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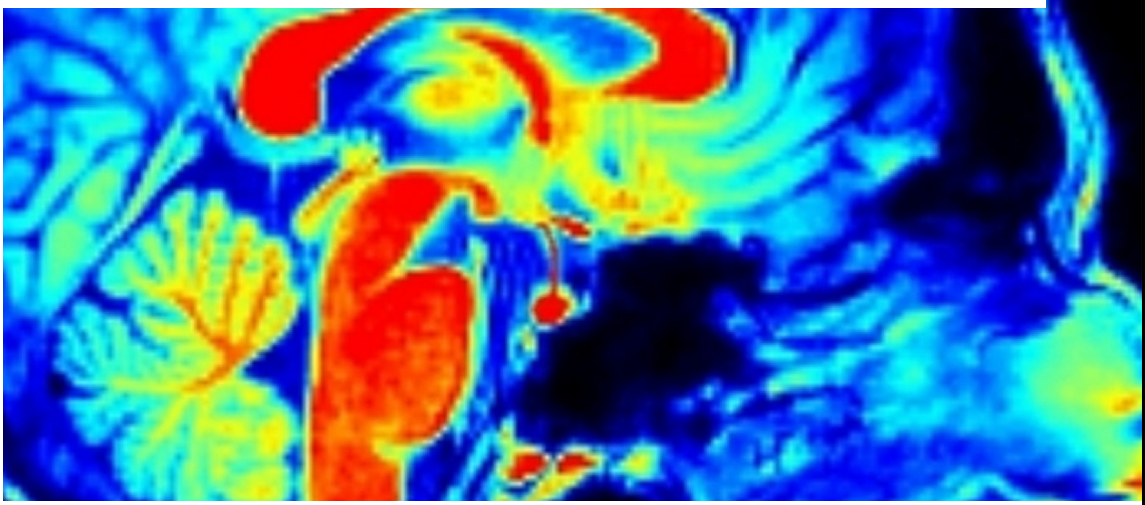
Stepani Bendel

Pituitary and Adrenal Response to Critical Illness



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EASTERN FINLAND

STEPANI BENDEL

Pituitary and Adrenal Response to Critical Illness

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ABSTRACT

The hypothalamo-pituitary-adrenal (HPA) axis plays a major role in the modulation of stress and inflammation in critically ill patients. HPA-axis dysfunction may negatively affect outcome. The objective of this study was to evaluate HPA function in different critically ill patient categories and to determine if HPA dysfunction is present.

A total of 237 critically ill patients were enrolled in the study. Sixty-six patients with severe aortic stenosis received either etomidate or propofol to induce anaesthesia, and 125 patients had severe sepsis or septic shock. Thirty patients had acute aneurysmal subarachnoid haemorrhage (aSAH), and 16 patients who underwent elective intracranial aneurysm surgery served as their control. The free and/or total serum cortisol response was evaluated in all patient categories, and the insulin-like growth factor-I (IGF-I) concentrations were measured in patients with aSAH.

In patients with severe aortic stenosis etomidate transiently depressed cortisol synthesis and thus shortly affected the inflammatory response. However, etomidate did not cause as mutch hypotension than propofol. In patients with severe sepsis, the free and total serum cortisol concentrations correlated well. The severity of aSAH did not affect the free or total serum cortisol concentrations. The adrenocorticotropic-cortisol profile of some patients indicated secondary adrenal insufficiency (AI) in the acute phase of aSAH. Patients with aSAH had low IGF-I concentrations in the acute phase of the disease.

Calculating free serum cortisol does not provide any advantages over measuring total serum cortisol in patients with severe sepsis, septic shock. Free serum cortisol was not helpful for predicting mortality in patients with severe sepsis or septic shock. The severity of aSAH does not affect free or total serum cortisol concentrations. In the acute phase, some patients may have secondary AI. Serum IGF-I may contribute to increased morbidity in patients with aSAH. Etomidate transiently decreases serum cortisol concentration. Propofol is twice as likely as etomidate to evoke hypotension

National Library of Medicine Classification: WC 240, WG 265, WK 515, WK 550, WK 755, WK 765, WL 355

Medical Subject Headings (MeSH): Adrenocorticotropic Hormone; Adrenal Insufficiency; Aortic Valve Stenosis; Critical Illness;Glucocorticoids; Hypopituitarism; Insulin-Like Growth Factor I; Intracranial Aneurysm/surgery Pituitary-Adrenal System; Pituitary Gland;Pituitary Hormones; Sepsis; Subarachnoid Hemorrhage

Bendel, Stepani. Aivolisäkkeen ja lisämunuaisen toiminta kriittisesti sairaalla potilaalla.
Publications of the University of Eastern Finland. Dissertations in Health Sciences; 12. 2010, 72 s

TIIVISTELMÄ

Aivolisäkkeen ja lisämunuaisen (HPA) toiminta on keskeinen kriittisesti sairaan potilaan stressi- ja tulehdusvasteen säätelijä. HPA-toiminnan häiriö saattaa huonontaa potilaiden ennustetta. Tämän tutkimuksen tarkoituksena oli selvittää HPA-toimintaa erilaisissa kriittisissä sairaustiloissa.

Tutkimusmateriaali koostui 237 tehohoitopotilaasta. Merkittävä aorttaläpän ahtauma oli 66 potilaalla ja heidän anestesiansa aloitusta tutkittiin antamalla heille joko propofolia tai etomidaattia. Sepsis tai septinen sokki oli 125 potilaalla ja 30 potilaalla oli lukinkalvonalainen verenvuoto (SAV). SAV-potilaiden kontrollipotilasryhmänä oli 16 suunniteltuun vuotamattoman aivovaltimopullistuman (aneurysma) leikkaukseen tullutta potilasta. Kaikilta potilasryhmiltä mitattiin seerumin vapaan ja/tai kokonaiskortisolin pitoisuus. SAV-potilailta mitattiin lisäksi seerumin insuliinin kaltaisen kasvutekijän (IGF-I) pitoisuus.

Etomidaatti pienensi lyhytaikaisesti aorttastenoosipotilaiden kortisolipitoisuuksia ja vaikutti siten tämän potilasryhmän tulehdusvasteeseen. Etomidaatti ei aiheuttanut yhtä paljon verenpaineen laskua kuin propofoli. Potilailla, joilla oli vakava sepsis vapaan ja kokonaiskortisolin pitoisuudet korreloivat hyvin. SAV:n vaikeusaste ei vaikuttanut seerumin vapaan tai kokonaiskortisolin pitoisuuksiin. Joidenkin SAV-potilaiden adrenokortikotrooppisen hormonin ja kortisolin pitoisuudet viittasivat sekundäärisen lisämunuaisen vajaatoimintaan. SAV-potilaiden IGF-I-pitoisuudet olivat matalia sairauden akuuttivaiheessa.

Potilailla, joilla on vakava sepsis, seerumin vapaan kortisolin laskemisesta ei ole hyötyä verrattuna seerumin kokonaiskortisolin mittaamiselle. Vapaan kortisolin mittaaminen ei ennustanut kuolleisuutta tällä potilasryhmällä. SAV:n vaikeusaste ei vaikuttanut vapaan tai kokonaiskortisolin pitoisuuksiin. Joillakin SAV-potilailla saattaa esiintyä sekundääristä lisämunuaisen vajaatoimintaa. Seerumin IGF-I-pitoisuus saattaa vaikuttaa SAV-potilaiden toipumiseen ja sairastavuuteen Etomidaatti vaikuttaa lyhytaikaisesti potilaiden seerumin kortisolipitoisuuksiin. Propofoli aiheuttaa kaksi kertaa useammin verenpaineen laskua kuin etomidaatti.

Luokitus: WC 240, WG 265, WK 515, WK 550, WK 755, WK 765, WL 355

Yleinen suomalainen asiasanasto: aivolisäke; aivoverenvuoto; aneurysma; aortta-ahtauma; ennusteet; kuolleisuus; lisämunuaiset; potilaat; sairastavuus; septinen sokki; tehohoito; tulehdus; verenmyrkytys

To critically ill patients

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Das Projekt scheint jetzt doch von “ali-tavoite” auf “tavoite” geklettert zu sein. Wer weiss, vielleicht wird daraus noch eines Tages ein “yli-tavoite.”

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Kuopio, April 2010

Stepani Bendel

List of original publications

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I Bendel S, Ruokonen E, Pölönen P, Uusaro A. Propofol causes more hypotension than etomidate in patients with severe aortic stenosis: a double-blind, randomized study comparing propofol and etomidate. *Acta Anaesthesiol Scand.* 2007;51:284-289.

II Bendel S, Karlsson S, Pettilä V, Loisa P, Varpula M, Ruokonen E. Free cortisol in sepsis and septic shock;Finnsepsis Study Group. *Anesth Analg.* 2008;106:1813-1819.

III Bendel S, Koivisto T, Ruokonen E, Rinne J, Romppanen J, Vauhkonen I, Kiviniemi V, Uusaro A**.** Pituitary-adrenal function in patients with acute subarachnoid haemorrhage: a prospective cohort study. *Crit Care.* 2008;12:R126.

IV Bendel S, Koivisto T, Ryynänen O-P, Ruokonen E, Romppanen J, Kiviniemi V, Uusaro A. Insulin-like growth factor I in acute aneurysmal subarachnoid haemorrhage: a prospective cohort study (submitted).

Contents

ABBREVIATIONS

ACA	anterior cerebral artery
ACoA	anterior communicating artery
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AI	adrenal insufficiency
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
aSAH	aneurysmal subarachnoid haemorrhage
AVP	arginine vasopressin
BBB	blood brain barrier
BIS	bispectral index
BP	binding protein
cAMP	cyclic adenosine monophosphate
CABG	coronary artery bypass grafting
CBG	cortisol binding globulin
GCS	Glasgow coma scale
CIRCI	critical illness-related corticosteroid insufficiency
CSF	cerebrospinal fluid
CSWS	cerebral salt wasting syndrome
CRH	corticotropin-releasing hormone
CRHBp	corticotropin-releasing hormone binding protein
CRH-R	corticotropin-releasing hormone receptor
CT	computed tomography
ECG	electrocardiographic
FSH	follicle stimulating hormone
GH	growth hormone
GHR	growth hormone receptor
GHRH	growth hormone releasing hormone
GnRH	gonadotropin releasing hormone
GOS	Glasgow outcome scale
GHS-R	growth hormone secretagogue receptor
H&H	Hunt and Hess
HPA	hypothalamic-pituitary-adrenal
HRQoL	health-related quality of life
ICA	internal carotid artery
ICU	intensive care unit
IGF	insulin-like growth factor
IL	interleukin
INOS	inductible nitric oxide synthase
ITT	insulin tolerance test
LH	luteinizing hormone
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MCA	middle cerebral artery
MOF	multiple organ failure
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
PCWP	pulmonary capillary wedge pressure
POMC	proopiomelanocortin
PRL	prolactin
SAPS	simplified acute physiology score
SD	standard deviation
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SOFA	sequential organ failure assessment

SRIF	somatotropin release-inhibiting factor
TBI	traumatic brain injury
TNF	tumour necrosis factor
TSH	thyroid stimulating hormone
TRH	thyrotropin releasing hormone
VBA	vertebrobasilar artery
VIP	vasoactive intestinal peptide

1 Introduction

Severe sepsis, septic shock, aneurysmal subarachnoid haemorrhage (aSAH), and aortic stenosis are devastating diseases with high mortality rates: 29-70% mortality in severe sepsis and septic shock (Karlsson 2007; Martin 2003) and 8-67% case fatality in aSAH (Nieuwkamp 2009). Aortic stenosis is the most common acquired valve disease, and patients with severe untreated symptomatic aortic stenosis have a life expectancy of only 1 to 3 years (Carabello 2009). All of these patient groups require specialised intensive care with substantial resources (Angus 2001; Niskanen 2004). Prolonged intensive care may be needed, and several comorbidities may develop during treatment (Gruber 1999; Karlsson 2007; Macmillan 2002; Zygun 2005). The activation of the stress-induced hypothalamo-pituitary-adrenal (HPA) axis is essential for survival under these circumstances. Moreover, the HPA axis and inflammation play major roles in all of these diseases, and the modulation of the inflammatory cortisol-HPA axis may affect outcome in all of these patient groups (Annane 2000; Schneider 2007; Shann 2006). This knowledge has encouraged studies of the use of corticoid therapy for modulating the inflammatory response in cardiac (Halonen 2007), septic (Marik 2008), and aSAH patients (Schneider 2007).

Recent studies have suggested that the HPA axis is disturbed in sepsis and septic shock (Marik 2008, 2009), and this imbalance in corticoid production and peripheral effects may affect morbidity and mortality. In aSAH, acute and secondary brain insults may cause pituitary insufficiency with an incidence as high as 36% one year after the primary bleeding (Tanriverdi 2007). These symptoms may be misleadingly interpreted as consequences of the brain injury itself. No data exist on the acute phase of HPA function in patients with aSAH.

All patients in intensive care may need haemodynamically stable anaesthetics, such as etomidate, for procedural sedation. Etomidate disturbs cortisol production by causing transient adrenal insufficiency (Ledingham 1983).

This study was carried out to study the effects of etomidate on haemodynamics and cortisol production in patients with severe aortic stenosis. Our aim was to assess the impact of free and total serum cortisol concentration on mortality in severe sepsis and septic shock. We hypothesized that secondary AI may develop in acute aSAH and serum insulin-like growth factor (IGF)-I concentrations may affect morbidity in aSAH patients. Therefore, we assessed the HPA axis and serum IGF-I concentrations following aSAH and 3 months later.

