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Original Article

Relative adrenal insufficiency is not associated with prognosis in patients undergoing cardiac surgery

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Abstract: Low cortisol levels (<276 nmol/L) are regarded as relative adrenal insufficiency (RAI) and associated with adverse events in critical illness. Whether RAI affects cardiac surgery patients is unknown. In this study, serum cortisol and adrenocorticotropic hormone (ACTH) levels were prospectively examined in 90 adult patients who underwent elective cardiac surgery from April to August, 2015. RAI was defined as basal cortisol <276 nmol/L at postoperative day 1. Perioperative outcomes were recorded. It was found that the incidence of RAI was 55.56% (50/90). Patients with RAI did not show worse outcomes as compared with patients with non-RAI (P>0.05). A longer duration of surgery and higher preoperative ACTH levels were shown to significantly delay weaning (B = 0.349, P<0.001; B = 1.367, P = 0.001, respectively) and prolong time spent in the ICU (B = 0.385, P<0.001; B = 1.255, P = 0.003, respectively). Age (B = 0.245, P = 0.012) and operation duration (B = 0.058, P = 0.002) prolonged the hospitalization. Cox proportional hazards regression showed that preoperative ACTH levels and New York Heart Association class were associated with a higher rate of 48-hour ICU hospitalization (hazard rate [HR] 0.977, P = 0.034; HR 0.568, P = 0.005, respectively). These results presented here indicated that RAI after heart surgery does not lead to worse outcomes, and the cut-off value of 276 nmol/L for cortisol is not appropriate for identifying RAI in patients who underwent cardiac surgery.

Keywords: Cortisol, relative adrenal insufficiency (rai), cardiac surgery, intensive care unit (icu) hospitalization time, mechanical ventilation

Introduction

Stress is an adaptive response of body for adapting to a changing environment, such as surgery, trauma, and infection. It is characterized by activation of the hypothalamic-pituitary-adrenal (HPA) axis, with release of cortisol. Release of cortisol could further affect anti-inflammatory reactions, permissive action, and restore homeostasis. During critical illness, many factors such as inflammatory cytokines, anoxia, and ischemia could impair this axis. These factors lead to a relatively inadequate cortisol response in relation to the severity of illness and stress, which was defined as relative adrenal insufficiency (RAI) [1].

Due to the differences in patients grouping and diagnostic criteria, the incidence of RAI varies from 30% to 70% [2, 3]. Despite that, critically ill patients with RAI have common features of refractory hypotension and vasopressor resistance, and administration of glucocorticoids is thought to be effective for treating these features. The concept of RAI was first proposed by Rothwell et al. in 1991, and is thought to be associated with worse outcomes [4]. In their study, patients who had a poor cortisol response (rise of <250 nmol/l) after a corticotropin stimulation test died and were diagnosed with RAI. However, because of its limited study populations, the diagnostic criteria of RAI in Rothwell et al.'s study was not widely accepted [4]. To date, there is no unified understanding of the diagnosable standard for RAI. Among these diagnostic criteria, a random total cortisol level <276 nmol/L (10 μg/dL) or a delta total serum cortisol level <248.4 nmol/L (9 μg/dL) after adrenocorticotropic hormone (ACTH, 250 μg) administration is widely accepted [5]. However, it is difficult to obtain a good stability and reproducibility of corticotropin stimulation test in

critical patients [6], and thus the RAI cannot be used to predict the end of diseases [7]. Under stressful conditions, secretion of cortisol is increased by endogenous ACTH stimulation. Exogenous corticotrophin stimulation may lead to adrenocortical exhaustion during the following days after the test [8, 9]. Therefore, we used criterion of a random total cortisol level <276 nmol/L (10 μg/dL) for RAI in this study.

Because of anesthesia, procedures, and the inflammatory response during cardiopulmonary bypass (CPB), cardiac surgery inevitably arouses the stress response. Previously, low cortisol levels (<276 nmol/L) are regarded as relative adrenal insufficiency (RAI) and associated with adverse events in critical illness, but the effects of RAI on cardiac surgery patients remains unknown so far. This study aimed to study whether RAI indicates a poor outcome for cardiac surgery patients.

