

## Cushing's surgery: Role of the anesthesiologist

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### ABSTRACT

Cushing's syndrome is a clinical situation, caused by excessive glucocorticoid level, resulting in several features such as central obesity, supraclavicular fat, "moon face," "buffalo hump," hyperglycemia, metabolic alkalosis, hypokalemia, poor wound healing, easy bruising, hypertension, proximal muscle weakness, thin extremities, skin thinning, menstrual irregularities, and purple striae. In the perioperative period, the anesthesiologist must deal with difficult ventilation and intubation, hemodynamic disturbances, volume overload and hypokalemia, glucose intolerance, and diabetes, maintaining the blood cortisol level and preventing the glucocorticoid deficiency. This syndrome is quite rare and its features make these patients very difficult to the anesthesiologist.

**Key words:** Adrenalectomy, anesthesia, Cushing's syndrome

### EPIDEMIOLOGY

The prevalence of Cushing's disease is 39.1 cases/million inhabitants and average incidence is 2.4 cases/million per year.<sup>[1]</sup> The annual incidence rate of endogenous Cushing's syndrome (CS) has been estimated at 13 cases/million individuals. Of these cases, approximately 70% are due to Cushing's disease, that is, a pituitary adrenocorticotropic-releasing hormone (ACTH)-producing tumor; 15% to ectopic ACTH and 15% to a primary adrenal tumor. The female-to-male incidence ratio is 5:1. Ectopic ACTH production is found more frequently in men than in women probably because of the increased incidence of lung tumors in the former. The incidence peaks at ages 25–40 years. Increased mortality in CS is likely to be due to cardiovascular disease, higher age, and the persistence of hypertension or diabetes.<sup>[1]</sup>

### CAUSES AND ASSOCIATED FINDINGS

Glucocorticoid excess (CS) results from either endogenous

oversecretion or chronic treatment with glucocorticoids at higher doses. Symptoms of glucocorticoid excess generally occur with the administration of oral steroids, injections of steroids, or inhalers. Patients with diseases (arthritis, allergies, and asthma) that respond to steroid therapy are especially likely to receive steroids and thus develop CS. Indeed, CS are reported even after steroid-based unguents administration.<sup>[2]</sup> Other causes are unilateral or bilateral adrenal hyperplasia, pituitary ACTH secreting adenoma (Cushing's disease), and ectopic tissues that produce ACTH.

There are similarities between CS and the metabolic syndrome as both are characterized by central obesity, hypertension, insulin resistance, glucose intolerance, and dyslipidemia. Diabetes occurs in approximately 80% of patients with CS but several data are reported about the prevalence of CS in patients with diabetes mellitus.

There are several studies that support the view that unknown CS is not rare among patients with diabetes mellitus.<sup>[3]</sup> Leibowitz *et al*,<sup>[4]</sup> enrolled in their study 90 diabetic patients with a body mass index >25 and glycosylated hemoglobin >9%, definitely diagnosing CS in three patients (3.3%). Catargi *et al*,<sup>[5]</sup> reported a 2% prevalence of previously unknown CS out of 200 obese patients with type 2 diabetes. Chiodini *et al*,<sup>[6]</sup> demonstrated a higher prevalence of subclinical CS in a cohort of 294 diabetic patients compared with 189 controls (9.4 vs. 2.1%).

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This is the first demonstration that screening for CS may be feasible at the clinical onset of diabetes in an unselected cohort of patients. Therefore, early diagnosis and treatment of CS may provide the opportunity to improve the prognosis of diabetes.