2 Review of literature

2.1 Anatomy

2.1.1 Hypothalamus

The hypothalamus is part of the diencephalon, which is a central portion of the brain located around the third ventricle. The diencephalon includes the structures known as the thalamus, hypothalamus, epithalamus, and subthalamus (Tamraz 2006; Tortora 2000). The hypothalamus lies inferior to the thalamus and can be divided into four major regions that include several nuclei: mamillary, tuberal, supra-optic, and pre-optic. The mamillary region forms the posterior hypothalamus and contains the two mamillary bodies. The tuberal region is the largest portion of the hypothalamus, containing the infundibulum, which connects the hypothalamus to the pituitary gland. The supra-optic region is above the optic chiasma and forms the nuclei from which the tracts to the posterior pituitary gland extend. The pre-optic region is located anterior to the supra-optic region and is vascularised by branches of the anterior cerebral artery and anterior communicating artery and internal carotid artery. The posterior regions are vascularised by the posterior cerebral artery and posterior communicating artery (Tamraz 2006). The anterior to posterior length of the hypothalamus is only roughly 10 mm.

2.1.2 Pituitary gland

The pituitary gland weighs less than 10 g and is roughly 10 mm in length. The gland is located in the sella turcica and hypophyseal fossa at the skull base (Fig. 1). The optic chiasma is anterosuperior to the pituitary gland and lateral to the cavernous sinuses surrounding the gland. Inferiorly, the venous structures are located between the sphenoid fossa and pituitary gland (Williams 1989).

The pituitary gland is connected to the hypothalamus by the pituitary stalk, the infundibulum. The pituitary gland can be divided into two anatomical and functionally different parts, both of which are of ectodermic origin: the anterior pituitary gland (adenohypophysis) and the posterior pituitary gland (neurohypophysis).

Figure 1. This T1 weighted 3T MR image shows the anatomy of the brain of a normal control individual in the mid sagittal and coronal plane.

The anterior pituitary gland comprises approximately 75% of the total weight of the pituitary gland and consists of the pars anterior, pars intermedia, and pars tuberalis. The anterior portion contains different cell types: somatotrophs, thyrotrophs, gonadotrophs, lactotrophs, and corticotrophs. Blood is supplied to the anterior pituitary gland by a complex portal system. Hypophyseal arteries, which originate from the internal carotid artery and posterior communicating artery, form the primary plexus of the hypophyseal portal system. This primary portal plexus is connected by hypophyseal portal veins to a secondary portal plexus at the adenohypophysis and drains into anterior hypophyseal veins (Tortora 2000; Williams 1989). Because of the complex anatomy and portal vessels, the pituitary gland is thought to be especially vulnerable to trauma and other acute intracranial pathology (Dusick 2008).

The posterior gland contains the pars posterior, infundibular stem, and median eminence. The neurohypophysis contains pituicytes and the terminal axons of neurosecretory cells that originate from the hypothalamus and hypothalamohypophyseal tract. Blood is supplied to the neurohypophysis by the inferior hypophyseal artery, a branch of the internal carotid artery. The capillaries form a capillary plexus of the infundibular process and drains into the posterior hypophyseal veins (Tortora 2000; Williams 1989).

2.1.3 Adrenal cortex

The adrenal glands are paired organs located superior to both kidneys. The left gland is usually larger than the right gland and they are roughly 3x2 cm in size and weigh approximately 5 g. The right gland is located behind the inferior vena cava and is abutted to the liver and kidney. The left gland is abutted to the bursa omentalis and ventricle, and occasionally the spleen, pancreas, splenic artery, and kidney (Tortora 2000; Williams 1989).
The adrenal glands are divided into two different functional and structural parts: the adrenal cortex and the adrenal medulla. The cortex comprises roughly 80% of the gland's mass and originates from the mesoderm. The adrenal cortex can be divided into three different cellular zones that secrete different hormones.
The zona glomerulosa forms the subcapsular part of the gland and secretes mineralocorticoids. The zona fasciculata is the largest of the three parts of the adrenal gland and secretes glucocorticoids. The innermost cellular zone is the zona reticularis and is responsible for androgen secretion (Tortora 2000; Williams 1989).

2.2 Physiology

2.2.1 Hypothalamic hormones with a special focus on GHRH, SRIF, ghrelin, and CRF

The hypothalamus regulates many essential homeostatic processes in the body and is essential for regulating temperature, osmotic pressure, circadian rhythm, visceral and somatic senses, and hormonal secretion, by which it regulates pituitary function. The hypothalamus secretes hormones either into the portal vessels of the hypophysis or directly affects the neurohypophysis; thus, secreting hormones directly into the general circulation.
Hypophyseal growth hormone (GH) secretion is regulated by hypothalamic hormones, including growth hormone releasing hormone (GHRH), somatotropin release-inhibiting factor (SRIF or somatostatin), ghrelin, and other hypothalamic peptides. GHRH was discovered in 1982 when Dr. Thorner suspected that some agent might stimulate GH secretion in his patient with an enlarged sella who had gone through pituitary surgery. The pathological specimen did not show any evidence of a pituitary tumour, but it did exhibit somatotroph hyperplasia (Thorner 2008). The pituitary was suspected to be stimulated by an extrinsic factor, which led to the finding of a GHRH-secreting pancreatic tumour and the discovery of GHRH (Esch 1982; Rivier 1982). GHRH is a 44-amino-acid peptide synthesized from a larger precursor, and its half-life is approximately 50 min (Aron 2007).
GHRH stimulates GH secretion and acts as a tropic hormone for somatotrophs in the pituitary gland. This mechanism was elucidated by measuring GHRH binding sites in the pituitary gland (Seifert 1985). GHRH administration rapidly increases GH secretion. The GHRH signal is transduced by adenylate cyclase, cAMP, and protein kinase (Anderson 2004) and causes intracellular calcium mobilization. GHRH is also essential in the pulsatile pattern of GH secretion (Goldenberg 2007), but the role of GHRH, SRIF, and ghrelin is still not definitively clear. GHRH is also responsible for different GH secretion patterns in women and men (Goldenberg 2007). GHRH concentration is regulated by a negative feedback system and by neural control systems, including sleep, age, and physical or emotional stress.

SRIF is a 14-amino-acid peptide that inhibits GH and TSH secretion and suppresses the secretion of ACTH and prolactin (Goldenberg 2007). Five subtypes of SRIF receptors are known, of which types 2 and 5 are the main mediators of SRIF effects (Goldenberg 2007). SRIF does not inhibit GH synthesis but suppresses the GH response to stimuli that usually cause GH secretion, such as exercise, stress, and hypoglycaemia. However, SFIR does not inhibit the pulsatile pattern of GH secretion and does not inhibit the nocturnal augmentation of GH, but it affects the amplitude and interpulse levels of GH (Dimaraki 2003).

Ghrelin is a 28-amino-acid peptide hormone discovered in the stomach as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) that stimulates GH, ACTH, and prolactin secretion (De Vriese 2008; Kojima 1999). Ghrelin is produced in the stomach, pituitary gland, small intestine, lung, heart, pancreas, kidneys, and testes. The peptide stimulates food intake and GH release, but it also has numerous other functions, including effects on the reproductive system, gastric motility, cardiovascular effects, modulation of cell proliferation, and anti-inflammatory effects. Ghrelin is as potent as GHRH in stimulating GH secretion in the pituitary gland, and ghrelin has an additive role in GH secretion from the pituitary gland when combined with GHRH (Goldenberg 2007; Kineman 2007).

Corticotropin-releasing hormone (CRH) is a 41-amino-acid peptide released from various tissues in the human body. The main function of CRH is the stimulation of ACTH secretion from the pituitary gland, but it is also involved in energy metabolism and immunology (Baigent 2001; Richard 2000). CRH is also the main activator of pituitary-adrenal stress-related glucocorticoid secretion and is essential for the behaviour and physical changes that occur during stress (Hillhouse 2006). Two types of CRH receptors (CRH-R) are known, and they have been found in brain structures, including the hypothalamus, pituitary gland, amygdale, and hippocampus, but also adipose tissue, the adrenal gland, and placenta (Hillhouse 2006). CRH binds to its carrier protein, CRHBP, which is thought to modulate the CRH response by blocking the activation of ACTH secretion from the anterior pituitary gland (Behan 1995).

Arginine vasopressin (AVP) is also a strong stimulator of ACTH. AVP is synthesized in the paraventricular nucleus of the hypothalamus from where it is directly released into the hypophyseal portal system. CRH and AVP synergistically stimulate ACTH secretion, but CRH is permissive for the action of AVP (Engelmann 2004).

2.2.2 Pituitary hormones with a special focus on GH and ACTH

GH was isolated from the pituitary gland of a human cadaver more than 50 years ago (Raben 1957). GH is a 191-amino-acid polypeptide hormone secreted by the somatotroph cells of the anterior pituitary gland under complicated physiological control. The main hormones regulating GH secretion are GHRH and SRIF, which react to various hormonal, metabolic, and neural factors. GH secretion is highly pulsatile, with roughly 70% of its secretion during the night time.

After GH binds to its receptor, GHR, it mediates the release of IGF-1, which is produced by the liver and other tissues. GH acts mainly via IGF-1, a peptide that circulates in blood bound to carrier proteins, IGFBP. Only approximately 1% of IGF-1 is free in the circulation (Brabant 2007). Because of its ability to bind proteins and

longer half-life than GH, IGF-1 is an attractive molecule to indirectly measure GH concentrations. However, IGF-1 concentrations are also regulated by other factors, including nutritional state and multiple hormones. Both GH and IGF-1 negative feedback loops regulate SRIF and GHRH secretion (Mesotten 2006).

The primary function of GH is to promote growth, but it also plays numerous other roles in important functions, including fat metabolism by increasing lipolysis; carbohydrate metabolism by affecting glucose uptake in extrahepatic tissues and decreasing insulin sensitivity; and protein metabolism by affecting nitrogen excretion (Aron 2007; Salvatori 2004). Many physiological factors modify GH secretion; exercise, stress, and sleep increase its secretion, as well as hypoglycaemia and various neurotransmitters. In addition, chronic renal failure and starvation may increase GH secretion, but it may be decreased by several hormones described above and obesity or hypo/hyperthyroidism (Aron 2007).

ACTH is a 39-amino-acid stress hormone produced from pro-opiomelanocortin (POMC) in the anterior pituitary lobe and is released mainly in response to hypothalamic CRH. The CRH stress response causes pituitary ACTH secretion in 5-10 seconds (Sapolsky 2000). ACTH mainly causes cortisol secretion, but it also affects androgen and mineralocorticoid secretion from the adrenal cortex minutes after the induction of stress.

Similar to cortisol, ACTH levels fluctuate with the highest values measured when awake. ACTH concentrations should be determined in the morning simultaneously with serum cortisol concentrations. ACTH pulsatility is not lost in primary adrenal insufficiency, but exogenous cortisol administration may blunt ACTH secretion (Aron 2007). ACTH concentrations are regulated by three mechanisms: 1) fast increase in serum cortisol levels that result in fast feedback; 2) the absolute level of serum cortisol that results in slower feedback; and 3) ACTH concentrations affect its own secretion.

An overview of the HPA hormones is presented in Figure 2.

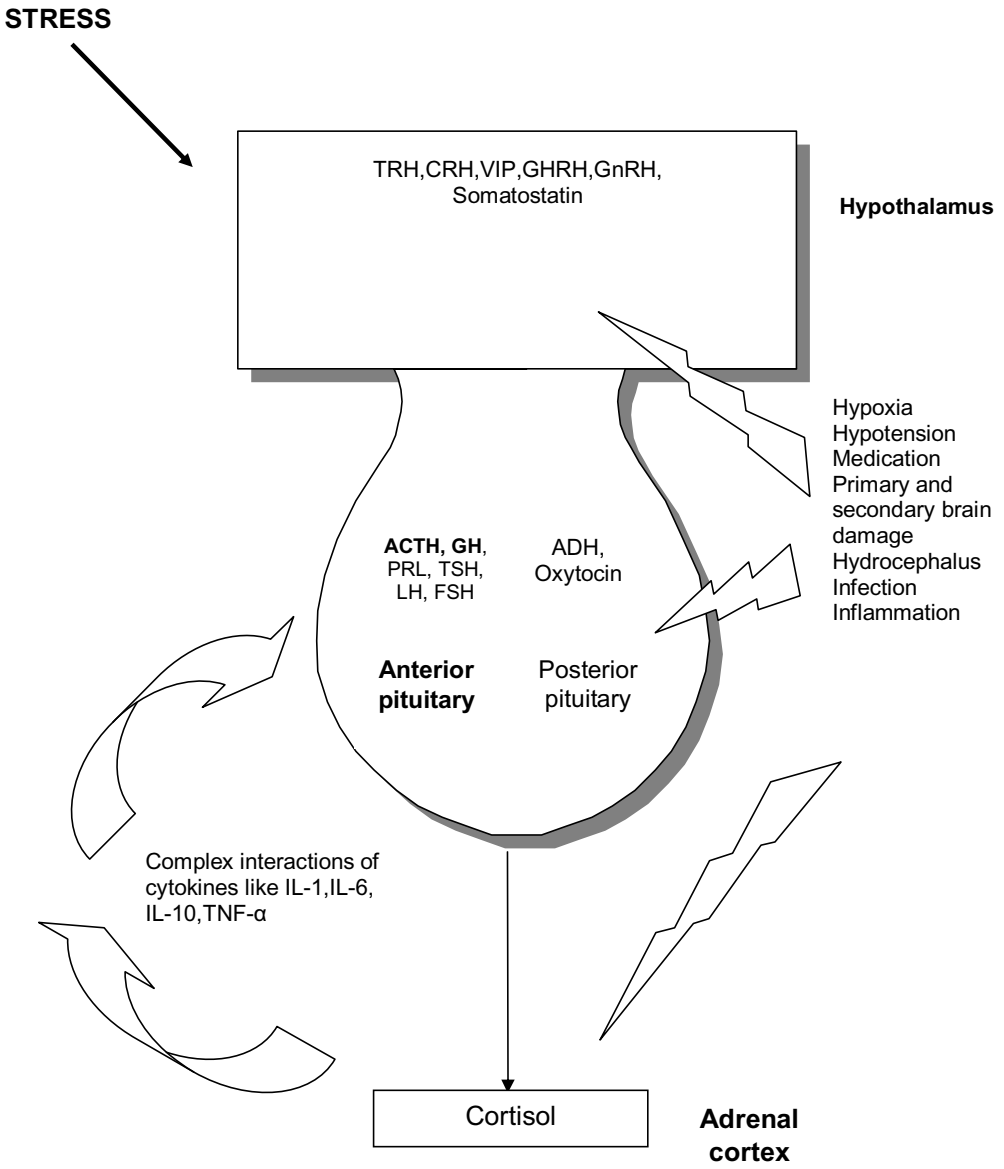


Figure 2. Hormones secreted by the hypothalamus and pituitary gland and the major factors affecting their regulation.