Materials and methods

Selection of patients and study design

We performed a prospective, observational study from April to August in 2015 and the postoperative care was provided in the cardiac intensive care unit (ICU). Local institutional ethics committee approval was given for the study protocol, and the study complied with principle of informed consent.

Study Populations: 90 adult patients who underwent selective cardiac surgery with or without cardiopulmonary bypass (CPB) support over 4 months were include in this study. The patients were divided into two groups based on the level of plasma cortisol: the patients with low cortisol levels (<276 nmol/L) were set as relative adrenal insufficiency (RAI group, n = 50) group, and the patients with higher cortisol levels (≥276 nmol/L) were set as non-relative adrenal insufficiency (non-RAI group, n = 40) group. Specific surgical procedures including coronary artery bypass graft procedures, valve replacements, repair of congenital heart disease, cardiac tumor resection, pericardium decortication, and aortic dissection repair were performed. Exclusion criteria were age <18 years, emergency surgery, pregnancy, a history of corticosteroid treatment, a history of autoimmune disease or immune suppression, failing to wean from CPB, and requiring extracorporeal membrane oxygenation.

Anesthetic management and procedure

All patients received the same anesthetic management protocol. Induction of anesthesia involved fentanyl (20-30 μg/kg), pipecuronium (0.08-0.12 mg/kg), midazolam (0.1-0.2 mg/kg), etomidate (0.2-0.3 mg/kg), and lidocaine (0.6-1.4 mg/kg). Maintenance anesthesia was achieved with continuous intravenous infusion of fentanyl (8-10 μg/kg/h), propofol (1.5-4.0 mg/kg/h), and inhalation sevoflurane (0.5-1.5 vol. %). Ventilation was provided with a breathing mixture of 50% oxygen and air to maintain end-tidal carbon dioxide at 35 mmHg. Basal vital signs (electrocardiography, blood pressure, oxygen saturation, central venous pressure), nasopharyngeal temperature and urine output were monitored intraoperatively.

All patients underwent surgery through median sternotomy, with or without CPB, depending on the surgeons. Patients were excluded once weaning from failed CPB, or when they needed extracorporeal membrane oxygenation. Nasopharyngeal temperature was maintained at 32°C to 35°C according to the type of surgery (on-pump or off-pump surgery). Central venous pressure (CVP) was maintained at 8 to 12 mmHg by crystalloids and colloids infusion. If mean arterial pressure was below 60 mmHg, norepinephrine was supplied.

Patients were transferred to cardiac ICU with intubation after surgery. The time of weaning from mechanical ventilation was determined by ICU physicians according to hemodynamic stability.

Data collection

Demographic data, including preoperative New York Heart Association (NYHA) functional class and intraoperative parameters (operation time, CPB duration), were collected. Cortisol and corticotropin levels were measured twice during the study period. One measurement was made before anesthesia and intubation on the operation day ($cortisol_0$, $ACTH_0$) and the other measurement was made on postoperative day (POD) 1 ($cortisol_1$, $ACTH_1$). Cortisol was measured by fluorescent magnetic particle enzyme immunoassay (ST AIA-PACK CORT, AIA-2000 ST; Tosoh Corporation, Tokyo, Japan). ACTH was measured by chemiluminescent immunoassay (MAGLUMI 2000 plus; SNIBE Co., Ltd., Guang-

Table 1. Demographic characteristics and perioperative variables between the groups

