

Critical Illness-Related Corticosteroid Insufficiency in Patients with Low Cardiac Output Syndrome after Cardiac Surgery

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Background: Low cardiac output syndrome (LCOS) after cardiac surgery usually requires inotropes. In this setting, critical illness-related corticosteroid insufficiency (CIRCI) may develop. We aimed to investigate the clinical features of CIRCI in the presence of LCOS and to assess the efficacy of steroid treatment. **Methods:** We reviewed 28 patients who underwent a rapid adrenocorticotrophic hormone (ACTH) test due to the suspicion of CIRCI between February 2010 and September 2014. CIRCI was diagnosed by a change in serum cortisol of $<9 \mu\text{g/dL}$ after the ACTH test or a random cortisol level of $<10 \mu\text{g/dL}$. **Results:** Twenty of the 28 patients met the diagnostic criteria. The patients with CIRCI showed higher Sequential Organ Failure Assessment (SOFA) scores than those without CIRCI (16.1 ± 2.3 vs. 11.4 ± 3.5 , $p=0.001$). Six of the patients with CIRCI (30%) received glucocorticoids. With an average elevation of the mean blood pressure by 22.2 ± 8.7 mm Hg after steroid therapy, the duration of inotropic support was shorter in the steroid group than in the non-steroid group (14.1 ± 2.3 days versus 30 ± 22.8 days, $p=0.001$). Three infections (15%) developed in the non-steroid group, but this was not a significant between-group difference. **Conclusion:** CIRCI should be suspected in patients with LCOS after cardiac surgery, especially in patients with a high SOFA score. Glucocorticoid replacement therapy may be considered to reduce the use of inotropes without posing an additional risk of infection.

Key words: 1. Critical illness
2. Adrenal insufficiency
3. Low cardiac output syndrome
4. Corticosteroids
5. Wound infection

Introduction

Low cardiac output syndrome (LCOS), which manifests with symptoms of hypotension, tachycardia, oliguria, and poor peripheral perfusion [1,2], is not rare after cardiac surgery in adults. Typically, high dose of inotropes are required to maintain adequate perfusion pressure in patients experiencing LCOS.

Persistent LCOS may lead to multiorgan failure, which results in postoperative morbidity and mortality. In this setting of critical illness and stress, critical illness-related corticosteroid insufficiency (CIRCI) may occur and aggravate hemodynamic instability. Conversely, CIRCI can be the cause of LCOS. However, insufficient evidence and guidelines exist regarding the management of CIRCI in patients

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Table 1. Preoperative characteristics of the patients

Preoperative variable	CIRCI(+) (n=20)	CIRCI(-) (n=8)	p-value
Age (yr)	63.8±12.4	57.1±13.1	0.21
Sex (female)	8 (40.0)	5 (62.5)	0.41
Body surface area (m ²)	1.55±0.16	1.67±0.19	0.12
Diabetes mellitus	4 (20.0)	1 (12.5)	1.00
Hypertension	6 (30.0)	4 (5.0)	0.40
Chronic renal failure	2 (10.0)	1 (12.5)	1.00
Cerebrovascular accident	1 (5.0)	0	1.00
Euro score	6.3±7.7	6.7±12.5	0.92
Emergency	7 (35.0)	0	0.07
Operation type			0.39
Valve	9	5	
Coronary	1	0	
Aorta	2	2	
Pericardiectomy	8	1	
Sequential Organ Failure Assessment score	16.1±2.3	11.4±3.5	0.001*
Lactate (mmol/L)	3.9±3.4	3.1±2.7	0.80
Total bilirubin (mg/dL)	11.7±9.2	4.9±4.3	0.01
Extracorporeal membrane oxygenation	5 (25.0)	0	0.28
Vent duration (day)	27.5±23.6	19.2±12.5	0.36
Intensive care unit stay (day)	75.1±146.9	29.1±14.8	0.39
In-hospital mortality	3 (15.0)	0	0.53

Values are presented as mean±standard deviation or number (%).
 CIRCI, critical illness-related corticosteroid insufficiency.
 *p<0.05.

with LCOS.

We aimed to investigate the clinical features of CIRCI in adult patients with LCOS after cardiac surgery and to assess the efficacy and safety of steroid treatment in these patients.

