

Relative Adrenal Insufficiency Is Associated With Prolonged Postoperative Hemodynamic Instability

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Background. We assessed the hypothesis that a significant proportion of patients undergoing cardiac surgery have postoperative relative adrenal insufficiency (RAI), and that this puts them at higher risk of persistent hemodynamic instability.

Methods. A prospective study included 135 patients who underwent cardiac surgery using cardiopulmonary bypass between July 2006 and December 2007. Adrenal function was assessed 36 hours after surgery using a 1- μ g cosyntropin (adrenocorticotrophic hormone [ACTH]) stimulation test. Relative adrenal insufficiency was defined as a peak cortisol level inferior to 500 nmol/L or an increase in cortisol of less than 250 nmol/L, or both, compared with baseline. The primary endpoint was hemodynamic instability at 48 hours after surgery, defined as persistent requirement for any vasoactive drug. The secondary endpoint was long-term survival.

Results. Postoperative RAI was diagnosed in 75 patients (56%). Compared with patients who showed a

normal response to the ACTH stimulation test, patients with RAI had significantly higher rates of hemodynamic instability at 48 hours (40% versus 22%, $p = 0.03$). On multivariable analysis, adrenal response to the ACTH test was a significant independent predictor of hemodynamic instability at 48 hours after surgery (odds ratio 1.06 [95% confidence interval: 1.02 to 1.11] per 10 nmol/L cortisol decrease; $p = 0.002$). At a mean follow-up of 8.3 ± 2.8 years, patients without perioperative RAI had survival equivalent to that of the general population, whereas patients with RAI had lower than expected survival.

Conclusions. Postoperative RAI is common among patients undergoing cardiac surgery and is associated with an increased risk of persistent hemodynamic instability.

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Glucocorticoid secretion is an essential endocrine response to stress and injury [1]. While primary adrenal insufficiency (Addison's disease) is rare [2], a distinct clinical entity termed relative adrenal insufficiency (RAI) has been described in critically ill patients in the intensive care unit [3]. It is defined as an inadequate response of the adrenal glands to the injection of adrenocorticotrophic hormone (ACTH) and is associated with increased intensive care unit mortality [4].

Cardiac surgery is associated with an intense physiological stress, not only because of the surgical stress but also because of the systemic inflammatory response associated with the use of cardiopulmonary bypass

[5, 6]. Maintenance of homeostasis requires an adequate adrenal response, namely, a sufficient increase in plasma cortisol levels. Little is known about the incidence of RAI after cardiac surgery. We hypothesized that a significant proportion of adult cardiac surgery patients have postoperative RAI and that this puts them at higher risk of persistent (more than 48 hours) hemodynamic instability.

The primary objectives of this study were (1) to quantify the frequency of postoperative RAI in our population of cardiac surgery patients by assessing the response to the ACTH stimulation test as described in the critical care literature, and (2) to compare the incidence of persistent postoperative hemodynamic instability among patients with postoperative RAI compared with patients with normal adrenal function after surgery. Secondary objectives were to assess the risk factors associated with RAI and hemodynamic instability, and to assess the impact of perioperative RAI on long-term survival.

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Patients and Methods

Study Population

A prospective, single-center, observational study was conducted at the Montreal Heart Institute. All consecutive patients aged more than 18 years undergoing cardiac surgery using cardiopulmonary bypass between July 2006 and December 2007 were eligible for study enrollment. Exclusion criteria included the following: patients who were corticosteroid dependent before surgery, patients who received corticosteroids during cardiopulmonary bypass, patients who were in cardiogenic shock at the 36th hour after surgery (cardiac index less than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, ΔpCO_2 greater than 8 mm Hg), patients who were hypovolemic at the 36th hour after surgery (pulmonary capillary wedge pressure less than 12 mm Hg), patients who had postoperative tamponade, and patients involved in another research project. The study cohort consisted of 135 patients. The study protocol was approved by the Institutional Research Ethics Board and written informed consent was obtained for all patients.