Variables	Relative adrenal insufficiency n = 50	Non-relative adrenal insufficiency n = 40	*P* value
Age (years)	49.54±13.68	50.75±13.75	0.678
Sex			
Male	27	19	0.540
Female	23	21	
Preoperative NYHA class			
II	14 (28.00%)	10 (25.00%)	0.0811
III	26 (52.00%)	28 (70.00%)	
IV	10 (20.00%)	2 (5.00%)	
Hypertension			
No	42 (84.00%)	30 (75.00%)	0.289
Yes	8 (16.00%)	10 (25.00%)	
Diabetes			
No	47 (94.00%)	34 (85.00%)	0.157
Yes	3 (6.00%)	6 (15.00%)	
Preoperative Scr, umol/L	73.50±14.91	80.67±25.73	0.102
Preoperative BUN, umol/L	6.00±1.94	6.31±2.41	0.495
$LVEF_0$ (%)	60.11±6.20	59.74±5.63	0.579
$Cortisl_0$, nmol/L	368.89±178.97	405.72±168.57	0.322
$ACTH_0$, pg/mL	21.50±15.30	26.81±20.98	0.169
Cardiopulmonary bypass			
On	35 (70.00%)	33 (82.50%)	0.170
Off	15 (30.00%)	7 (17.50%)	
Surgery duration, minutes	208.90±65.86	221.08±78.75	0.427
$Cortisol_1$, nmol/L	155.93±76.08	581.22±281.21	<0.001
$ACTH_1$, pg/mL	15.149 (11.59, 19.94)	495.23 (14.07, 38.67)	<0.001
Mechanicalventilation, hours	21.00 (18.75, 45.5)	20.00 (18, 80.5)	0.717
Hospital stay, days	30.96±13.41	31.75±13.32	0.781
Lactate peak, mmol/L	5.75±3.35	7.11±4.67	0.125
Glucose peak, mmol/L	352.42±265.62	403.10±326.84	0.240
Inotropic support admission to ICU	8.00 (5, 11)	7.5 (5, 10.75)	0.823
Inotropic support 1st postoperative day	7.94±4.23	10.80±8.71	0.206
Postoperative Scr, umol/L	103.56±35.66	117.94±52.71	0.127
Postoperative BUN, mmol/L	7.60±3.13	8.62±3.70	0.160
Postoperative LVEF (%)	60.59±8.57	57.62±6.75	0.076
Urine output 24 hours postoperatively, mL	3540.00±1048.94	3867.63±998.34	0.136
Fluid balance 24 hours postoperatively, mL	-166.90±931.71	-486.25±1017.62	0.125
Death			
Yes	1 (2%)	2 (5%)	0.431
No	49 (98.00%)	38 (95.00%)	

NYHA indicates New York Heart Association. Scr indicates serum creatinine. BUN indicates blood urine nitrogen. $Cortisol_0$ and $ACTH_0$ indicate cortisol levels and adrenocorticotropic hormone levels at preoperation, respectively. $Cortisol_1$ and $ACTH_1$ indicate cortisol levels and adrenocorticotropic hormone levels on the first postoperative morning, respectively. $LVEF_0$ indicates preoperative left ventricular ejection fraction. Inotropic support 1st indicates inotropic support on the first postoperative morning. Comparisons between the two groups were analyzed by the *t* test.

dong, China). Other postoperative parameters, such as the duration of mechanical ventilation, ICU stay, albumin levels, urine output, and inotropic support (IS), were recorded on the morn-

Table 2. Correlation analysis for the factors of hospitalization, ICU duration, and mechanical ventilation

Variables	Hospitalization		ICU duration		Mechanical ventilation	
	r	P	r	P	r	P
Age[a]	.300	.004‡	.176	.097	.293	.005*
BSA[a]	-.018	.864	.132	.216	.111	.299
CPB[b]	.027	.801	-.174	.100	-.188	.077
Operation duration[a]	.354	.001‡	.348	.001§	.260	.013*
$Cortisol_0$[a]	.105	.327	.283	.007§	.216	.041*
$ACTH_0$[a]	.102	.338	.353	.001§	.385	<.001*
Δcortisol[a]	.136	.200	.117	.272	-.147	.166
ΔACTH[b]	.027	.801	-.174	.100	-.363	<.001*
$LVEF_0$%[b]	-.054	.612	-.313	.003§	-.164	.122
Urine volume[a]	.024	.824	.182	.086	.126	.237
Sex[b]	-.054	.614	-.064	.547	-.112	.292
NYHA[b]	.055	.604	.301	.004§	.333	.001*
Hypertension[b]	.077	.470	.119	.264	.036	.733
Diabetes[b]	.148	.163	-.045	.674	-.123	.248

Δcortisol = $cortisol_1$ C $cortisol_0$, ΔACTH = $ACTH_1$-$ACTH_0$. [a]Values were analyzed by Spearman's correlation coefficient; [b]values were analyzed by Pearson's correlation coefficient. *P<0.05 for analysis of mechanical ventilation; §P<0.05 for analysis of ICU stay; ‡P<0.05 for analysis of hospital stay.

ing of POD 1. IS was evaluated as follows: 1 × dopamine or dobutamine dose (mcg/kg/min) + 10 × milrinone or phenylephrine dose (mcg/kg/min) + 100 × epinephrine or norepinephrine dose (mcg/kg/min) + 10,000 × vasopressin dose (U/kg/min) [10, 11].

