an aortic aneurysm [3, 6, 7], but the association between postoperative renal events and preoperative hypertension remains undetermined. According to our results, HT was associated with

Table 6 Incidence of AKI in patients undergoing DHCA

Reference	Incidence of AKI (%)	Definition	Note[a]
Arnaoutakis et al. [3]	48	Elevation of Scr > 50% or GFR decline > 25%	
Goldstein et al. [6]	8.3	Elevation of Scr > 50%	1
	29.2	Elevation of Scr > 50%	2
Mora Mangano et al. [7]	38	25% reduction of CrCl	1
	39	25% reduction of CrCl	2
Augoustides et al. [8]	39.1	Elevation of Scr > 50%	
	48.2	25% reduction of CrCl	
Augoustides et al. [9]	29.2	Elevation of Scr > 50%	
	22.9	Elevation of Scr > 50% With an abnormal peak creatinine	3
	38.2	25% reduction of CrCl	

Scr serum creatinine level, *GFR* glomerular filtration rate, *CrCl* creatinine clearance

[a] 1, without aprotinin; 2, with aprotinin; 3, an abnormal peak creatinine (>1.3 mg/dl for men; >1.0 mg/dl for women)

AKI, but the mechanism of its involvement in the development of AKI has not been clarified. Patients with pulse pressure hypertension >80 mmHg were three times more likely to die a renal-related death, compared with those without hypertension, in the setting of coronary surgery [16]. Indeed, Aronson et al. [16] identified blood pressure, specifically pulse pressure, as the main predictor of renal failure. In this previous study, a relationship existed between an increase in the pulse pressure and renal-related death.

In our study population, most of the emergency AAS cases were performed for acute DeBakey type I dissections (Table 2). DeBakey type I dissection, particularly cases involving the origin of the renal artery, may lead to preoperative renal hypoperfusion. Renal hypoperfusion resulting in renal ischemia following a ruptured aortic aneurysm or cardiac tamponade most likely results in the development of AKI. Thus, emergency surgery may have been indirectly associated with the development of AKI and might be regarded as an independent risk factor for AKI. As emergency AAS can easily lead to harmful renal situations, a novel solution to protect the kidneys is needed.

We also observed that the duration of DHCA was an independent risk factor for AKI. Hypoxic damage to the kidney during DHCA is considered an important contributor to AKI [11, 12]. Therefore, a longer duration of DHCA may lead to a higher incidence of AKI. One of the principal problems surrounding postoperative complications of AAS has been neurological impairment, an issue that led to the introduction of DHCA [5]. DHCA during AAS provides some measure of protection to the brain by reducing cellular metabolism and thus attenuating the production of free radicals during surgery [17]. Although renal protection during AAS has not gained a higher priority, strategies for protecting the kidneys during DHCA are now needed. Also, as the small odds ratio probably represents a weak association between the duration of DHCA and the incidence of AKI, further clinical investigations are needed to clarify the correlation between these two variables.

The safety of aprotinin in cardiac or aortic surgery remains controversial. Despite its ability to reduce intraoperative blood loss, its negative effects on renal and cardiac outcome have been major concerns [6, 7, 18, 19]. The marketing suspension of aprotinin, as requested by the U.S. Food and Drug Administration in November 2007, was recognized in response to a strong and consistent negative mortality trend associated with aprotinin [20]. The present study, however, suggests that the use of aprotinin was not associated with the development of AKI or mortality in patients undergoing DHCA.

A high incidence of AKI during AAS under DHCA was confirmed, similar to the results of previous clinical studies. In emergency cases with a history of HT, the higher probability of AKI should be recognized, and the postoperative creatinine level should be carefully monitored. Also, if the duration of DHCA is prolonged because of the complexity of the surgery, the undeveloped intensive monitoring of renal function is warranted. Because AKI is highly associated with aortic surgery, as shown in the present study as well as previous ones, novel approaches for protecting the kidneys other than deep hypothermia are needed. Although efforts to prevent AKI have been made through a variety of drugs [21–24], a low level of evidence for renal therapeutic intervention has been detected and further study is required. In this context, the standardization of the diagnostic criteria for AKI is mandatory for evaluating the renal outcome, and the present study provides important information.

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