Several studies have demonstrated the concomitance of CS and several tumor diseases. They are reported in literature current CS and pheochromocytoma,<sup>[7,8]</sup> sarcoidosis,<sup>[9]</sup> pancreatic acinar cell carcinoma,<sup>[10]</sup> preeclamptic findings,<sup>[11]</sup> malignant gastrinoma,<sup>[12]</sup> bronchial carcinoid lung tumor,<sup>[13]</sup> pancreatic neuroendocrine tumor and Hippel–Lindau disease,<sup>[14]</sup> and mesenteric neuroendocrine carcinoma.<sup>[15]</sup>

### CLINICAL FEATURES AND DIAGNOSIS

The clinical manifestations of CS are variable and multiple as well. Often the patients manifest weight gain, especially in the face, supraclavicular region, and neck. That kind of weight gain produces “moon facies,” “buffalo hump,” and central obesity. Another frequent physical signs are purple striae, skin thinning, and easy bruising. The patients often report difficulties ongoing upstairs, because of proximal muscle weakness. Osteopenia makes the patient prone to spontaneous bone fractures. Amenorrhea, infertility, menstrual irregularities, and decreased libido are some of the clinical manifestation as well. The presence of virilization in women may suggest CS. Due to cortisol, excess sodium and water retention is presented, leading to hypertension. Impairment glucose metabolism and hyperglycemia, metabolic alkalosis, and hypokalemia are common findings in CS. The clinical features are summarized in Table 1.

Cushing disease can be manifested by the above signs and other signs and physical findings because of pituitary adenoma. Pituitary adenoma can cause visual disturbances, head ache, elevated intracranial pressure, and clinical manifestations of pituitary hormones’ oversecretion.

The diagnosis is made using imagery and laboratory tests. The laboratory tests tend to confirm the elevation in plasma, night salivary, and urinary cortisol levels, urinary 17-hydroxycorticosteroids, and plasma ACTH. If one of

these test results positive, then the diagnosis is suggested.<sup>[16]</sup> The next steps consist in several measurements of ACTH and cortisol blood levels in order to determine if it is CS or Cushing’s disease due to pituitary adenoma.<sup>[17]</sup>

The dexamethasone suppression test serves to determine if the hypersecretion of glucocorticoid is due to pituitary or adrenal gland as well. Pituitary adenoma often is associated with depression in cortisol and 17-hydroxycorticosteroid levels when a high dose of dexamethasone is administered because of negative feedback control, while adrenal tumors do not. Ultrasonography, angio-computed tomography, and magnetic resonance imaging can also confirm the diagnosis. Ectopic glucocorticoid secreting tissues can be also detected using technetium 99-labeled octreotide shintigraphy examinations. Octreotide scintigraphy may be helpful in detecting ectopic ACTH tumors because some neuroendocrine tumors typically have cell surface receptors for somatostatin.<sup>[13]</sup>

A consensus statement regarding diagnosis was proposed by several authors<sup>[18]</sup> as presented in Figure 1.

### MEDICAL AND SURGICAL TREATMENT

Multidisciplinary teams that involve an endocrinologist, neurosurgeon, general surgeon, or urologist, and anesthesiologist can guarantee the effective diagnosis and management of CS and disease.

Several drugs are used to inhibit the release and synthesis of glucocorticoids. Hypercortisolism can be controlled with adrenal enzyme inhibitors, such as ketoconazole,

**Table 1: Clinical manifestation of glucocorticoid excess**

Central obesity	Thin extremities
Supraclavicular fat	Proximal muscle weakness
Moon face	Hypertension
Buffalo hump	Hyperglycemia
Abdominal striae	Metabolic alkalosis
Skin thinning	Hypokalemia
Easy bruising	Menstrual irregularities
Osteopenia	Poor wound healing