2.2.3 Cortisol

The anti-inflammatory effects of cortisol were first described in 1949 when Hench showed that cortisol has anti-inflammatory effects in rheumatoid arthritis (Hench 1949), and new mechanisms for the actions of cortisol, such as the differentiation of anti-inflammatory monocytes, have since been discovered (Ehrchen 2007). Glucocorticoids are widely used because of their ability to inhibit the expression of pro-inflammatory genes (Lasa 2002). HPA activation and the resulting cortisol secretion is an essential mechanism for adapting to stress and maintaining homeostasis. In healthy patients, cortisol secretion has a great diurnal variation that is lost in critical illness (Cooper 2003).

The adrenal gland has small amounts of free, immediately available cortisol for secretion, and the majority of cortisol has to be synthesized from cholesterol. ACTH induces the conversion of cholesterol to pregnenolone. The cascade ends in 11β-hydroxylation, with 11-deoxycortisol being hydroxylated to form cortisol. In humans, a mean of 9.2 mg of cortisol is synthesized per day (Aron 2007).

Glucocorticoid receptors are found in almost all human cells (Rhen 2005). Roughly 90% of cortisol is bound to cortisol binding globulin (CBG) and albumin, and only approximately 10% of cortisol is in its free and active form. Free cortisol is responsible for its physiological effects. Any alterations in the binding proteins may affect the free serum cortisol concentrations, which might be important in critical illness (Christ-Cain 2007; Ho 2006; le Roux 2003).

Cortisol acts via the glucocorticoid receptor to induce gene expression (Aron 2007). Because of the pleiotropic effect of cortisol, the results of the activation of the glucocorticoid receptor may be either stimulatory or inhibitory (Rhen 2005).

The anti-inflammatory effects of glucocorticoids are mediated by three different receptor-glucocorticoid mechanisms: non-genomic activation, DNA-dependent activation, and protein interference regulation (Rhen 2005). The result is an inhibition of the effects of cytokines and inflammatory mediators.

Glucocorticoids induce several anti-inflammatory proteins. Annexin-I protein inhibits the formation of arachnoid acid and prostaglandins, leukotrienes, prostacyclins, and thromboxanes by inhibiting the formation of cytosolic phospholipase A2α. Mitogen-activated protein kinase (MAPK) is activated, for example, by bacteria, viruses, and free radicals, and this anti-inflammatory pathway inhibits the formation of phospholipases, cytokines, adhesion molecules, and matrix metalloproteinases (Lasa 2002; Rhen 2005). Glucocorticoids also block the activation of nuclear factor-κB (NF-κB), resulting in diminished formation of tumour necrosis factor (TNF)-α, cytokines, and adhesion molecules (De Bosscher 2003). Glucocorticoids also enhance the production of endothelial nitric oxide (Hafezi-Moghadam 2002). Recent studies have suggested that glucocorticoids may have complex properties for modifying monocytes in inflammation and diminishing tissue damage in infection (Ehrchen 2007).

Glucocorticoids improve the reactivity of catecholamines with their receptors, which was described in 1966 (Besse 1966). This feature is important in the clinical setting, for example, of septic shock. Glucocorticoids also have several effects on many end organs. Glucocorticoids affect blood glucose levels by increasing gluconeogenesis in hepatic cells, inducing peripheral insulin resistance, and they increase lipolysis and are catabolic by decreasing

protein synthesis (Aron 2007). Glucocorticoids also cause bone and fibroblastic loss, affect calcium metabolism, and inhibit growth in excess amounts.

2.3 Defining critical illness

Intensive care units (ICUs) provide care for patients with severe illness and underlying organ failure. Because of limited resources and patient heterogeneity in ICUs, the critical illness that should be handled in an ICU environment should be defined. For adequate resource allocation of ICU treatment, not treating patients "too well to benefit" or "too sick to benefit" is necessary (Egol 1999). The symptoms and/or underlying disease leading to intensive care should be temporary, and the ICU intervention should provide therapies not available elsewhere (Egol 1999).

Critical illness is usually defined as life threatening but treatable symptoms. Certain guidelines exist for the clinical, laboratory, and radiological findings that can be used as criteria to assess patients for intensive care (Egol 1999). Typically, such patient groups include those who are haemodynamically unstable (e.g., severe sepsis, cardiac insufficiency), underwent major operations (e.g., cardiac surgery), have altered consciousness (e.g., subarachnoid haemorrhage, traumatic brain injury [TBI]), and those who have primary respiratory failure (e.g., pneumonia). All such critically ill patients may need ventilatory support and vasoactive therapy. Thus, any of these patients may present multiorgan failure during their stay in the ICU.

The need for effective and ethical treatment has led to the development of general scoring systems, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) (Knaus 1985; Le Gall 1984, 1993), to assess the severity of illness and predict outcome in order to better assess the prognosis and performance of different ICUs. Also, organ specific severity scoring, such as the Sequential Organ Failure Assessment (SOFA) (Vincent 1998), has been used to assess disease severity. Along with the general ICU disease severity scorings, additional disease-specific scores are used. In aneurysmal subarachnoidal hemorrhage (aSAH), the most common severity classification is the Hunt & Hess grading scale (Hunt 1968) in which the clinical condition of the patient is divided into five different classes. An other important classification score commonly used is the World Federation of Neurosurgical Societes (WFNS) scale (Report of…1988) in which the severity of aSAH is divided as well in five different classes. Moreover, the Fisher classification of blood on computed tomography is divided into four classes (Fisher 1980). In aortic stenosis, the pre-operative aortic valve area and/or stenosis gradient is used for these purposes, and an aortic valve area of less than 1.0 cm^2 and a mean transvalvular gradient of more than 40 mmHg are considered as severe aortic stenosis (Carabello 2009). However, assessing the clinical symptoms of these patients in addition to echocardiographic findings is essential because severe clinical symptoms have a huge impact on mortality (Carabello 2009).

Furthermore, all of these patients are in acute, fulminate stress that activates the hypothalamo-pituitary axis to secrete essential hormones for adapting to the situation and have a risk of developing HPA insufficiency (Vanhorebeek 2006). The mechanisms for developing HPA insufficiency may be different in the subgroups of

different patient categories. Notably, the ICU environment predisposes patients to several drugs that may influence the function of the HPA axis (Ambrogio 2008).

2.3.1 Severe sepsis and septic shock

Sepsis is currently defined according the guidelines from 1992 (Bone 1992). Sepsis is described as a systemic response to infection. Septic symptoms without infection are called systemic inflammatory response syndrome (SIRS). Sepsis is a continuum of clinical and pathophysiological symptoms and severity degrees which have negative impact on patient outcome. Therefore, severe sepsis and septic shock criteria have been defined. Severe sepsis is sepsis with at least one organ dysfunction. Additionally, in septic shock, hypotension is presented despite adequate fluid resuscitation (Table 1).

The incidence of severe sepsis varies in different studies. In a large retrospective study the incidence was 3/1000 population in the USA (Angus 2001). In Finland a recent prospective study showed an incidence of severe sepsis of 0.38/1000 in adult population (Karlsson 2007).

Patients with severe sepsis and septic shock have high mortality rates. In Finland, cumulative ICU, hospital, 1-year, and 2-year mortalities are 15.5%, 28.3%, 40.9% and 44.9% (Karlsson 2007,2009).

Table 1. Definition and criteria of sepsis (Bone 1992).

Infection	Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Bacteremia	The presence of viable bacteria in the blood.
Systemic inflammatory response syndrome (SIRS)	SIRS to a variety of severe clinical insults. The response is manifested by two or more of the following conditions. 1.temperature >38ºC or < 36ºC 2.heart rate >90/min, respiratory rate >20/min, $PaCO_2$<4.3kPa 3.white blood cell count > 12 x 10^6/mm^3 or > 10% immature (band) forms
Sepsis	The systemic response to infection, manifested by two or more SIRS criteria.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

2.3.2 Aneurysmal subarachnoid haemorrhage as a systemic disease

Twenty-three to forty-two percent of deaths following aSAH are assumed to be due to extracerebral organ dysfunction (Stevens 2007). However, these figures differ substantially between studies (Schuiling 2005). Despite aSAH is primarily affecting the brain, it has widespread systemic and extracerebral manifestations.

Cardiac dysfunction is classically thought to be due to catecholamine storm (Naredi 2000), and an imbalance between humoral and neural function may exist (Stevens 2007). ECG changes related to acute brain catastrophes have been known for decades; aSAH may cause ST-segment elevations or depressions, T-wave abnormalities, and several conduction disturbances (Macrea 2005). Also, several echocardiographic changes, such as left ventricular diastolic and systolic dysfunction, have been reported (Mayer 1999; Tung 2005). Serum CK-MB and troponin concentrations may also be elevated (Naidech 2005; Stevens 2007). Cardiac and haemodynamic complications have a negative impact on the outcome in patients with aSAH (Naidech 2005; Stevens 2007).

Neurogenic pulmonary oedema may occur in patients with aSAH, and it is described as pulmonary oedema with only aSAH being the identifiable precipitating factor. More severely ill aSAH patients seem to suffer more often from neurogenic pulmonary oedema than less severely ill patients. The overall incidence of neurogenic pulmonary oedema is reported to have a wide variability and is reported to be 2-42% (Friedman 2003; Stevens 2007). Pneumonia, acute lung injury, and acute respiratory distress syndrome (ARDS) may also complicate the clinical course of aSAH (Stevens 2007). Pulmonary complications are the most common non-neurological causes of in-hospital deaths in patients with aSAH, accounting for 11% in one study (Solenski 1995).

In addition, aSAH may cause immunological and metabolic disturbances. Anaemia is common in aSAH patients and may also have a negative impact on outcome (Kramer 2009). Furthermore, platelet dysfunction may appear (Juvela 1991).

Fever is a common finding in patients with aSAH that negatively affects outcome (Fernandez 2007) and may reflect the pro-inflammatory state of aSAH (Stevens 2007). aSAH is well known to cause major electrolyte disorders, such as the syndrome of inappropriate ADH secretion (SIADH) or cerebral salt wasting syndrome (CSWS) affecting sodium balance (Kao 2009). Moreover, treatment with the electrolyte magnesium may be beneficial in patients with aSAH (Mees 2007).

All of these non-neurological complications require attention and a multidisciplinary therapeutic approach.

2.4 Pathophysiology of the pituitary-adrenal axis

2.4.1 Pathophysiology of the pituitary-adrenal axis in severe sepsis and septic shock

Activation of the HPA axis is essential for survival, and it is activated by several mechanisms in severe sepsis. Glucocorticoids are essential when the vasomotor tone of the vasculature is impaired and affect the distribution of body fluids. Glucocorticoids are also essential for sensitizing the catecholamine receptors (Rhen 2005). Serum cortisol concentrations increase in response to stress in critical illness (Briegel 2009). However, CBG concentrations decrease and, therefore, free serum cortisol is elevated in sepsis (Hamrahian 2004).

A vast amount of literature has been published during the last years about sepsis and AI. The HPA axis and peripheral tissues are involved in a complex manner, causing either HPA insufficiency and/or peripheral glucocorticoid receptor insufficiency (Marik 2009). Meduri et al. (2002) showed that the affinity of glucocorticoid receptors to glucocorticoids may be altered, and the nuclear glucocorticoid receptor activity may be especially impaired in critically ill patients (Kino 2003; Meduri 2005).

The most potent glucocorticoid secretion activators are CRH and AVP secreted from the hypothalamus (Marik 2007, 2009). CRH and ACTH secretion is modulated by complex responses to different cytokines and interleukins. Cytokines, such as TNF-α, affect NF-κB, and glucocorticoids affect transcription factors involved in cytokine gene transcription, potentially inhibiting cytokine synthesis (Auphan 1995; Barnes 1997).

Because of the vulnerable low pressure blood supply system of the pituitary gland, these structures are susceptible to low blood pressures. This condition was classically shown in Sheehan's syndrome in which cardiovascular collapse causes pituitary necrosis (Kelestimur 2003). Sharshar et al. (2004) performed a prospective autopsy study in which they compared ICU patients who died due to septic shock, non-septic shock, and extracranial injury. The researchers measured ischemic/haemorrhagic areas in different locations of the brain and analysed TNF-α, IL 1-β, iNOS, and apoptosis. A significant increase in ischemic lesions in the hypothalamic regions was reported in patients who died due to septic shock. Also, the apoptotic scores were higher in patients with septic shock than in patients without sepsis. Apoptotic mechanisms are involved in brain autonomic nuclei dysfunction and may affect CRH secretion (Sharshar 2003), which may be induced by TNF-α and IL-6 (Soni 1995). Apoptotic mechanisms play a major role in brain dysfunction, and the main stimulators of apoptosis appear to be the inflammatory mediators and mechanisms involved in sepsis: TNF-α, IL 1-β, interferon-γ, and ischemia (Lee 2001; Yuan 2000). Moreover, the cytokines play a pivotal role in modulating the enzyme cascades responsible for glucocorticoid uptake into cells (Marik 2009).