Statistical analysis

Normally distributed variables are shown as mean ± standard deviation (SD) and non-normally distributed variables are presented as median and interquartile range (IQR). Comparisons between groups were analyzed by the *t* test or the Mann-Whitney test. Discrete variables were analyzed by the χ^2 test or Fisher's exact test, when appropriate. Correlations were analyzed by Pearson's or Spearman's correlation coefficient. Associations were analyzed with multivariable linear regression. Kaplan-Meier survival analysis was used to describe the time of ventilation and ICU duration within 48 hours, and the time of hospitalization within 28 days. The Cox proportional hazards model was used to identify significant predictors of the rate of weaning from ventilation, ICU discharge rate of 48 hours, and hospital discharge rate of 28 days. Two-sided *P* values less than 0.05 were considered statistically significant. All of the calculations were performed by SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The mean age of 90 patients was 50±14 years old. Among them, 22 patients underwent off-pump surgery and 68 patients underwent on-pump surgery. The mean CPB time was 97.50 minutes (IQR, 42.90-189.60 minutes). Demographic and operative data for all of patients are shown in Supplementary Table 1. The distribution of operations is shown in Supplementary Table 2. The main types of diseases were valve disease and congenital heart disease, which could be the reason for a low prevalence of hypertension (20%) in this study.

At a cut-off of $cortisol_1$ levels <276 nmol/L, the incidence of RAI was 55.56% (50/90). Baseline values were equal between RAI group and non-RAI group (age, preoperative left ventricular ejection fraction% [$LVEF_0$%], operation duration, $cortisol_0$, and $ACTH_0$). Although the proportion of patients with NYHA class IV appeared to be higher in RAI group than in non-RAI group (20% vs 5%), there was no significance (P = 0.08). Mortality rates were 2% (1/50) and 5% (2/40) in RAI group and non-RAI group, respectively, with no significant difference between the two groups (χ^2 = 0.621, P = 0.431). Patients in RAI group did not have a longer postoperative mechanical ventilation time (P = 0.717), time of ICU hospitalization (P = 0.807), or length of hospital stay (P = 0.781), as compared with patients in non-RAI group. Patients in RAI group also did not have higher plasma lactate peak levels, glucose peak levels, or IS scores compared with those in non-RAI group (**Table 1**).

We further investigated related factors of mechanical ventilation, ICU duration, and hos-

Table 3. Multivariate analysis for factors associated with mechanical ventilation, ICU duration and hospitalization

Variables	Mechanical Ventilation			ICU Duration			Hospitalization		
	B	Std. Error	*P* Value	B	Std. Error	*P* Value	B	Std. Error	*P* Value
Operation duration*	.349	.095	<.001	.385	.099	<.001	.058	.018	.002
$Cortisol_0$	.069	.041	.096	.073	.043	.092			
$ACTH_0$*	1.367	.398	.001	1.255	.413	.003			
NYHA	14.110	11.055	.205	16.073	11.586	.169			
ΔACTH	-.060	.082	.467						
$LVEF_0$%				-1.317	1.197	.274			
Age*							.245	.095	.012

*P<0.05 for regression analysis of mechanical ventilation.