Methods

1) Study population

From February 2010 to September 2014, 5,038 patients underwent cardiac surgery at Asan Medical Center. A rapid adrenocorticotrophic hormone (ACTH) stimulation test was performed in 36 of these patients. Patients who were in blood culture-proven septic shock or exposed to steroids before surgery for any medical causes were excluded. Finally, 28 patients who underwent an ACTH test due to the suspicion of CIRCI with LCOS were included and reviewed retrospectively. The diagnosis of CIRCI was made by a change in the total serum cortisol of <9 μg/dL after the administration of 250 μg of ACTH or a random total cortisol level of <10 μg/dL, ac-

ording to the recommendations of the American College of Critical Care Medicine [3]. The Institutional Review Board of Asan Medical Center approved this study (IRB approval no., 2018-0534) with a waiver of the requirement for individual patient consent.

2) Strategy of hydrocortisone replacement therapy

The decision to use corticosteroid replacement therapy was made at the discretion of an attending surgeon or an intensivist. The initial dose varied from 50 to 240 mg per day. Efforts to shorten the duration of steroid use were made. Within 3 days after the initiation of steroid therapy, the daily dose was tapered down by about 20% of the last dose over a week. A rapid ACTH test was repeated 2 days after the cessation of steroid therapy. If the repeated results still met the criteria for CIRCI, a low dose of oral hydrocortisone was resumed and we consulted the endocrinology department for further management. The main reason not to use steroids in some patients was concern about possible wound infection.

Table 2. Comparison between patients who did and did not receive steroid therapy

Operative variable	Steroid(+) (n=6)	Steroid(-) (n=14)	p-value
Ventilator duration (day)	18.8±14.4	31.2±26.2	0.29
Duration of inotropes (day)	14.1±2.3	30±22.8	0.001*
Intensive care unit stay (day)	25.3±11.1	29.9±23.8	0.66
Infection	0	3 (21.4)	0.5
In-hospital mortality	1 (16.7)	2 (14.3)	1.00

Values are presented as mean±standard deviation or number (%).

*p<0.05.

3) Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Data are expressed as mean±standard deviation for continuous variables and as numbers and percentages for categorical variables. Preoperative and post-operative measurements were compared using the Student paired t-test. The chi-square test or the Fisher exact test was used to compare categorical variables and to assess the statistical significance of differences between the 2 groups. All p-values of 0.05 or less were considered to indicate statistical significance for all comparisons.

Results

Among the 28 patients who underwent a rapid ACTH test due to the suspicion of CIRCI, 20 patients met the diagnostic criteria for CIRCI. To investigate the clinical features of CIRCI patients, the patients with CIRCI patients were compared to the patients without CIRCI, as summarized in Table 1. Most of the patients with CIRCI (82%) had undergone valvular surgery or pericardiectomy. The patients with CIRCI showed higher Sequential Organ Failure Assessment (SOFA) scores and higher serum bilirubin levels at the time of diagnosis than the patients without CIRCI (p=0.001 and p=0.01, respectively). In-hospital mortality only occurred in the patients with CIRCI (10.7%), although this discrepancy was not statistically significant.

Only 6 of the 20 CIRCI patients (30%) received corticosteroid therapy. Their mean blood pressure was elevated by an average of 22.2±8.7 mm Hg on the day after the initiation of steroid replacement therapy, and the total duration of inotropic support was significantly shorter in the steroid therapy group (p=0.001), as shown in Table 2. The mean duration

of steroid use was 51±66 days, including 3 patients who received a daily maintenance oral corticosteroid dose of 10–20 mg due to a change in serum cortisol of <9 µg/dL on a repeated rapid ACTH test after the discontinuation of intravenous corticosteroid therapy. Infection only developed in the patients who did not receive steroid therapy (n=3), although this trend was not significant. Ventilator duration and survival did not differ between the 2 groups (p>0.05).

Discussion

Although a consensus has been established regarding the efficacy of corticosteroid replacement therapy in sepsis [4], the diagnosis and management of CIRCI in adults remains controversial, and firm evidence is lacking. Even though recommendations for CIRCI were reported in 2008 by the American College of Critical Care Medicine [3], they focused on patients with septic shock and severe acute respiratory distress syndrome, commenting that role of glucocorticoids in the management of patients undergoing cardiac surgery required further investigation.