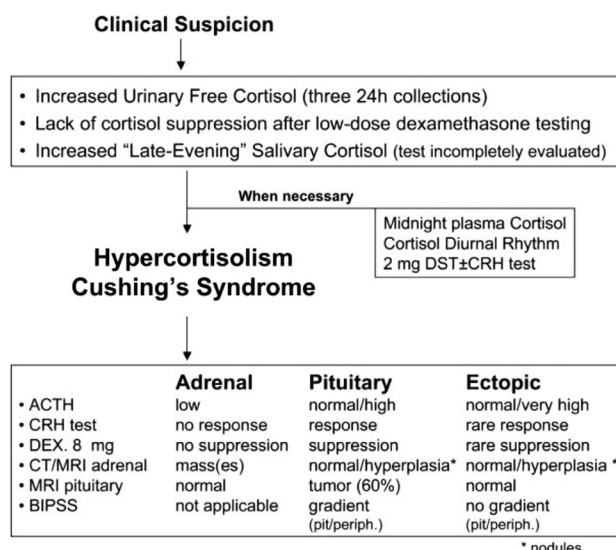


Figure 1: Diagnostic steps of CS<sup>[18]</sup>

metyrapone, mitotane, or aminoglutethimide, given alone or in combination.<sup>[19]</sup>

The treatment of choice for patients with Cushing's disease is transsphenoidal microadenectomy, if a microadenoma is identified. Another non-surgical approach is pituitary irradiation (linear accelerator, gamma knife), and if that fails, bilateral total adrenalectomy is to be performed. Pituitary irradiation also reduces the incidence of Nelson's syndrome (enlarged, locally invasive, and corticotropin-secreting pituitary tumor).<sup>[20]</sup>

Adrenalectomy is also performed when a corticosteroid secretor adrenal hyperplasia is verified. Laparoscopic adrenalectomy remains gold standard but CS is associated with longer hospitalizations, more frequent major complications, and higher advanced care requirements, especially for bilateral adrenalectomy.<sup>[21]</sup> It is generally accepted that the laparoscopic approach offers some advantages, including early return of bowel function, early ambulation, less postoperative pain, low rate of wound infection, and hernia. Several effects are reported during laparoscopy. In the Trendelenburg position (cholecystectomy), the increased IAP can reduce the venous return and cardiac filling pressure, whereas in the anti-Trendelenburg position (prostatectomy) may occur the opposite.<sup>[22]</sup> The blood pressure is usually slightly increased because of carbon dioxide induced increased sympathetic tone and systemic vascular resistance.<sup>[23]</sup> Pneumoperitoneum reduces the splanchnic blood flow,<sup>[24]</sup> including renal flow as well. The reduced renal flow leads to reductions in urine output and creatinine clearance.<sup>[25,26]</sup> During laparoscopic surgery, carbon dioxide absorption is a consistent finding in laparoscopic surgery especially during extraperitoneal procedures, such as nephrectomy, adrenalectomy, and hernia repair.<sup>[27]</sup> Pneumoperitoneum worsens the effects of general anesthesia in lung mechanic, such as reduced functional residual capacity, increased intrapulmonary shunts, and increased dead space. The net result may be hypoxemia.<sup>[28,29]</sup> Increased plasma levels of catecholamines, cortisol, renin and, antidiuretic hormone are also verified.<sup>[30]</sup>

## ANESTHETIC CONSIDERATIONS

### Preoperative optimization and evaluation

It is logical to expect a missing class between American Society of Anesthesia (ASA) 2 and ASA 3 for a systemic disease which is neither mild nor severe but is of moderate nature. Generally CS patients are classified as ASA 2 or 3 because of systemic involvement of the disease [Table 2].

As we cited above, the patients are often hypertensive and hypervolemic. The patients are under chronic

**Table 2: American Society of Anesthesia physical status classification**

Grade I	A normal healthy patient
Grade II	A patient with mild systemic disease
Grade III	A patient with severe systemic disease
Grade IV	A patient with severe systemic disease that is a constant threat to life
Grade V	A moribund patient who is not expected to survive without the operation
Grade VI	A declared brain-dead patient whose organs are being removed for donor purposes

antihypertensive drugs also. All the drugs must continue till the morning of surgery except the angiotensin converting enzyme inhibitors (captopril, enalapril, lisinopril, enalaprilat, and ramipril) and angiotensin II receptor blockers (valsartan). These drugs are associated with such severe hypotension with standard anesthetic induction, and under spinal anesthesia also. Clopidogrel should be discontinued 5–7 days before surgery, except in the coronary-stented patients in which the risk of stent occlusion is high.<sup>[31,32]</sup> The drugs used to inhibit the release and synthesis of glucocorticoids (ketoconazole, metyrapone, mitotane, or aminoglutethimide) must continue preoperatively and discontinue after the surgery.