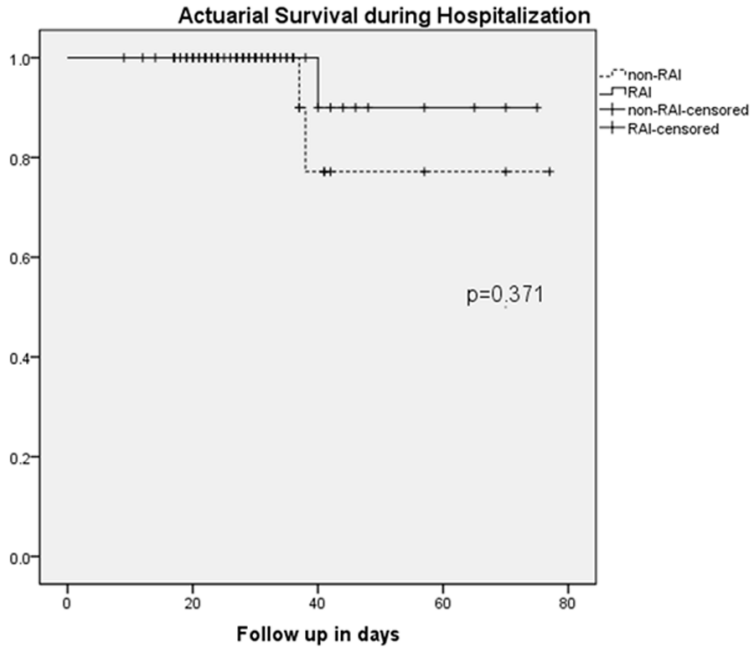

Figure 1. Kaplan-Meier survival curves during the hospital stay by study group. RAI, relative adrenal insufficiency; non-RAI, non-relative adrenal insufficiency.

pitalization. Mechanical ventilation time was positively correlated with age (r = 0.293, P = 0.005), the length of the operation (r = 0.260, P = 0.013), $cortisol_0$ levels (r = 0.216, P = 0.041), $ACTH_0$ levels (r = 0.385, P<0.001), and NYHA functional class (r = 0.333, P = 0.001), and negatively correlated with ΔACTH ($ACTH_1$-$ACTH_0$) (r = -0.363, P<0.001). ICU duration was positively correlated with the length of the operation (r = 0.384, P = 0.001), $cortisol_0$ (r = 0.283, P = 0.007), $ACTH_0$ (r = 0.353, P = 0.001), and NYHA functional class (r = 0.301, P = 0.004), and negatively correlated with $LVEF_0$% (r = -0.313, P = 0.003). Hospital stay was positively correlated with age (r = 0.300, P = 0.004) and the length of operation (r = 0.354, P = 0.001, **Table 2**). Multivariable linear regression showed that a longer duration of surgery or higher $ACTH_0$ tended to delay weaning (B = 0.349, P<0.001; B = 1.367, P = 0.001, respectively) and prolonged ICU duration (B = 0.385, P< 0.001; B = 1.255, P = 0.003, respectively). Factors that prolonging the hospitalization were age (B = 0.245, P = 0.012) and operation duration (B = 0.058, P = 0.002) (**Table 3**).

We followed up all of the patients they were discharged from hospital or died in hospital. The median follow-up time was 31 days (9-77 days). Kaplan-Meier survival analysis showed that the median survival time in hospital was 71.0 days (95% confidence interval, 64.6, 77.2), with no significant difference between RAI and non-RAI groups (71.5 vs 68.0 days, P = 0.371, **Figure 1**). The actuarial rate of mechanical ventilation for longer than 48 hours was 20% in RAI group and 25% in non-RAI group (P = 0.925, **Figure 2**). The proportions of patients with an ICU stay longer than 48 hours were 32% in RAI group and 30% in non-RAI group (log-rank test, P = 0.801, **Figure 3**). The rate of total hospital stay for longer than 28 days was 52% in RAI group and 57.5% in non-RAI group (P = 0.567, **Figure 4**). Adjusted hazard ratios for 48-hour weaning