2.4.2 Pathophysiology of the pituitary-adrenal axis in aneurysmal subarachnoid haemorrhage

The mechanisms behind pituitary-adrenal insufficiency in patients with aSAH have not been identified in any clinical study. Certain types or locations of intracerebral aneurysms that could cause more pituitary deficiencies than others have not been identified in any clinical or systematic neuropathological study. Some pathophysiological mechanisms and cascades leading to secondary brain injury are quite similar in patients with TBI and patients with aSAH. Thus, the mechanisms causing general pituitary insufficiency in aSAH may be similar to the mechanisms causing pituitary insufficiency in patients with TBI.

Hypopituitarism following brain trauma was reported as early as 1918 (Cyran 1918) when a patient with a fracture of the base of the scull and pituitary damage was described. Several reports have been published since that first description (Benvenga 2005), but the recognition of post-traumatic hypopituitarism has been poor. Since the 1950s, some autopsy studies in which pituitary and/or hypothalamic lesions were described in patients with fatal head injuries have been published (Daniel 1959), and the first large case series were published in 1986 (Edwards 1986) and 2000 (Benvenga 2000). The first reports of pituitary lesions in aSAH were published in 1963 (Crompton 1963). In this autopsy study, hypothalamopituitary lesions were identified in patients who died after acute aSAH.

Crompton et al. (1963) found that patients who had died due to the rupture of an anterior or posterior communicating artery had more frequent hypothalamus lesions; micro- and macrohaemorrhages, necrosis, and ischemic lesions were found in the hypothalamus. Haemorrhages in the pituitary regions were proposed to originate from obstruction of the venous drainage by increased intracranial pressure. The first patient with hypopituitarism to survive aSAH was described in 1963 and had hypopituitarism due to the rupture of the anterior communicating artery (Hoff 1961). For decades, large cerebral aneurysms have been known to cause hypopituitarism (White 1961).

One factor causing HPA insufficiency may be direct damage of the hypothalamic/pituitary vasculature at the time of aneurysm bleeding and/or vasoconstriction (Schneider 2007). The vulnerable anatomical location in the sella turcica and the fragile infundibulum puts the pituitary at risk with any acute intracranial pathology, leading to hormonal disturbances (Dusick 2008). Secondary insults, such as hypoxia, hypotension, and anaemia, may also contribute to pituitary insufficiency in acute brain catastrophes (Dusick 2008; Schneider 2007). Inflammatory mediators, such as cytokines, might play a role in these situations as well (Dimopoulou 2004).

2.5 Pathophysiology of the GH-IGF-I axis in aneurysmal subarachnoid haemorrhage

GH is secreted from the pituitary in a pulsatile manner. In the acute phase of critical illness, GH secretion is increased, and the situation resembles starvation (Hartman 1992; Mesotten 2006). IGF-I concentration is low in the acute phase of critical illness, though the bioavailability of IGF-I may be increased due to changes in IGF-I binding proteins (Baxter 1998; Timmins 1996). Some evidence for GH receptor resistance in septic situations has also been reported (Defalque 1999). If critical illness is sustained, the pulsatility of GH secretion diminishes and the total GH concentration is low.

Alterations in GH secretion are the most common pituitary deficiencies in aSAH and TBI (Aimaretti 2004; Dimopoulou 2004). Why the GH-IGF axis is the most vulnerable pituitary hormone pathway remains unclear, but it may be reasonable to think that the mechanism of GH deficiency in TBI is similar to the mechanism in aSAH. In this context, the special vulnerability of the somatotrophs located in the lateral wings of the anterior pituitary gland may explain why GH deficiency is the most common pituitary deficiency in aSAH (Popovic 2005). The actions of GH are mediated via IGF-I, a potent regulator of neuron growth (Kooijman 2006, 2009) that has substantial effects on apoptosis. Neuronal cell death and new concepts of the mechanism of early brain injury are important in the pathophysiology of aSAH (Cahill 2006).

2.6 Defining GH and IGF-I insufficiency, with a special focus on aneurysmal subarachnoid haemorrhage

GH and IGF-I insufficiency are diagnosed by several methods, and the method used can essentially affect the results. Guidelines exist for diagnosing adult GH deficiency (Gasco 2008; Ghigo 2005). Generally, a provocative test for diagnosing adult onset GH deficiency should be done (Gasco 2008; Ghigo 2005). If a GH sample is taken during the pulsatile cycle when GH concentration is low, it does not confirm GH deficiency. The insulin tolerance test (ITT) is the gold standard for diagnosing GH deficiency (Aron 2007; Gasco 2008). The ITT evokes stress-mediated activation of the HPA axis with increases in GH concentration. In the setting of acute aSAH, the ITT test cannot be performed because of the risk of severe hypoglycaemia, which could be deleterious for the patient. Furthermore, the test is contraindicated in patients with cerebrovascular or ischemic heart disease and seizure disorders (Aron 2007; Ghigo 2005). The ITT has good specificity and sensitivity (Biller 2002). GHRH-arginine test is as reliable in detecting GH deficiency as the ITT when adequate cut-off limits are used (Biller 2002); however, it is contraindicated in patients with severe liver or renal disease or acidosis.

The role of single IGF-I measurements in detecting GH deficiency is controversial. Normal IGF-I values do not rule out pituitary GH deficiency (Gasco 2008). Patients with panhypopituitarism may even have normal IGF-I values (Aimaretti 2003, 2004). Biller et al. (2002) showed that an IGF-I level of less than 77 µg/l may be used. Hartman et al. (2002) found that patients with appropriate clinical history and/or other pituitary deficiencies could be diagnosed with GH deficiency by measuring IGF-I.

Aging is a confounding factor in the assessment of IGF-I concentrations because the concentration decreases with age (Aimaretti 2003). Insulin, stress, liver function, and nutritional status may also influence IGF-I concentrations.

In particular, obese patients may have normal, or even high, IGF-I concentrations despite GH deficiency (Maccario 2000).

Kelly et al. (2000) defined GH insufficiency using the ITT at least 3 months after TBI or aSAH. As a result, 18.2% of examined individuals had GH deficiency using the ITT criteria and none were GH deficient using the IGF-I criteria. Hypoxia, brain swelling, low initial GCS-values, and hypotension were associated with hypopituitarism.

Brandt et al. (2004) showed that, in the chronic phase of aSAH, IGF-I levels were at the lower limit in some patients.

Dimopoulou et al. (2004) reported that, 12 to 24 months after aSAH, a morning IGF-I concentration of less than 2 standard deviations for the appropriate age range was considered to be GH deficiency; The severity or functional outcome of aSAH did not correlate with hormonal disturbances.

Aimaretti et al. (2004, 2005) used the GHRH-arginine test to evaluate the GH-IGF-I axis in aSAH patients 3 to 12 months after ICU discharge; the incidence of GH deficiency was 25% and 2.5% using IGF-I measurements.

GH deficiency is the most common pituitary disturbance in aSAH patients at 3 months. In a follow-up study from 3 months to 1 year, Aimaretti et al. (2005) found severe GH deficiency 1 year after aSAH in 21.8% of patients and partial GH deficiency in 15.6% of patients.

Tanriverdi et al. (2007) studied pituitary function within 24 hours of admission and at 12 months in patients with aSAH. A GHRH test was used at 12 months. In the acute phase, 22.7% of patients were GH deficient and 36.4% were GH deficient at 12 months. IGF-I concentrations were similar in GH deficient and sufficient patients. Hypopituitarism was not associated with the grade of aSAH as assessed by Hunt & Hess or Fisher CT scales.

Although hypopituitarism and outcome have not been extensively studied in patients with aSAH, they are generally associated with high morbidity and mortality (Agha 2005; Cohan 2005; Schneider 2007). Kreitscmann-Andermaht et al. (2007) reported that low cortisol or GH deficiency may negatively affect quality of life 1 year after aSAH.

Although IGF-I reflects the function of the pituitary-GH axis, new aspects of its pivotal role in neuroprotection have been revealed (Kooijman 2009). In addition to mostly experimental animal studies (Kooijman 2006, 2009), recent studies have shown the potential role of IGF-I in protection against brain ischemia (Bondanelli 2006).

2.7 Defining ACTH and cortisol insufficiency in severe sepsis and septic shock

Both ACTH and serum cortisol secretion have a circadian rhythm (Aron 2007), which must be taken into account when measuring serum concentrations in humans. Basal total serum cortisol concentrations should be measured in the morning (e.g., 8-9 am) (Aron 2007) because the concentrations are highest at that time.

Both basal and stimulated serum cortisol concentrations are used to define AI in critically ill patients. Basal concentrations are usually higher in critically ill patients compared to healthy volunteers (Hamrahian 2004). Several cut-off limits for basal serum cortisol concentrations are used for detecting AI in critically ill patients. A basal cortisol level of less than 165 nmol/l has been used to define absolute AI in unstressed subjects, and a serum cortisol concentration of less than 300 nmol/l is suspicious of primary AI (Arlt 2003). In critical illness, random

serum cortisol concentrations of less than 414 nmol/l are proposed to be indicative of AI (Cooper 2003). Marik et al. (2003) reported that, in patients with septic shock, a basal total cortisol concentration of <690 nmol/l is a good discriminator of AI. In the retrospective Corticus cohort study (Lipiner 2007), the baseline and stimulated cortisol levels were compared in relation to mortality in severe sepsis and septic shock. Basal serum cortisol concentrations were not associated with clinical outcome. The incidence of AI varies depending on the cut-off value used for AI (Bernard 2006; Lipiner 2007).

The simultaneous determination of serum ACTH and cortisol concentrations makes it possible to differentiate between primary and secondary AI (Arlt 2003). Long lasting (>4 weeks) ACTH deficiency causes adrenal gland atrophy and ACTH receptor down-regulation (Arlt 2003). By administering synthetic ACTH, the adrenal gland can be induced to produce cortisol and, thus, evaluate the reserve of the gland to produce cortisol (Aron 2007). Usually, 250 µg of synthetic ACTH analogue is administered intravenously, and the cortisol response is evaluated by blood samples 30 and 60 minutes after administration.

In patients with severe sepsis or septic shock, the concept of relative AI was introduced in 1991 (Rothwell 1991). Relative AI is defined as normal, or even elevated, serum cortisol that is inadequate for meeting the needs of stress. Rothwell et al. (1991) demonstrated that patients who have a blunted response (<250 nmol/l) to stimulated cortisol production have a worse outcome in septic shock than those with a response to the ACTH stimulation test of >250 nmol/. Several years passed before Annane et al. (2000) confirmed that patients with septic shock are more likely to die if they do not respond to exogenous ACTH due to increasing cortisol levels (>248 nmol/l). These results have been confirmed in several studies (Annane 2006; Bollaert 2003). The ACTH stimulation test is also used to determine the need for glucocorticoid therapy. Patients with a blunted response (serum cortisol increase of <248 nmol/l) after ACTH stimulation, in particular, would benefit from cortisol replacement therapy (Annane 2002). Moreover, some studies demonstrated that, regarding of the response to an ACTH stimulation test and/or simply giving low dose hydrocortisone reveals shock more rapidly (Annane 2002; Bollaert 1998; Briegel 1999; Oppert 2005).

In the Corticus study (Sprung 2008) a cortisol increase of less than 248 nmol/l in the ACTH stimulation test was used to define AI. No mortality differences were detected between patients defined as having AI and those who did not, or between patients who received hydrocortisone and those who did not. Hydrocortisone reversed shock more quickly than not receiving hydrocortisone.

The ACTH test is not capable of detecting secondary AI because the adrenal gland response may be normal (Aron 2007; Streeten 1996). The ACTH test does not assess the integrity of the HPA axis and it does not provide any information about the adequate amount of cortisol needed for particular stress. Moreover, timing and reproducibility of the ACTH test has been questioned (Loisa 2005).

In the standard ACTH stimulation test, the supraphysiological amount of ACTH is used. A low dose ACTH stimulation test is possible by administering 1 µg of ACTH. This method has not been better than the standard method in critically ill patients (Arafah 2006).

Beishuizen et al. (2001) found extremely low CBG values at the beginning of septic shock, and the free cortisol index (cortisol/CBGx100) was high at the beginning of septic shock, reflecting high free cortisol concentrations. After several days, the free cortisol index normalised and no impact on mortality was detected.

A study of free serum cortisol found that patients who were hypoalbuminemic had low total serum cortisol, whereas hypoalbuminemia did not affect free serum cortisol concentrations (Hamrahian 2004). The authors concluded that measuring free serum cortisol may be important in critically ill patients and recommended a threshold of 55.2 nmol/l free serum cortisol in patients at risk for AI. However, blood CBG concentrations also vary among healthy individuals (Dhillo 2002). Ho et al. (2006) compared calculated and measured free serum cortisol concentrations with total serum cortisol concentrations in patients with sepsis and septic shock. Measured and calculated free serum cortisol correlated well. Free serum cortisol concentrations better reflected circulating glucocorticoid activity.