CS is also associated with hypokalemic metabolic alkalosis. Treating preoperatively the patients with spironolactone will decrease the potassium loss.<sup>[33]</sup>

Hyperglycemia is another problem faced by the anesthesiologist in the perioperative period. Increased glucose blood level is found to be associated with increased mortality, higher rates of infections, and longer hospitalization.<sup>[34-36]</sup> Oral agents are generally discontinued before surgery.<sup>[37]</sup> The regimen insulin is necessary to maintain the glucose blood level within the normal values. The anesthesiologist must take care to prevent hypoglycemia as well. The goal is to maintain blood glucose levels within 120–180 mg/dl [6.67 to 10 mmol/l] during the perioperative period.<sup>[38]</sup> The guidelines of American Association of Clinical Endocrinologists and the ADA have recommended target values to 140–180 mg/dl for ICU and 100–180 mg/dl as a target for the diabetic patients in medical and surgical wards.<sup>[29]</sup> In the perioperative period, the regular insulin is the most commonly used one. The doses depend on glucose blood level and the desired target, so frequent glycemia monitoring is mandatory. In order to prevent hypoglycemia, subcutaneous route would be the most suitable choice. The intravenous doses and change rates are summarized in Tables 3 and 4. After the patient starts taking orally liquids, the oral agents substitute the insulin.

Obesity is a major problem faced in CS. Morbidly

**Table 3: The insulin regimen perioperative therapy**

Regular insulin	Type 1 DM (male)	Type 1 DM (female)	Type 2 DM
Initial bolus	0.05–0.1 U/kg	0.05–0.1 U/kg	0.05–0.1 U/kg
Infusion	1 U/h	0.5 U./h	1 U/h

**Table 4: Glucose blood level and insulin dose changes**

Glucose blood level (mg/dl)	Infusion rate change (U/h)
≤70	Reassessment within 30 min
70–120	↓ 0.3
121–180	No change
181–240	↑ 0.3
241–300	↑ 0.6
≥300	↑ 1

obesity is considered when body mass index (body mass index = weight [kg]/height<sup>2</sup> [m]) is over 36. Obesity is associated with hypertension, dyslipidemia, ischaemic heart disease, diabetes mellitus, osteoarthritis, liver disease, and obstructive sleep apnea.<sup>[39]</sup> The cardiorespiratory risk increases with the duration of obesity (fat years). As a result of increased pulmonary blood volume and the adipose tissue around the thoracic cage, lung and chest wall compliances are usually decreased. The reduced compliance contributes in FRC reduction, atelectasis, ventilation/perfusion (V/Q) mismatching, intrapulmonary shunt, and finally hypoxemia and rapid desaturation. Blood volume, cardiac output, ventricular workload, oxygen consumption, and CO<sub>2</sub> production are all increased. These may lead to systemic and pulmonary hypertension and later cor pulmonale and right ventricular failure. The increased left ventricular (LV) wall stress and hypertrophy are secondary to systemic hypertension, later resulting in LV dilatation. Finally, the ischemic heart disease is a common finding in obese patients.

Hypertension, obesity, hyperglycemia, inability to make a normal physical activity, and hypercoagulable state can also contribute to increased risk for deep venous thrombosis and pulmonary embolism (PE). The prevention of perioperative venous thromboembolism and PE can be realized using low-molecular weight heparin (enoxaparin, dalteparin, etc.) or fondaparinux, and lower extremity compression devices.<sup>[40]</sup> Warfarin is also recommended in high-risk patients.<sup>[41]</sup> Early mobilization is also essential and very useful.

Because of osteopenia and easy bruising, the anesthesiologist must take care during positioning and taping the patient, in order to prevent bone fractures and skin damages.