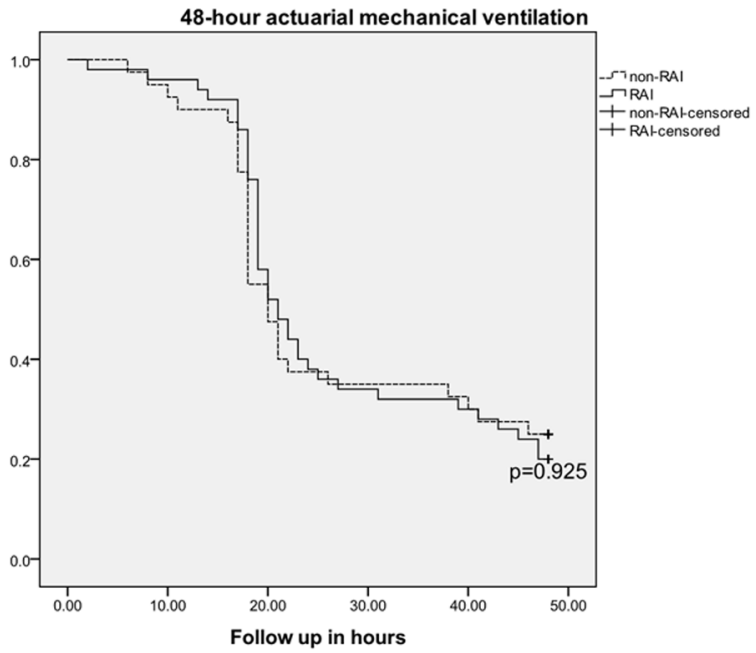

Figure 2. Kaplan-Meier curves of actuarial mechanical ventilation at 48 hours postoperatively. RAI, relative adrenal insufficiency; non-RAI, non-relative adrenal insufficiency.

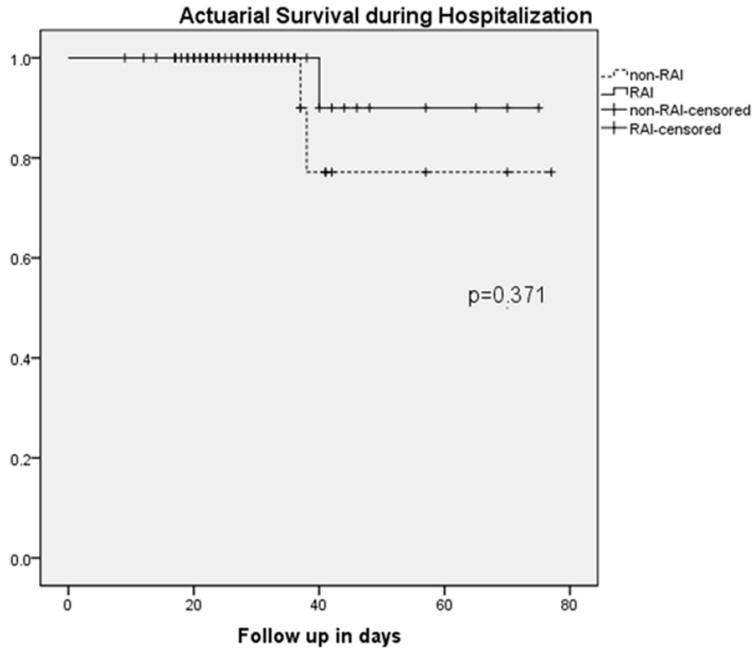

Figure 3. Kaplan-Meier curves of actuarial ICU hospitalization at 48 hours postoperatively. RAI, relative adrenal insufficiency; non-RAI, non-relative adrenal insufficiency.

and ICU discharge, and 28-day hospital discharge between the two groups were analyzed by Cox proportional hazards model (**Tables 4-6**). Age and CPB duration were associated with longer than 48-hour mechanical ventilation (hazard ratio [HR] 0.964, P<0.001; HR 0.994, P = 0.004, respectively). ACTH levels and NYHA class before the operation were associated with a longer than 48-hour ICU stay (HR 0.977, P = 0.034; HR 0.568, P = 0.005, respectively). Patients who were not supported by bypass were more likely to be discharged from the ICU within 48 hours (HR 1.998, P = 0.025). Age and surgery duration were associated with a longer than 28-day hospitalization (HR 0.965, P = 0.003; HR 0.994, P = 0.020, respectively).

Discussion

RAI is a syndrome that is characterized by relatively lower cortisol levels under stress. RAI is caused by HPA axis disorder, and finally leads to an inadequate adaptive response to disease. Recent studies of RAI have mostly focused on patients with sepsis or sepsis shock, but rarely paid attention to surgical or trauma patients. In our study, the morbidity of RAI was 55.56% (50/90) by using the criterion of a random plasma cortisol level <276 nmol/L. However, we did not perform an ACTH test for the following considerations. After ACTH (250 μg) administration, an increment of cortisol <276 nmol/L reflects a relative lack of reserve capacity in the adrenal gland for an extra stressful episode. This amount does not indicate that the degree of stress response is insufficient at that moment. Since our study aimed to evaluate the degree of postoperative stress on temporal serum cortisol levels, the corticotropin stimulation test was therefore not suitable for this study.