In pneumonia, measuring free serum cortisol was not superior to measuring total serum cortisol (Christ-Crain 2007). Annane et al. (2006) used metyrapone testing to detect AI in patients with sepsis compared to healthy volunteers and found that a free serum cortisol concentration of less than 22 nmol/l predicted AI, but measuring free serum cortisol did not have any advantages over measuring total serum cortisol. These studies led to free serum cortisol measurements not being recommended for routine use at this time (Marik 2008). The reason for the recommendation is the fact that the test methods are not routinely available and no normal range values are available for critically ill patients.

In 2008, a consensus statement was developed for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients (Marik 2008). Experts recommend avoiding the description of absolute or relative AI and critical illness-related corticosteroid insufficiency (CIRCI) should be used. Adrenal insufficiency in critical illness should be defined as an increase of <248 nmol/l in an ACTH stimulation test or as a random total cortisol concentration of <275 nmol/l. An ACTH stimulation test should not be used to guide glucocorticoid therapy in septic shock; glucocorticoid therapy should be used in patients who respond poorly to fluids and vasopressor agents.

2.8 Defining pituitary adrenal insufficiency in aneurysmal subarachnoid haemorrhage

Subarachnoid haemorrhage may cause adrenal and/or pituitary insufficiency. Cut-off values for serum ACTH and cortisol concentrations are mostly derived from endocrinological studies performed in healthy patients or from patients with known pituitary deficiency (Schneider 2007). No consensus exists on the reference values for serum cortisol or ACTH concentrations in acute neurosurgical catastrophes like aSAH (Table 2).

A preliminary study of HPA dysfunction in patients with aSAH months after the insult found that, using the ITT, aSAH does not seem to cause any ACTH and/or cortisol insufficiency (Kelly 2000). Another study found that pituitary-adrenal function is preserved in patients with syndromes of fatigue after aSAH (Brandt 2004).

Aimaretti et al. (2004, 2005) studied the incidence of pituitary deficiency 3 and 12 months after discharge from the ICU using multiple endocrine testing. At 3 months, no aSAH patient presented with total hypopituitarism and

only one patient out of 40 had secondary AI. In their follow-up study (3 months to 1 year), none of the aSAH patients with normal pituitary function at 3 months developed pituitary dysfunction at 1 year. However, one of the 32 patients had secondary AI at 3 months and two had secondary AI at 1 year. Regarding all pituitary hormones, patients with some pituitary deficits at 3 months may develop new deficits up to 1 year. Kreitschmann-Andermahr et al. (2003) published a short report of pituitary deficiency 12 to 60 months after aSAH in which aSAH was shown to cause corticotropin deficiency in 29% of patients. In 2004, the same group published a study in which 32.5% of patients with aSAH had isolated corticotroph deficiency indicated by the ITT 1 year after bleeding (Kreitschmann-Andermahr 2004). In another study (Dimopoulou 2004), 10% of patients with aSAH were hyporesponsive in an ACTH stimulation test 12 to 24 months after aSAH. Tanriverdi et al. (2007) studied aSAH patients within 24 hours of admission and after 12 months, finding that 22.7% of patients were ACTH deficient in the acute phase and 13.6% were ACTH deficient after 1 year.

To date, the only study evaluating free serum cortisol in patients with aSAH was performed by Savaridas et al. (2004), but only six patients in the study had acute aSAH. However, the study found that the CBG concentration declined in patients with aSAH and the free fraction of cortisol may better reflect serum cortisol concentrations.

Table 2. A selection of studies investigating aSAH and pituitary-adrenal insufficiency (AI).

Study	No. of patients	Diagnostic test	Diagnostic criteria	% having AI	Time of assessment
Kelly et al. 2000	2	ITT	Out of 95% CI of reference values for healthy controls	0	Not specified
Savaridas et al. 2004	6	None	Total serum cortisol <140-690 nmol/l	Not assessed	Within 5 days of SAH
Brandt et al. 2004	10	ITT	Not given	0%	Within 4-16 months post SAH
Aimaretti et al. 2004	40	Basal hormone screening and urinary cortisol measurement	Morning total serum cortisol <220 nmol/l, free urinary cortisol < 83 nmol/l, and other than cortisol deficit	2.5%	3 months after ICU discharge
Aimaretti et al. 2005	32	Basal hormone screening	Morning total serum cortisol <220 nmol/l	3.1-6.25%	3 and 12 months after SAH
Kreitschmann-Andermahr et al. 2004	40	ITT	Total serum cortisol < 500 nmol/l after ITT	32.5%	12-72 months after SAH
Kreitschmann-Andermahr et al. 2003	21	ITT	Total serum cortisol < 500 nmol/l after ITT	29%	12-60 months after SAH
Dimopoulou I et al. 2004	30	Low dose ACTH test	Total serum cortisol < 500 nmol/l after ACTH test	10%	12-24 months after SAH
Tanriverdi et al. 2007	22	Basal hormone screening, glucagon test	Total serum cortisol <193 nmol/l, glucagon test serum cortisol <302 nmol/l	at 24h 22.7%, at 12 months 13.6%	24 h after SAH and at 12 month follow-up

ACTH=adrenocorticotrophic hormone, aSAH= aneurysmal subarachnoidal hemorrhage, ITT=insulin tolerance test

2.9 Etomidate in critical illness

Etomidate is a short acting anaesthetic agent used to induce anaesthesia in haemodynamically unstable patients because it carries a low risk of hypotension (Gooding 1979; Jabre 2009; Lindeburg 1982; Reich 2005). Etomidate is a water soluble 75% protein bound, imidazole derivative metabolized in the liver and excreted by the kidneys.

In 1983, Ledingham et al. found that patients sedated with etomidate for more than 5 days in the ICU had a higher mortality than patients who received a different sedation protocol (Ledingham 1983). Etomidate was suggested to play a role in the inhibition of cortisol synthesis. After these results, several studies were performed that showed etomidate suppressing cortisol synthesis for several hours, even after a single bolus. Etomidate has a dose-dependent and reversible inhibitory effect on the enzyme 11-β-hydroxylase, which converts 11-deoxycortisol to cortisol and causes a reduction in cortisol synthesis and elevates plasma ACTH (Allolio 1985).

Because of its haemodynamic profile, etomidate has also been popular as an induction agent in rapid sequence intubation of ICU patients. Because AI is common in patients with sepsis and the fact that etomidate may further diminish cortisol production, etomidate may be relatively contraindicated in septic patients (Annane 2005). However, if etomidate is used for patients having sepsis, steroid substitution may be recommended (Jackson 2005).

Malerba et al. (2005) studied the risk factors for AI in critically ill patients who required mechanical ventilation for more than 24 hours and showed that a single bolus of etomidate suppresses adrenal function. In addition, Mohammad et al. (2006) showed that the incidence of relative AI determined by an ACTH stimulation test in a retrospective study of 152 patients with septic shock was higher among patients who received etomidate as a single bolus.

Because AI is common among septic patients retrospective studies have been made to find out whether septic patients had received etomidate or not. In the study of Sprung et al. (2008) the originally effects of hydrocortisone in septic shock were investigated. Patients who received etomidate (~20%) had a higher mortality than patients who did not receive etomidate.

Recently a substudy of the Corticus study was published by Cuthbertson et al. (2009), who showed that a single bolus of etomidate in patients with septic shock may cause increased mortality and an inadequate response to corticotropin.

Moreover, etomidate is a risk factor for AI when used as an induction agent in paediatric meningococcal sepsis (den Brinker et al. 2005).

However, there are studies showing that a single bolus of etomidate does not cause excess mortality in critically ill patients (Ray 2007), and that it may be safe for patients needing intubation in the emergency department (Schenarts 2001). Patients with abdominal septic shock who were anaesthetized using etomidate did not have a higher mortality than patients who were anaesthetized with other anaesthetics (Riche 2007).

Recently, Jabre et al. (2009) compared etomidate and ketamine for emergency intubation in critically ill patients and found that ketamine is safe to use in these patients. Etomidate causes more AI than ketamine, but etomidate does not cause excess morbidity or mortality among trauma or septic patients.

3 Aims of the study

The objective of the present study was to evaluate the pituitary and adrenal response in critically ill patients. The specific objectives were:

1) To study the effects of a single bolus of etomidate on serum cortisol concentrations. To compare the haemodynamic effects, particularly the incidence of hypotension, of propofol and etomidate when used to induce anaesthesia in patients with severe aortic stenosis.

2) To assess the relationship and behaviour between total and calculated free cortisol concentrations in severe sepsis and septic shock. To evaluate the predictive power of calculated free and total serum cortisol in regard to hospital mortality in sepsis and septic shock.

3) To characterise the function of the HPA axis acutely and over time (up to 3 months) in patients with aSAH. To assess if secondary AI is present. To investigate if disease severity and endocrinological changes correlate. To assess the relationship, behaviour, and capability of detecting AI of calculated serum free compared to total cortisol concentrations in aSAH.

4) To characterise the acute behaviour of IGF-I and GH in acute aSAH (up to 3 months) and to relate these findings to morbidity assessed by GOS and HRQoL at 3 months.

4 Patients and methods

4.1 Patients

A total of 237 critically ill patients were enrolled in the study. Sixty-six patients had severe aortic stenosis, 125 patients had severe sepsis or septic shock, 30 patients had acute aSAH, and 16 patients served as controls. Patient demographics are partly presented in Table 3.

Aortic stenosis was defined as severe because of the need for surgical intervention. Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine criteria (Bone 1992). Acute aSAH was defined as evidence of cerebral vascular aneurysm and subarachnoid bleeding within 72 hours of study entry.

Studies I, III, and IV were performed at Kuopio University hospital. Study II was a multicentre substudy of the Finnsepsis (Karlsson 2007) study performed in the majority of Finnish intensive care units.

Table 3. Patient demographics and study inclusion criteria. Data are presented as ± SD when appropriate.

	Study I	**Study II**	**Study III+IV**
Study design	Double-blind randomized	Prospective cohort	Prospective cohort
Number of patients	66	125	46
Inclusion criteria	Elective operative treatment of aortic stenosis	Severe sepsis or septic shock	Acute aneurysmal SAH
Age (years)	65 ± 9	59 ± 15	52 ± 13
SAPS II score	-	41 ± 15	30 ± 13
APACHE II score	-	23 ± 9	15 ± 6
Hospital mortality (%)	0	21%	10%

4.2 Exclusion criteria

Patients under 18 years of age were excluded from all studies. In study I, the exclusion criteria were known adrenocortical insufficiency, chronic corticoid therapy, porphyria, allergy to any of the induction agents, a BMI exceeding 35 kg/m^2, expected intubation difficulty, gastric reflux disease, a serum creatinine level above 160 mmol/l, and other types of valvular heart disease. In study II, the exclusion criterion was corticoid therapy at study entry. In study III, any corticoid treatment (including inhaled), use of etomidate before study entry or during the study period, unknown exact bleeding day, previous history of aSAH, bleeding for more than 3 days before inclusion, traumatic aSAH, known pituitary insufficiency, and/or a moribund state of the patient were exclusion criteria. In the control group, the exclusion criterion was also endovascular treatment of the aneurysm.

4.3 Methods

4.3.1 Study design

All studies were approved by the local ethics committee.

Study I

Study I was a double-blind randomised study comparing the haemodynamic effects of etomidate and propofol in patients scheduled for elective aortic valve replacement due to severe aortic stenosis. We also evaluated the effects of these drugs on cortisol synthesis.

Sixty-six patients (n=33 each group) were enrolled in this study (Fig. 3). All patients over 18 years of age and scheduled for elective aortic valve replacement due to aortic stenosis were assessed for eligibility for the study. The patients provided informed written consent to participate in the study and the hospital ethics committee approved the study protocol. Serum cortisol concentrations were measured in 24 patients who received etomidate and 26 patients who received propofol.

Our hospital pharmacy randomised the patients to receive either propofol (Propofol Lipuro, BBraun, Melsungen, Germany) or etomidate (Etomidate Lipuro, BBraun) in lipid emulsion in identical 20-ml syringes, which were coded. Sealed opaque envelopes were used for randomisation. The clinicians were unaware of which induction agent was being used. When the study was completed and all patients had been recruited, the drug codes were opened. Patients were pre-medicated with 0.2 mg/kg oral diazepam 1 h before entering the operating room and were monitored using an arterial line and a pulmonary artery catheter, both inserted before anaesthesia induction. The bispectral index (BIS; A-1000, Aspect Medical System, Natick, MA) was used to titrate the induction agent, achieving a BIS of 60 or less. Induction agents were given in small boluses. Alfentanil (50 mg/kg) and pancuronium (0.1 mg/kg) were administered when BIS of 60 was achieved. Intubation was performed 3 min after the administration of pancuronium. The mean arterial pressure (MAP) and heart rate (HR) were collected in

a database every 10 s. The median of five consecutive values were used for statistical analysis. The median values were collected at different time points: -1, before induction; 0, at the time of induction; 1, BIS of 60; 2, 2 min after BIS of 60. The cardiac output and pulmonary capillary wedge pressure (PCWP) were measured when patients were awake before the induction of anaesthesia and 2 min after induction.

The mean value of three consecutive measurements was used. An episode of hypotension was the main end-point of the study. If the MAP decreased below 70 mmHg for more than 30 s, a minimum of 0.05 mg phenylephedrine was given. We did not use a protocol for fluid therapy; this was left to the discretion of the attending anaesthesiologist. No inotropic drugs were given during the study, which ended at the time of intubation. Total serum cortisol concentrations were measured before the operation at 08:00 h, immediately after the operation, and the next morning at 08:00h.