Predicting difficult intubation is essential. Several parameters such as Mallampati score, mouth opening, neck extension, tireomental and sternomental distances, and Wilson score<sup>[42]</sup> are used to predict difficult intubation. Generally an obese patient may have normal airways but a higher rate for respiratory failure. A full blood count, electrolytes, renal and liver function tests, and blood glucose form a basic set of investigations. Arterial blood gas analysis may be useful in those suspected of respiratory comorbidity. Pulmonary functionally test (PFT) is useful to evident the high-risk patient for postoperative respiratory failure. PFT shows the restrictive component of respiratory dysfunction (a normal FEV1/VC, but reduced forced expiratory volume in the first second [FEV1] and vital capacity [VC]). Electrocardiography and echocardiography are essential to estimate stroke volume, LV and RV dimension and contractility, pulmonary hypertension, arrhythmia, and valve structure.

The choice of premedication drugs depends on the anesthesiologist preferences and the physical status of the patient. Preoperative deep sedation in the ward must be avoided because of respiratory failure. The anesthesiologist should promptly secure the airways. As a general rule, a small dose of a benzodiazepine (midazolam 1 mg intravenous) may be sufficient.

#### Intraoperative considerations

Obesity can contribute to increased risk for gastric aspiration. The prevention of gastric aspiration can be realized administering metoklopramide 10 mg, ranitidine 50 mg intravenously, and sodium citrate 30 ml orally just before the induction.

Several possible respiratory complications may be faced. The mask ventilation may be difficult because of obesity. Hypoventilation may occur as a consequence of obesity and proximal muscle weakness, contributing to hypoxia and hypercapnia. The suitable preoxygenation is responsibility of the anesthesiologist and can prevent hypoxia episodes if a difficult intubation occurs.

There are no specific recommendations regarding the anesthetic technique or medication in patients with CS. Sodium thiopentone and propofol can be used. Ketamine should be avoided because of its sympathetic effects. Etomidate blocks the cortisol synthesis and can be used in Cushing's surgery. The commonly used opioids are fentanyl, sufentanil, and remifentanil as well. It is well-known hypotension and reduced heart rate using remifentanil, but its ultrashort effect can also contribute in reduced respiratory depression and enhanced recovery. Total intravenous anesthesia using the combination of



propofol and remifentanyl is also a preferred anesthetic technique. When significant skeletal muscle weakness is present, a conservative approach to the use of muscle relaxants is warranted. Short-acting neuromuscular blocking drugs such as vecuronium, cisatracurium, and rocuronium are preferred, because of reduced rate of postoperative respiratory complications.

Induction of anesthesia and endotracheal intubation must be realized using "rapid induction sequence." During the intubation, often hypertension and arrhythmias can occur. So the anesthesiologist must blunt this sympathetic response using opioids, lidocaine, clonidine, and esmolol,<sup>[43]</sup> preventing further deterioration of the patient.

Standard and invasive monitoring of the patient is mandatory. Standard monitoring includes non-invasive blood pressure, temperature, end-tidal carbon dioxide, pulse oximetry, and electrocardiography. Invasive monitoring includes invasive blood pressure monitoring through an arterial catheter cannulation, and if necessary Swan-Ganz pulmonary artery catheter.

Large bore peripheral vein catheters must be placed. The anesthesiologist must routinely cannulate a central vein, helping for administration of the massive liquids and blood transfusions during the surgery if necessary. Normal saline or ringer lactate solutions are suitable choice and refilling is usually done in the rate 10–15 ml/kg/h. In order to prevent third space losses, we must combine crystalloids (normal saline, ringer lactate solutions) with colloids (gelofusine, dextran, hydroxyethylstarch 130/0.4). The fluid management is guided by urine output, blood pressure, filling pressures, and cardiac output if available. Transesophageal echocardiography also helps guiding the fluid management.