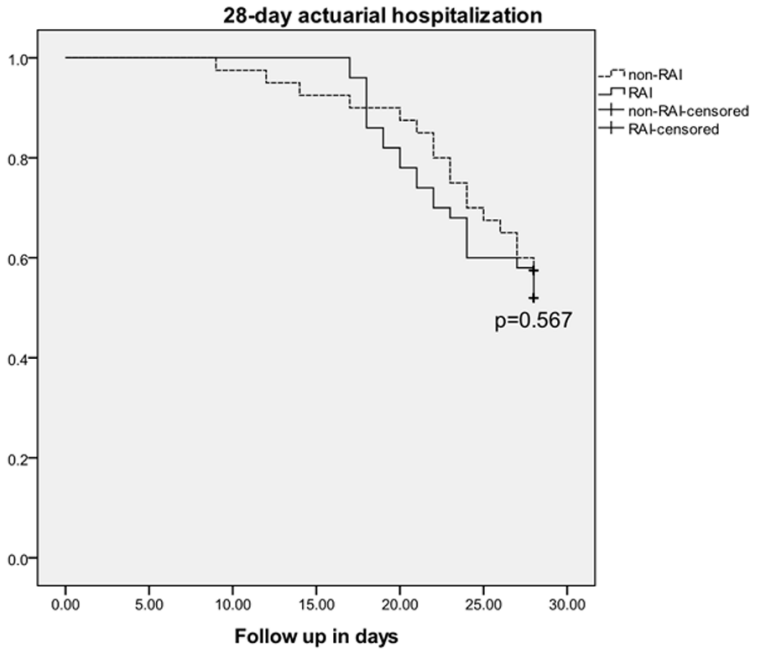

Figure 4. Kaplan-Meier curves of actuarial hospitalization at 28 days. RAI, relative adrenal insufficiency; non-RAI, non-relative adrenal insufficiency.

Table 4. Multivariable Cox proportional hazards model for 48-hour mechanical ventilation

Predictor	B	HR	95.0% CI		*P* value
Age	-.036	.964	.947	.982	<.001
CPB duration	-.006	.994	.990	.998	.004

HR, hazard ratio; CI, confidence interval; CPB, cardiopulmonary by pass.

Table 5. Multivariable Cox proportional hazards model for 48-hour ICU hospitalization

Predictor	B	HR	95.0% CI		*P* value
Age	-.032	.969	.949	.988	.002
CPB (no/yes)	.692	1.998	1.089	3.663	.025
$ACTH_0$	-.023	.977	.956	.998	.034
NYHA	-.565	.568	.382	.846	.005
Operation duration	-.005	.995	.991	.998	.003

HR, hazard ratio; CI, confidence interval; CPB, cardiopulmonary bypass; $ACTH_0$, adrenocorticotrophic hormone level on the morning of the operation; NYHA, New York Heart Association.

Table 6. Multivariable Cox proportional hazards model for 28-day hospitalization

Predictor	B	HR	95.0% CI		*P* value
Age	-.036	.965	.943	.988	.003
Operation duration	-.006	.994	.988	.999	.020

HR, hazard ratio; CI, confidence interval.

In the present study, patients with RAI did not have a higher mortality than those without RAI. Furthermore, less people died in RAI group than in non-RAI group. But there was no significant difference. McKee et al. [12] reported that patients with septic shock and RAI suffered from higher mortality and adverse outcomes than patients with septic shock only. Although we did not observe this finding, this previous result is supported by many recently published studies [13, 14], in which reported that lower plasma cortisol levels do not increase mortality. Harish et al. [15] performed a prospective, observational study on 23 neonates with congenital heart disease to observe the association between postoperative cortisol profile and early outcomes. They showed that higher postoperative cortisol levels were associated with increased postoperative morbidity and indicators of a more complicated perioperative course. Such a large difference in prognosis for RAI in critical illness is mainly due to inconsistent definitions.