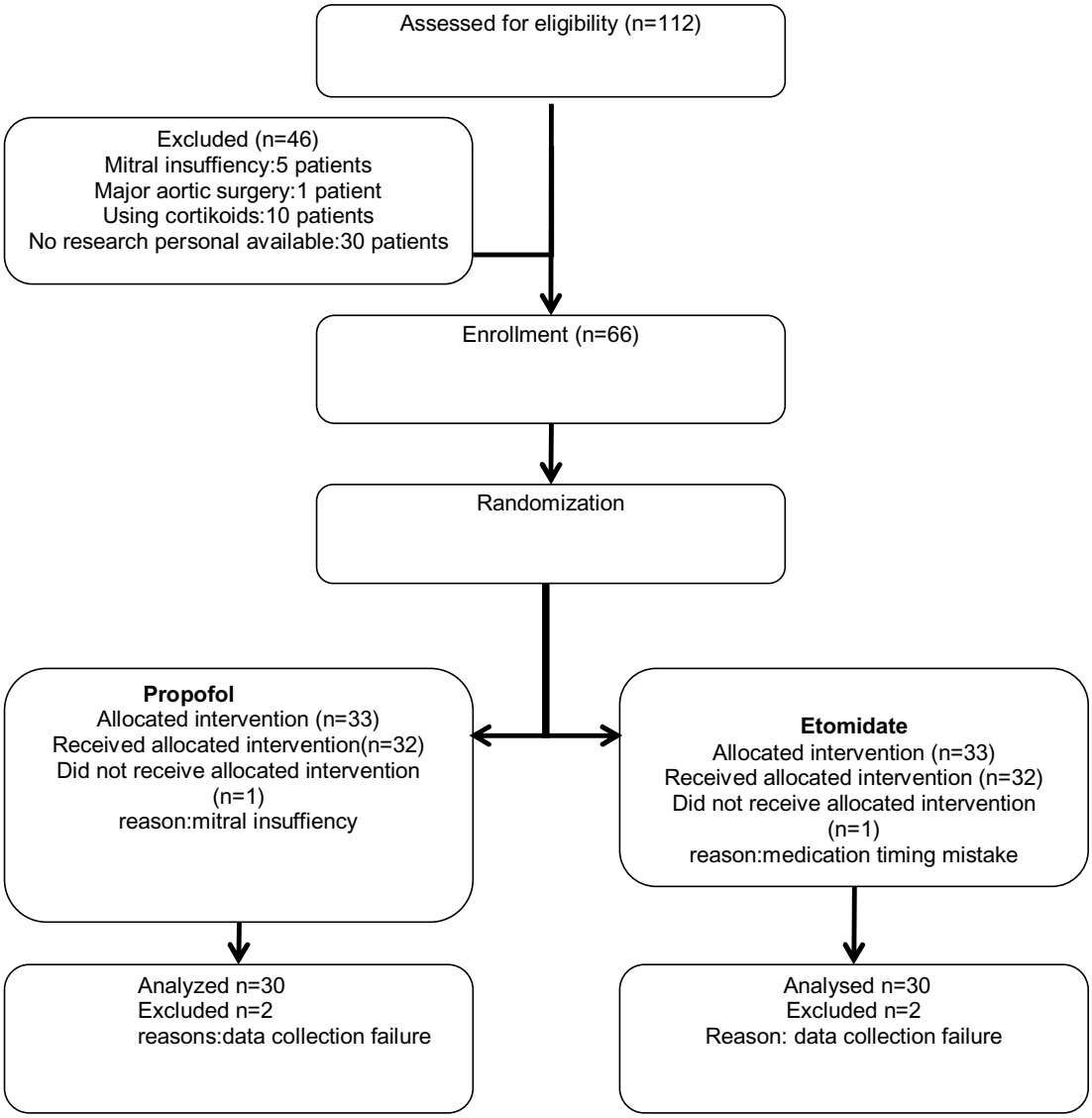


Figure 3. Flow chart for study I.

Study II

Study II was a prospectively defined substudy of Finnsepsis (Karlsson 2007), which was a prospective observational cohort study investigating the incidence, associated organ failures, and outcome of severe sepsis in Finland. In our study, the aim was to assess the relationship between total and calculated free cortisol in severe sepsis and septic shock. In addition, we evaluated the predictive power of calculated free and total serum cortisol with regard to hospital mortality in sepsis and septic shock. A flow-chart of the study is presented in Figure 4. The ethics committee approved the study. Study entry was the time when all criteria for severe sepsis were met. Blood samples were obtained after receiving written informed consent within 24 h of a definitive diagnosis of sepsis or septic shock.

The cut-off values for free cortisol were based on previous studies (Annane 2006; Hamrahian 2004; Moran 1994). A free cortisol concentration of less than 22 nmol/l and total cortisol concentration of less than 275 nmol/l was considered to be absolute AI (Annane 2006). A free cortisol concentration between 22 and 55 nmol/l (Hamrahian 2004; Marik 2003) and total cortisol concentration between 275 and 500 nmol/l (Marik 2003), or alternatively between 275 and 690 nmol/l (Marik 2003), were used to define relative AI.

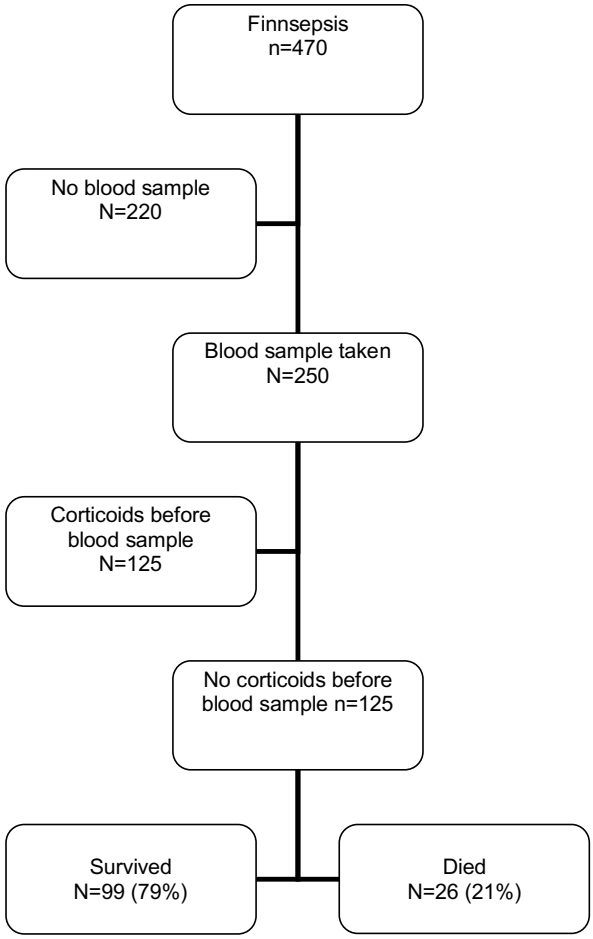


Figure 4. Flow chart for study II.

Study III

Study III was a prospective cohort study aiming to characterise the behaviour of ACTH, total cortisol, stimulated total cortisol, and free cortisol in acute aSAH. The control group consisted of patients over the age of 18 years who were scheduled for elective unruptured aneurysm surgery. All patients aged 18 years or older who were treated for aSAH and admitted to the Kuopio University Hospital in Finland between 29 March and 30 November 2006 were prospectively assessed for eligibility. Only surgical patients were enrolled in the control group because the pre-scheduled hospital stay for patients with embolised aneurysms was too short. The hospital ethics committee approved the study protocol, and informed written consent was obtained from the patients or their next of kin. A flow chart of the study is presented in Figure 5.

The following blood samples were collected from patients with subarachnoid haemorrhage the first to the seventh morning after bleeding: serum (s) cortisol (reference value, 170-540 nmol/l), s-corticoid-binding globulin (s-CBG; male reference value, 22-55 ng/l; female reference value, 40-154 ng/l), and s-albumin (reference value, 36-45 ng/l). Samples for ACTH analysis (reference value, 0-11 pmol/l) were collected on the first and seventh days. An ACTH-stimulating test (250 μg of tetracosactide [Synachten, Ciba-Geigy, France] administered intravenously) was performed on the first morning in the ICU and 7 days after the bleeding. A total cortisol response of less than 248 nmol/l to exogenous 250 μg ACTH (Annane 2000) was used as a marker of relative AI.

On the second and sixth days in the ICU, 24-hour urinary cortisol excretion (reference value, 100-380 nmol) was measured.

Equivalent blood samples were collected from control patients, with the second ACTH sample collected on day 5. The first cortisol samples were drawn and an ACTH test performed the day before surgery and post-operative day 5 before discharge. On day 2, 24-hour urinary cortisol excretion was measured.

At the scheduled three-month follow-up visit, the total serum cortisol concentration was measured and free cortisol concentration calculated at 9 am, followed by an ACTH-stimulation test in both groups.

We used a random total serum cortisol concentration of less than 500 nmol/l to indicate AI (Aron 2007; Marik 2003). For free cortisol, we used a concentration of less than 55 nmol/l as the cut-off for a risk of AI (Hamrahian 2004). We also tried to identify patients with low total (less than 350 nmol/l) and/or free (less than 22 nmol/l) serum cortisol concentrations and a low serum ACTH concentration (less than 5 pmol/l) to search for those at risk of secondary AI (Aron 2007).

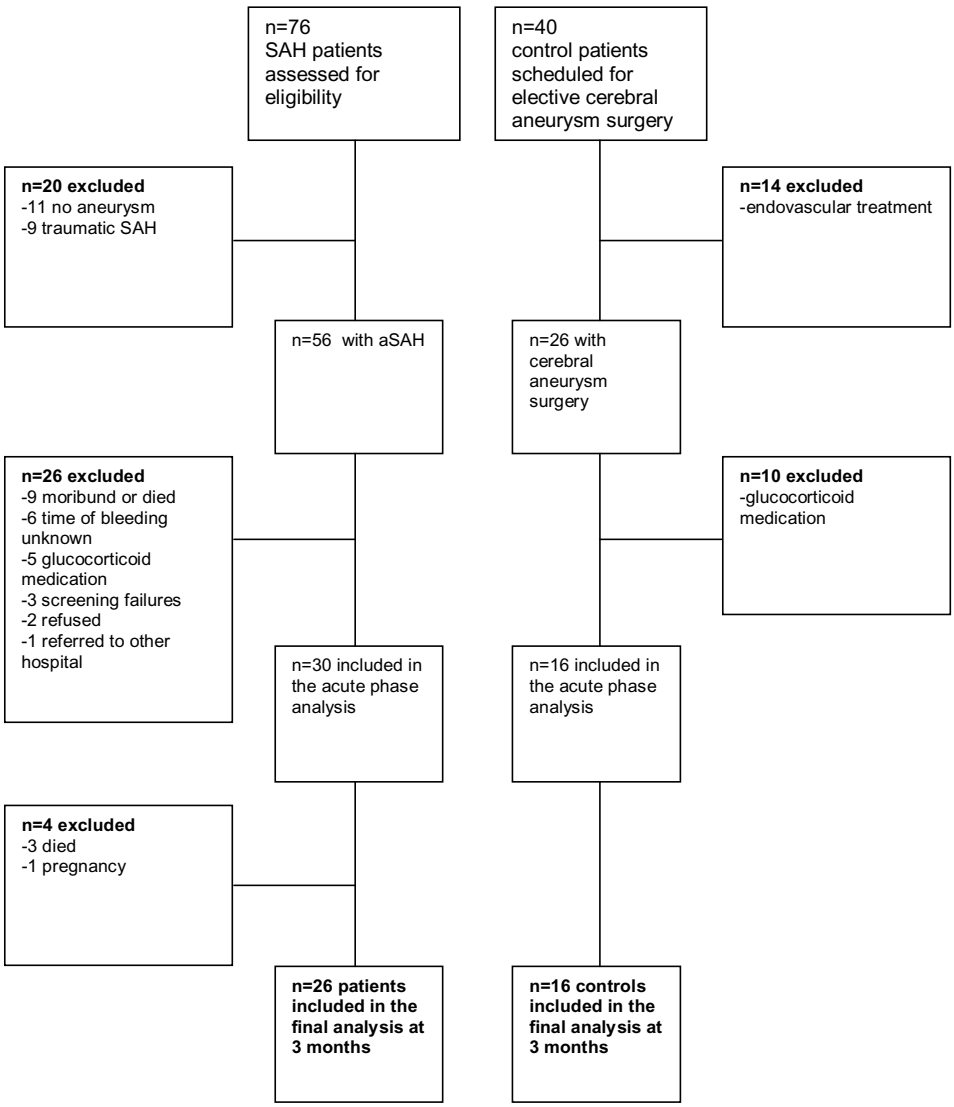


Figure 5. Flow chart of aSAH patients and controls in studies III and IV (Figure 1 in the original article for study III). Seventeen patients with aSAH underwent endovascular treatment and 13 patients underwent open surgery. Study IV

Study IV was a prospective cohort study aiming to characterise the acute behaviour of IGF-I and GH in aSAH and up to 3 months afterwards. We evaluated the relationship between IGF-I, morbidity assessed by GOS and health related quality of life (HRQoL) 3 months after aSAH and hypothesized that low cumulative IGF-I concentrations may negatively influence morbidty. Study IV was a substudy of study III, and the same patients were used for data analysis.

The following blood samples were collected from aSAH patients the first to the seventh morning after bleeding: serum (s) GH (reference value, 0-11.5 mU/l), s-IGF-I (reference values for ages 21-30 years, 15-45 nmol/l; 31-50 years, 14-36 nmol/l; 51-70 years, 10-29 nmol/l; and >70 years, 8-23 nmol/l). In control patients, the corresponding blood samples were collected from the first to the fifth post-operative day after the patients were discharged. Additional routine daily laboratory parameters, such as electrolytes, were recorded.