Acute stress during critical illness activates the hypothalamic-pituitary-adrenal (HPA) axis, increasing the secretion of cortisol. However, this pathway seems impaired in critically ill patients [5-7]. The incidence of adrenal insufficiency in critically ill patients varies from 10% to 20%, and can be as high as 60% in patients experiencing septic shock, according to published data [8]. The major effect of adrenal insufficiency in critically ill patients is manifested through alterations in the systemic inflammatory response and cardiovascular function. Even though the mechanisms leading to dysfunction of the HPA axis are poorly understood, several hypotheses have been proposed, including structural damage to the adrenal gland from either hemorrhage or infarction, de-

creased production of cortisol or ACTH, and the failure of activated glucocorticoid receptors (GRs), which is known as systemic inflammation-associated glucocorticoid resistance [9]. Several studies have suggested that significant systemic inflammation, including pancreatitis, burns, liver failure, and post-cardiopulmonary bypass, may impair the synthesis and action of cortisol by acting on the HPA axis and the GR signaling system [10-12].

Cardiac surgery, regardless of whether cardiopulmonary bypass is used, may be a major stressor to patients in conjunction with the systemic inflammatory response. Furthermore, after cardiac surgery, patients usually require inotropes to support cardiac contractility and vasomotor tone. Sometimes, a high vasopressor dose for a long duration or even mechanical circulatory support, such as extracorporeal membrane oxygenation to maintain circulation, may be required depending on the severity of heart disease and function. Such a situation, in which circulation and organ perfusion is barely maintained with a high dose of 2 or more inotropic agents including epinephrine, was defined as LCOS [1,2,13]. The long-term use of high-dose vasopressors in patients with LCOS can lead to other postoperative complications, such as multiorgan failure and bowel ischemia. Several studies reported hydrocortisone administration to be effective in cases of persistent LCOS, mostly in pediatric patients [2,14-18]. Our study also demonstrated hemodynamic improvements with the use of hydrocortisone in LCOS in adults. Despite the unclear mechanism, it was found that patients with LCOS after cardiac surgery may develop CIRCI at any point postoperatively, and they did not respond to volume replacement or vasopressors. As cortisol has several important physiologic actions, such as increasing sensitivity to vasopressors and angiotensin II, as well as increasing endothelial nitric oxide synthase to maintain microvascular perfusion, blood pressure and peripheral perfusion improve with corticosteroid replacement. In our study, the duration of vasopressor use in the patients who received steroid therapy was significantly shorter than in those who did not.

However, steroid use has well-known risks, including osteoporosis, avascular necrosis, glaucoma, diabetes mellitus, and serious infections. As wound infection or mediastinitis after cardiac surgery is one

of the most dangerous complications, caution should be taken regarding steroid use in the immediate postoperative period, which is the main reason why surgeons were reluctant to use steroid therapy in patients with LCOS in this study. However, despite this concern, randomized controlled trials of short-term and low-dose steroids in patients with rheumatoid disease have generally shown little or no increased risk of infection [19,20]. In our study, the mean duration of steroid use was 51 ± 66 days, and none of the patients receiving steroid therapy developed any kind of infection. Instead, some patients in the non-steroid therapy group experienced infections, leading to in-hospital mortality. We tentatively conclude that the benefits from the hemodynamic improvements caused by short-term, cautious corticosteroid use may outweigh the possible risk of infection or prolonged vasopressor use.

1) Limitation

There are several major limitations in our study. First, this was a retrospective observational study, not a randomized controlled study. Therefore, the comparison between the 2 groups could have been biased, with potential confounding factors. Second, the study population was very small. Because CIRCI patients were likely to have been present among the unscreened LCOS patients, the entire LCOS group could not be used as the control group. Additionally, the strict inclusion criteria that were adopted to improve the homogeneity of the study population are also a reason for the small population. This was also partly due to the poor understanding of possible CIRCI in adult cardiac surgery patients. Third, treatment decisions and strategies were somewhat arbitrary and varied across individuals due to the absence of an established diagnostic method or guideline for CIRCI after cardiac surgery.

2) Conclusions

CIRCI may develop in patients with LCOS after cardiac surgery. Therefore, CIRCI should be suspected, especially in patients with a high SOFA score. Short-term corticosteroid replacement therapy may be considered with caution, as it is expected to lead to blood pressure elevation and a rapid reduction of the vasopressor dose without increasing the risk of infection. Further prospective studies in a large study

cohort may be needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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