The endogenous production of excessive amounts of glucocorticoids has also been described as the stimulus for immunosuppression, with resultant development of opportunistic infections.<sup>[44]</sup> So the prophylaxis with right antibiotics is mandatory in order to prevent the infections. The prophylaxis is mainly based on own protocols and bacterial colonization of each institute.

The use of epidural anesthesia is helpful although few cases for its use in CS are reported.<sup>[45]</sup> Using epidural has been demonstrating to reduce the surgery-induced proinflammatory response,<sup>[46]</sup> the cardiovascular and respiratory complications,<sup>[47]</sup> the intraoperatively blood loss, and the incidence of PE. Epidural analgesia is also effective in controlling postoperative pain. If epidural opiates are used for postoperative analgesia, a loading dose

of hydromorphone (0.5–1.0 mg) is usually administered 1 h before the end of surgery.

During the laparoscopic adrenalectomy, the anesthesiologist must take care of hemodynamic perturbations (rationally filling the patient) and laparoscopic respiratory consequences (modifying the ventilator parameters related to capnography changes).

Patients undergoing adrenalectomy may require intraoperative glucocorticoid replacement, so we administered intraoperatively 100 mg hydrocortisone succinate. Finally, the strict intraoperatively monitoring of glucose blood level and electrolytes is of great importance.

Transsphenoidal resection is the surgical technique applied when an ACTH pituitary tumor is verified (Cushing's disease). Standard precautions regarding difficult intubation or ventilation and monitoring are also recommended. The muscle relaxant dose must be reduced. With adequate anesthesia and the head in the Mayfield–Kees skeletal fixation, the movements are unlikely. The anesthesiologist must use a reinforced endotracheal tube, to prevent kinking while the surgeon is working. Before the extubation, the anesthesiologist must be assured that all the blood accumulated in the back of the throat is suctioned out. Replacement therapy with steroids is necessary until the pituitary normal function return. Occasionally patients may develop diabetes insipidus which is treated with prompt fluid administration and vasopressin therapy.

The patient should be alert, warm, hemodynamically stable, and fully reversed from muscle relaxants before the extubation. Table 5 summarizes the most important issues to do or to avoid.

### Postoperative care

In the postoperative period, the anesthesiologist must take care to prevent respiratory complications (atelectasis, hypoxemia) by effectively postoperative pain relieving, early mobilization, and respiratory exercises. The postoperative acute pain treatment may be realized by systemic analgesic drugs (patient controlled analgesia pumps or through epidural route). The early mobilization also helps preventing deep venous thrombosis and PE. The cortisol, glucose, and electrolytes blood levels must be routinely checked. The replacement of cortisol must continue in the postoperative period, guided by cortisol blood level. The glucose blood level can be maintain within the recommended levels, using insulin regimen or orally drugs. The antihypertensive drugs continue judging the patient's hemodynamic status. Finally, after the patient discharged, he must be referred to an endocrinologist for further consultation.

**Table 5: The most important thing to do, or not to do**

Remember to do	Remember not to do
Airway evaluation	Not preoperative deep sedation
Careful cardiovascular evaluation (ECG, ECHO)	Excessive dose of muscle relaxants
Careful respiratory evaluation (X-ray, blood gases, PFT)	Incorrect patient position
Stabilize glycemia (insulin regimen)	Aggressive taping
Acid base and electrolytes corrections (spironolactone, potassium)	
Prevention of gastric aspiration (metoklopramide, ranitidine, sodium citrate)	
Invasive monitoring	
Infection prophylaxis	
Extubate when the patient is alert, warm, hemodynamically stable, and fully reversed from muscle relaxants	
Routinely postoperative monitoring of cortisol, glycemia, and electrolytes	
Prevention of cortisol deficiency (hydrocortisone succinate)	
After the hospital discharged, the patient must be referred to the endocrinologist	

## CONCLUSION

Surgery in CS presents a challenge to the anesthesiologist. The control of perioperative hypertension, hyperglycemia, hypokalemia, and cortisol blood level are hallmarks of the anesthesiologist's role treating the patients with Cushing's syndrome.

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