At the scheduled three-month follow-up visit, s-GH and s-IGF-I samples were collected at 9 am, and a 15-dimension quality of life assessment (Sintonen 2001) was performed. We used age and sex-matched IGF-I-concentration to determine low IGF-I and suspected GH deficiency. We also used IGF-I levels of less than 11 nmol/l as the cut-off for low IGF-I (Hartman 2002).

The health-related quality of life (HRQoL) was measured using the 15D scale (*www.15d-instrument.net)* (Sintonen 2001), a generic and standardised HRQoL instrument consisting of 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental functioning, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each dimension has five grades of severity. For each dimension, the respondent must choose one of the five levels (best level = 1; worst level = 5) that best describes his or her state of health at the moment. The results of the 15D can be presented as a single index or as a profile of all 15 dimensions. A change of ≥0.02–0.03 points in the health utility index or 15D score was considered clinically important. The values on a 0–1 scale reflect the levels relative to no problems in the dimension (1) and to being dead (0). The mean score of the Finnish population aged 50-59 years was previously measured to be 0.92 (0.91-0.92) (Mattila 2009). In this study, HRQoL-indexes were classified into three groups: normal (0.8 - 1.0), limited (0.6 - 0.79), and poor (<0.6).

4.3.2 Laboratory methods

All laboratory analyses were performed in Kuopio University Hospital.

We used our laboratory's 08:00 h reference range of 170–540 nmol/l for the total serum cortisol concentration in all studies.

In study I, enzyme immunoassay (DPC Immulite 2000; Cortisol DPC, Los Angeles, CA) was used to measure total cortisol in the serum. All cortisol samples were analysed immediately following collection.

In studies II and III, blood samples were stored for late analysis at -80°C and -70°C, respectively. In both studies, the same personnel performed all analyses in one laboratory at the Kuopio University Hospital. We used

electrochemiluminescence immunoassay (Elecsys Cortisol, Roche Diagnostics, Mannheim, Germany) as the diagnostic method.

The Coolens equation was used to calculate the concentration of free cortisol in serum (Coolens 1987): $U2K\,(1 + N) + U\,[1 + N + K\,(G - T)] - T = 0$, where $K = 3 \times 10^{-7}$ M^{-1}(affinity of CBG to cortisol at 37°C), G = CBG, U = unbound cortisol, T = cortisol, and N = ratio of albumin bound to free cortisol (1.74). U was calculated as follows:

$$U = \sqrt{Z^2 + \frac{T}{(1+N)K}} - Z \text{, where } Z = \frac{1}{2K} + \frac{G-T}{2(1+N)}$$

Serum CBG concentrations were analysed by radioimmunoassay (BioSource Europe S.A., Nivelles, Belgium). After dichloromethane extraction, free urinary cortisol concentrations were analysed using the same method employed for measuring total serum cortisol. Plasma ACTH concentrations were analysed using an immunoluminometric assay (IMMULITE; Diagnostic Products Corporation, Los Angeles, CA).

In study II, an ACTH stimulation test was performed. Tetracosactide (0.25 mg; Synachten, Ciba-Geigy, France) was administered intravenously and serum cortisol concentrations analysed 30 and 60 minutes later.

Serum GH concentrations were analysed using specific time-resolved fluoroimmunoassay (TR-FIA) by AutoDelfia (PerkinElmer Life and Analytical Sciences Wallac Oy, Turku, Finland). Serum IGF-I concentrations were analysed using a quantitative sandwich enzyme immunoassay (ELISA) technique (Quantikine Human IGF-1 Immunoassay; R&D Systems, Minneapolis, MN, USA).

4.3.3 Statistical methods

Studies I and III were based on sample size calculations. In both studies, a power of 80% and a two-sided α-level of 0.05 were used. In study I, propofol was assumed to decrease blood pressure in 50% of patients, and etomidate was assumed to do so in 10% of patients. A decrease in blood pressure was arbitrarily defined as MAP<70 mmHg for more than 30 s. In study III, we assumed that 25% of patients with aSAH and none of the elective surgical patients would develop AI.

Generally, data are presented as mean ± standard deviation (SD), as absolute values and percentages, or as medians and interquartile ranges. Parameter distribution was assessed using the Kolmogorov-Smirnov test. For normally distributed parameters, the student's *t*-test was used to compare the means of different groups. The Mann-Whitney U test was used for nonparametric testing between groups. In study I, analysis of variance (ANOVA) was used for repeated measurements between groups.

In studies III and IV, a mixed models method was used for testing between the groups, allowing for heterogeneity between the groups. The Bonferroni correction was used to adjust for multiple testing. In all studies, Spearman and/or Pearson correlations were used depending of the distribution of the data.

In study II, predictive power regarding hospital mortality was assessed by areas under the receiver operating curves (AUC). Outcomes were presented according to the Kaplan–Meier method, and groups were compared using the log-rank method.

All statistical analyses were performed using SPSS software (SPSS, Chicago, Ill, USA).

To identify the factors associated with poor HRQoL or death, we constructed a Bayesian prediction model in aSAH patients using P-course. P-course is a web-based Bayesian classifier that is able to use multidimensional priors; for example, separate priors for the outcome variable in general and for the outcome variable according to each predicting variable. The methods have equalled or outperformed novel logistic regression, especially in small data sets in terms of prediction accuracy (Lau 2002; Ng 2002), variable selection, and multiple performance measures. The methods perform well with incomplete or complex data typical to small data sets. This data modelling was achieved without informative *a priori* information.

The outcome variable was poor HRQoL measured by 15D and dichotomized into normal (0.80 - 1.00) or poor (0 - 0.79), where the value 0 indicates death. In the first phase, there was a set of 355 potential predicting variables. By using the P-course classifier, this number was reduced to 22 variables from 30 aSAH patients. To avoid over-fitting the model, we formed four sets of 25 randomly selected patients, and a prediction model was made for each set. We obtained four slightly different sets of prediction variables.

5 Results

5.1 Effect of etomidate on the cortisol response in patients with aortic stenosis

Table 4. Anaesthetic and haemodynamic data of the patients from study I.

	Etomidate group	**Propofol group**	**p-value**
Anaesthetic dose in mg (range)	13 (4-20)	77 (40-400)	-
Aortic stenosis gradient (mmHg)	75 ± 14	75 ± 18	NS
Phenylephedrine dose (mg)	0.14 ± 0.08	0.14 ± 0.08	NS
Patients needing phenylephedrine before intubation	8	20	0.002

NS = not significant

The effect of a single bolus of etomidate on cortisol concentrations and haemodynamic parameters was studied in study I. Anaesthetic data are presented in Table 4. Etomidate caused a transient depression of the serum cortisol concentration in patients with severe aortic stenosis (Fig. 6), and it blocked the acute cortisol response to acute stress caused by open heart surgery. Etomidate caused less hypotension than propofol in patients with severe aortic stenosis (Fig. 7).

Pre-operative serum cortisol concentrations were comparable in both groups (Fig. 6). Cortisol concentrations immediately after the operation were lower in the patients who received etomidate, but no difference was observed the next morning. The difference in cortisol concentrations between the two measurement points was 404±27 nmol/l in the propofol group and -34±162 nmol/l in the etomidate group ($p<0.001$).

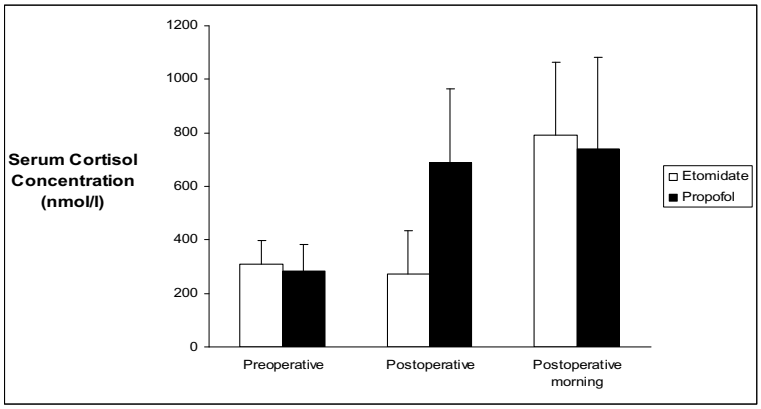


Figure 6. Serum cortisol concentrations before, immediately after, and the morning after surgery. Baseline cortisol concentrations were not different between groups. Immediately after the operation, the cortisol concentration was lower in the patients who received etomidate ($p<0.001$). Serum cortisol levels are presented as mean ± SD.

Aortic occlusion times were similar in both groups (propofol 116±35 min vs. etomidate 112±38 min, $p=0.68$). There was no difference in the perfusion time between the groups (propofol 140±39 min vs. etomidate 137±45 min, $p=0.78$). There were no differences between the patients who received propofol or etomidate in regards to length of ICU stay, number of re-operations, incidence of infection after operation, re-admission rate to ICU, length of hospital stay, hospital mortality, or postoperative serum creatinine MBm-fraction concentration.

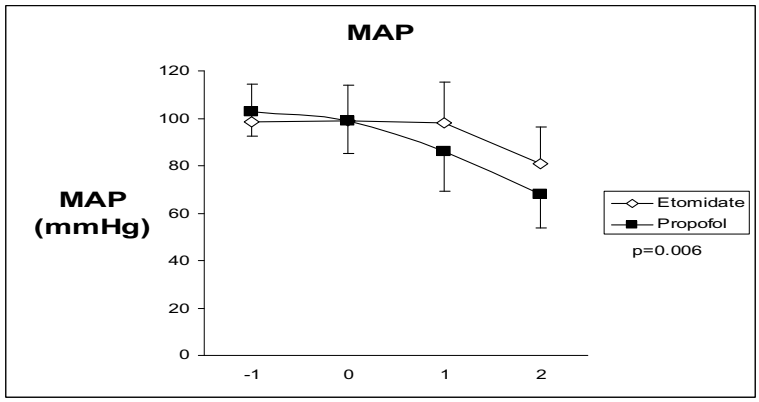


Figure 7. Time course of MAP. The MAP decreased in both groups ($p=0.001$). Propofol decreased the MAP more than etomidate ($p=0.006$). Data are presented as mean ± SD. Time points refer to the following time course:-1, before induction; 0, the time of induction; 1, BIS ≤ 60; 2, minutes after BIS≤60.

The correlation between the administered etomidate dose and serum cortisol concentration is presented in Figure 8.

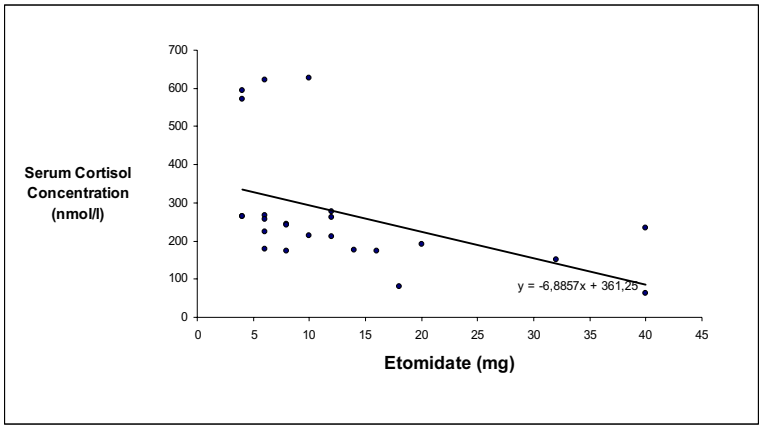


Figure 8. An inverse correlation between the administered etomidate dose and immediate postoperative serum cortisol concentration. Correlation coefficient = -0.453, p<0.026. Two cortisol concentrations at 4 mg etomidate (264 nmol/l and 265 nmol/l) and 8 mg etomidate (242 nmol/l and 244 nmol/l) overlap.

5.2 Free and total cortisol in severe sepsis and septic shock

The relationship and association between outcome and free and total serum cortisol concentrations in severe sepsis and septic shock was evaluated in study II. The causes of sepsis were pneumonia (n=53), intra-abdominal infection (n=35), cellulitis (n=14), urinary tract infection (n=7), central nervous system infection (n=5), endocarditis (n=5), head/neck infection (n=2), and unknown (n=8). The hospital mortality was 21%. Detailed mortality data are presented in Table 5**.**

No difference in mortality was detected between patients who received corticoids (n=35) and those who did not receive corticoids (n=90; p=0.18) after blood samples were drawn. There was also no difference in mortality between patients who received corticoids for sepsis and those who did not.

Patients who received hydrocortisone had higher baseline total serum cortisol concentrations than patients who did not receive hydrocortisone (1030±460 nmol/l vs. 707±385 nmol/l, p=0.002), higher calculated free cortisol concentrations (234 ±145 nmol/l vs. 118±112 nmol/l, p=0.001), and higher free/total serum concentrations (21±7% vs.14±7%, p<0.001).

Absolute AI, in terms of calculated free serum cortisol <22 nmol/l, was detected in 12 patients, and all of them survived. Altogether, 25 patients (20%) had relative AI, in terms of calculated free serum cortisol <55 nmol/l, and three of the patients died in the hospital. Four patients with relative AI, in terms of calculated free cortisol concentrations <55 nmol/l, received corticoids, three of whom died. The remaining 88 patients had free cortisol concentrations > 55 nmol/l; their hospital mortality was 26%.

Absolute AI, in terms of total serum cortisol <275 nmol/l, was detected in 10 patients, and all survived. Relative AI, in terms of total serum cortisol concentration <500 nmol/l, was detected in 27 patients, three of whom died. Relative AI, in terms of total serum cortisol concentration <690 nmol/l, was detected in 58 patients, nine of whom died (13%; p=0.023)

Table 5. Total and free serum cortisol concentrations and mortality in severe sepsis and septic shock.