Perioperative Management

All operations were performed with cardiopulmonary bypass using roller pumps and phosphorylcholine-coated circuits. Intraoperative mediastinal shed blood was routinely sequestered and processed with a cell salvage machine before readministration to the patient. Intraoperative aprotinin (Hammersmith protocol) and tranexamic acid were used routinely. Aspirin was continued until the day before surgery in all patients with coronary artery disease. Postoperative pain management was tailored to the individual patient and left to the discretion of the treating intensivist.

Definitions

Adrenal function was assessed 36 hours after surgery using a 1- μg cosyntropin (adrenocorticotrophic hormone [ACTH]) stimulation test (Cortrosyn; Amphastar Pharmaceuticals, Rancho Cucamonga, CA) [7, 8]. Relative adrenal insufficiency was defined as a peak cortisol level less than 500 nmol/L or an increase in cortisol of less than 250 nmol/L, or both, compared with baseline.

The primary endpoint was hemodynamic instability at 48 hours after surgery. Patients were considered hemodynamically unstable if they were still receiving any vasoactive drug (vasopressin, epinephrine, norepinephrine, or dopamine). Patients who were not hemodynamically unstable served as a control group. Operative mortality was defined as death occurring within 30 days or during the index hospitalization.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD when normally distributed or as median and interquartile range (IQR) when not normally distributed, and were compared by means of Student's *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables are expressed as frequency (%) and were

compared by means of Pearson's χ^2 test or Fisher's exact test, as appropriate.

Risk factors for postoperative hemodynamic instability were assessed using a multivariable logistic regression model. The main independent variable of interest was maximal increase in cortisol level during ACTH stimulation test. Other variables screened as potential confounders were the preoperative baseline characteristics listed in Table 1. All variables with a *p* value less than 0.20 on univariate analysis were considered as having a potential confounding effect. A nonautomated variable

Table 1. Baseline Characteristics of Patients on Admission to Intensive Care Unit

Patient Characteristics	RAI (n = 75)	No RAI (n = 60)	<i>p</i> Value
Demographics			
Age, years	64.8 $\pm$ 11.0	65.4 $\pm$ 9.2	0.75
Male	55 (73)	42 (70)	0.67
Cardiovascular risk factors			
Body mass index, kg/m ²	27.9 $\pm$ 5.2	28.4 $\pm$ 5.6	0.55
Diabetes mellitus	20 (27)	13 (22)	0.50
Hypertension	49 (65)	45 (75)	0.23
Dyslipidemia	35 (74)	29 (21)	0.68
Smoking	26 (35)	21 (35)	0.97
Associated conditions			
Peripheral vascular disease	12 (16)	13 (22)	0.40
COPD	11 (15)	5 (8)	0.26
Hypothyroidism	13 (17)	5 (8)	0.13
History of stroke	7 (9)	0 (0)	0.015
Recent AMI, <6 weeks	13 (17)	7 (12)	0.36
Preoperative LVEF $\leq$ 50%	19 (25)	15 (25)	0.97
Previous cardiac surgery	10 (13)	5 (8)	0.36
Intraoperative data			
Urgent procedure	6 (8)	3 (5)	0.49
Use of etomidate	8 (11)	1 (2)	0.037
Procedure			0.30
CABG	27 (36)	28 (47)	
Valve	28 (37)	14 (24)	
Other	7 (9)	4 (7)	
Combined	13 (17)	13 (22)	
Circulatory arrest	0 (0)	3 (5)	0.06
Vasopressors used during surgery^a			0.06
0–1	11 (15)	17 (29)	
2	43 (57)	32 (55)	
>2	21 (28)	9 (16)	
Aortic cross-clamp time, minutes	60 (40–79)	56 (37–69)	0.34
Cardiopulmonary bypass time, minutes	87 (58–110)	83 (63–101)	0.68

^a Including vasopressin, epinephrine, norepinephrine, or dopamine.

Values are mean $\pm$ SD, n (%), or median (interquartile range).

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; RAI = relative adrenal insufficiency.

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