Normally, cortisol is secreted in a diurnal rhythm, which originates from a hypothalamic "pulse generator" [16] and a negative feedback loop in the HPA system [17, 18]. Patients undergoing surgery or with diseases respond to stress, and their HPA axis may be attacked by other factors, such as inflammatory stressors [19, 20]. In critical illness, secretion of cortisol loses its intrinsic circadian rhythm, but still has the characteristics of an impulse mode [14]. Ben et al. [21] found that the pulse amplitude of cortisol may be as high as 600 nmol/L within 2 hours after cardiac surgery. If the finding of Ben et al. [21] is credible, a single measurement of cortisol does not represent the overall levels of cortisol, or even the cortisol levels of 1 hour later. This is because the measurement time point may be either at the peak or nadir of this pulse. Therefore, there is considerable controversy about the definition of RAI. Consequently, monitoring dynamic changes in plasma cortisol levels may reflect the actual condition of the body adapting to stress.

Iribarren et al. [9] showed that RAI induced postoperative vasopressor dependency in a group of patients who underwent CPB. The IS in our study was not significantly different between RAI and non-RAI groups. We speculated that patients in RAI group had less negative fluid balance than those in non-RAI group at 24 hours postoperatively. Therefore, patients with RAI were likely to have a high liquid load.

Multiple regression showed that $ACTH_0$ and the duration of operation mainly affected ventilator weaning and ICU stay. With a rise in $ACTH_0$ levels and extension of operation duration, weaning from the ventilator is delayed and the ICU stay is extended. The Cox proportional hazards model showed that each additional unit of $ACTH_0$ reduced the probability of ICU discharge by 0.997 times. This result confirms the important role of HPA axis in critical illness, which is closely associated with the outcome of heart surgery patients. After the concept of RAI was first suggested, researchers attempted to find an appropriate cut-off value to define RAI, and also show that cortisol levels below the cut-off value indicated a poor outcome for patients under stress of a critical illness. Unexpectedly, the criteria of RAI definition are still controversial [9, 21, 22]. Some researchers fail to find worse outcomes of RAI [23] and others even find the opposite results [24]. Therefore, a moderate degree of stress response should be paid with more attention, because extremely low and extremely high cortisol levels are harmful, and an appropriate cortisol level needs to be determined.

Study limitations

The study has several limitations. The number of cases was small, but this was only a pilot study. We intend to increase the number of patients and dynamic observations on function of the HPA axis in ongoing study. We only used random plasma cortisol measurements without an ACTH stimulation test, which prevented us from observing diurnal changes. However, such tests could not be reliably used in this cohort of complex and frequently unstable patients.

Conclusion

In heart surgery patients, the incidence of RAI is 55.56% (50/90) by the criterion of a cut-off cortisol level <276 nmol/L on POD1. Patients with RAI do not show a more complicated perioperative course than those without RAI. Lower cortisol levels are not associated with worse outcomes. However, the higher basal corticotropin levels are, the longer mechanical ventilation time and the ICU stay are. In future studies, an appropriate stress response level needs to be determined that is neither especially low nor exceptionally high.

Acknowledgements

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Base-line of the 90 study populations

Variables	Baseline Characteristics
N	90
Age, (years)	50±14
Male	46 (51%)
Preoperative NYHA functional class	
I	0 (0%)
II	24 (27%)
III	54 (60%)
IV	12 (13%)
Hypertension	18 (20%)
Diabetes	9 (10%)
$LVEF_0$ (%)	61.00 (58.45, 63.00)
Preoperative Scr, umol/L	93.83±30.47
$Cortisol_0$, nmol/L	385.26±174.43
$ACTH_0$, pg/mL	20.92 (14.23, 27.28)

$Cortisol_0$ and $ACTH_0$ stand for cortisol level and adrenocorticotropic hormone level pre-operation respectively. $LVEF_0$ indicates preoperative left ventricular ejection fraction.

Supplementary Table 2. Cardiac surgery

	Relative adrenal insufficiency n = 50	Non-relative adrenal insufficiency n = 40	*P* value
Coronary artery bypass graft	14 (28.00%)	5 (12.5%)	0.085
Valve replacement (aortic/mitral valve or both)	21 (42.00%)	16 (40.00%)	
Congenital heart disease repair	13 (26.00%)	10 (25.00%)	
Pericardial stripping	1 (2.00%)	2 (5.00%)	
Aortic dissection repair	0 (0.00%)	4 (10.00%)	
Cardiac tumor resection	1 (2.00%)	3 (7.50%)	