	All patients n=125			Survivors n=99			Nonsurvivors n=26		
	Severe sepsis n=62	Septic shock n=63	p	Severe sepsis n=49	Septic shock n=50	p	Severe sepsis n=13	Septic shock n=13	p
APACHE II score	21±9	24±9	0.12	20±8	23±9	0.11	27±8	29±9	0.67
SAPS II score	38±14	45±16	0.01	36±14	42±15	0.05	45±14	58±15	0.04
SOFA on day 1	6±3	9±3	<0.001	6±3	8±3	<0.001	8±3	10±3	0.08
SOFA max	9±4	11±4	0.003	8±3	11±3	0.002	12±3	14±5	0.3
ICU mortality, N (%)	5 (8%)	9 (14%)	0.27	--	--	--	5 (8%)	9 (14%)	0.27
Hospital mortality, N (%)	13 (21%)	13 (21%)	0.96	--	--	--	13 (21%)	13 (21%)	0.96
Total cortisol (nmol/l)	728±386	793±439	0.38	677±355	729±411	0.5	920±452	1040±474	0.5
Free cortisol (nmol/l)	116±115	158±132	0.06	98±93	140±123	0.05	187±159	231±146	0.4
Free/total	13±7	17±7	0.002	12±7	16±7	0.002	18±7	21±13	0.27
CBG (µg/ml)	34±12	27±10	<0.001	36±13	27±10	<0.001	29±9	26±13	0.04

Nonsurvivors had higher free, total, and free/total serum cortisol concentrations than survivors. The cortisol concentrations in survivors and non-survivors are presented in Table 6, and the concentration in patients who received or did not receive hydrocortisone treatment in Table 7.

Table 6. Cortisol concentrations in survivors and nonsurvivors.

	Survivors (n=99)	**Nonsurvivors (n=26)**	**p-value**
APACHE II score	21±9	28±8	0.001
SAPS II score	39±14	52±16	<0.001
SOFA on day 1	7±3	9±3	0.009
Serum total cortisol (nmol/l)	704±383	980±458	0.002
Free cortisol (nmol/l)	119±111	209±151	0.002
Free/total	14±7	19±7	0.003
CBG (μg/ml)	31±12	27±11	0.1

Table 7. Demographic data for patients who received glucocorticoid treatment after blood samples were taken and patients who did not receive glucocorticoid treatment.

	No glucocorticoid treatment (N=90)	**Glucocorticoid treatment (N=35)**	**p-value**
Age (years)	59±16	59±14	0.99
No. of males	65 (72%)	25 (71%)	0.93
APACHE II score	21±10	25±8	0.07
SAPS II score	40±15	45±16	0.10
SOFA on day 1	7±3	8±3	0.11
ICU mortality, N (%)	8 (9%)	6 (7%)	0.19
Hospital mortality, N (%)	16 (18%)	10 (28%)	0.18

The AUCs for calculated free and total serum cortisol concentrations are presented in Figure 9. We found no superiority of free or total serum cortisol concentration or the free-total cortisol ratio in assessing mortality.

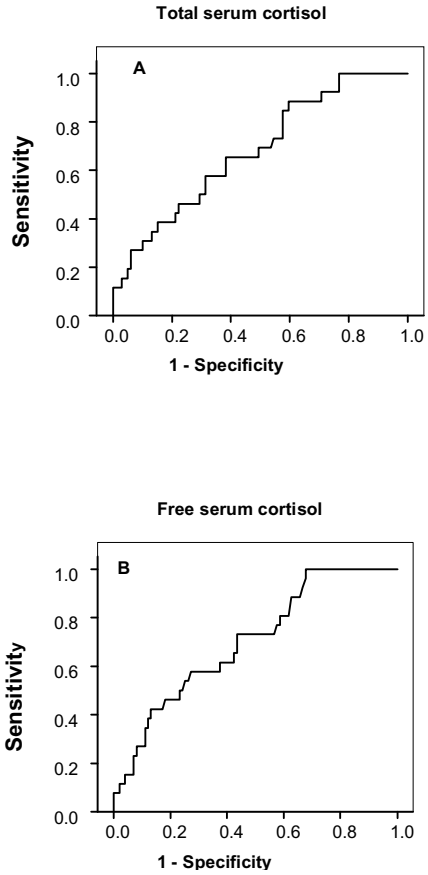


Figure 9. Receiver operating characteristic curves regarding hospital mortality for total (A) and free (B) serum cortisol. The area under the curve (AUC) for total serum cortisol was 0.68 (CI 0.57-0.80), and for free cortisol was 0.70 (95% CI 0.60-0.81).

In general, there was a good correlation between calculated free and total cortisol (Spearman correlation coefficient 0.90, p<0.001; Fig. 10).

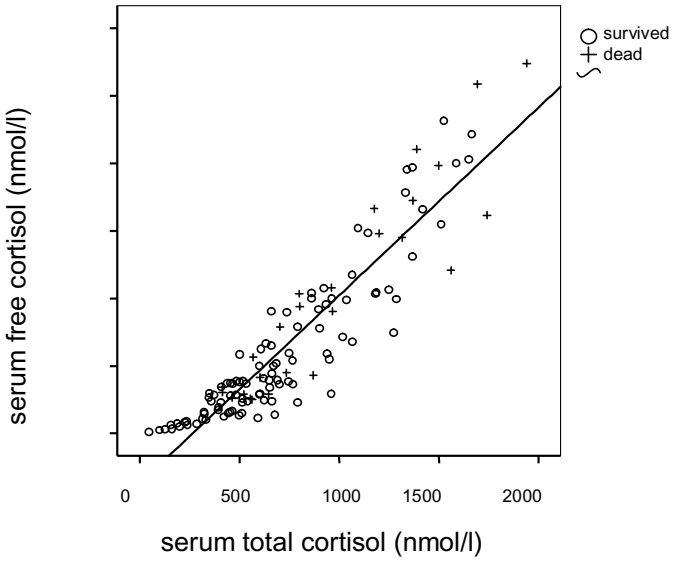


Figure 10. Baseline total and free serum cortisol concentrations. Spearman correlation coefficient 0.90, p<0.001.

No difference in mortality was detected when comparing free and total serum cortisol concentrations using cut-off values of 500 nmol/l for total serum cortisol or 55 nmol/l for free serum cortisol (Fig. 11).

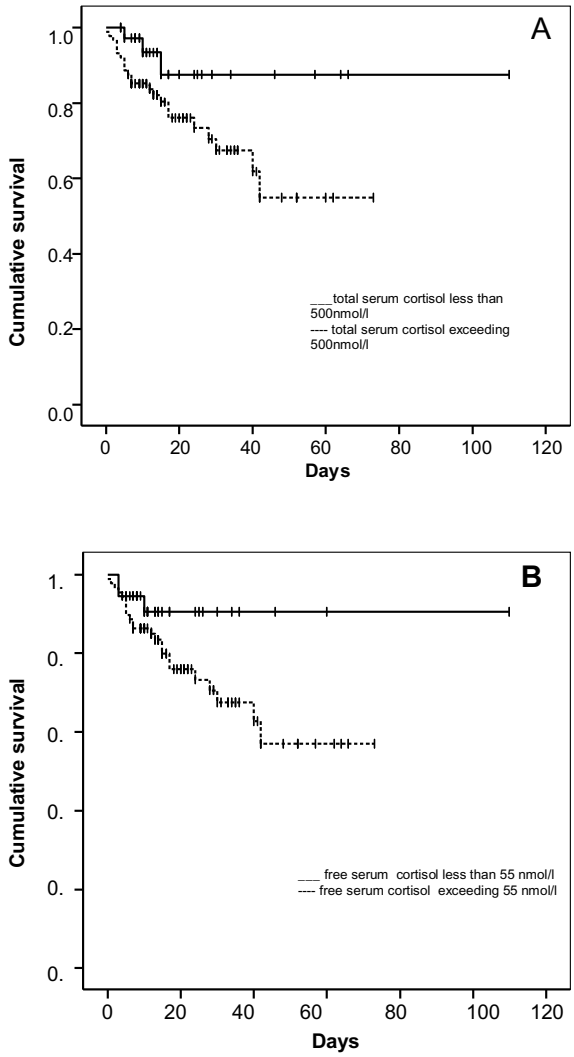


Figure 11. Kaplan-Meier curves for (A) total serum cortisol greater than or less than 500 nmol/l ($p=0.054$) and (B) free serum cortisol greater than or less than 55 nmol/l ($p>0.1$).

5.3 Pituitary-adrenal function in acute aneurysmal subarachnoid haemorrhage

Study III investigated the ACTH-cortisol response in acute aSAH. Thirty patients with aSAH and 16 control patients assessed for elective cerebral aneurysm surgery were enrolled in the study (Table 8).

Table 8. Demographic data of the patients in study III. Data are presented as numbers or mean ± SD unless otherwise indicated. ICA=internal carotid artery, MCA=median cerebral artery, AcoA=anterior communicating artery, ACA=anterior cerebral artery, VBA=vertebrobasilar artery, ICU=intensive care unit, HDU=high dependency unit, LOS=length of stay, SAPS=Simplified Acute Physiology Score, Apache=Acute Physiology and Chronic Health Evaluation

	aSAH Clipped (n=13)	**aSAH** Coiled (n=17)	p-value for clipped vs. coiled	**Control** (n=16)	p-value for aSAH vs. controls
Age, years (range)	50 (25-73)	54 (21-78)	0.53	50 (37–64)	0.53
Gender M/F	5/8	9/8	0.41	4/12	0.15
Aneurysm location					
ICA	2	4		6	
MCA	8	0		10	
ACoA	1	10		0	
ACA distal	1	1		0	
VBA	1	2		0	
Hydrocephalus on admission	2	4		0	
Fisher grade					
I–II	2	2			
III–IV	11	15			
Hunt & Hess initial					
I–II	5	10			
III	3	3			
IV–V	5	4			
SAPS II	27 ± 12	33 ± 14	0.27		
APACHE II	14 ± 5	16 ± 6	0.53		

Daily free and total serum cortisol concentrations were measured up to day 5 for control patients and day 7 for aSAH patients. The aSAH patients had higher cortisol concentrations than control patients only at day 1 (Fig. 12).

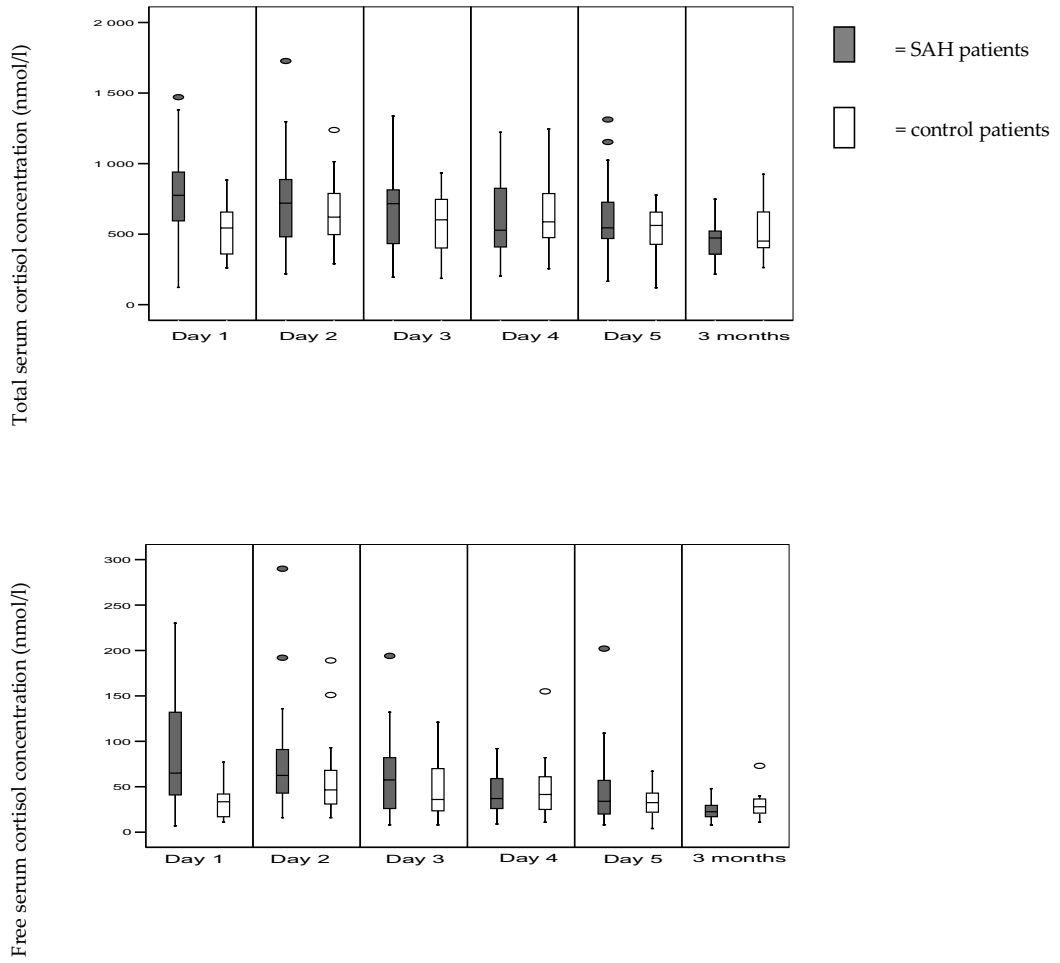


Figure 12. Free and total serum cortisol concentrations. Patients with aSAH had higher initial (A) total serum cortisol ($p = 0.001$) and (B) free serum cortisol concentrations ($p < 0.001$) than control patients. At later time points, there were no differences between the groups. Data are presented as median, interquartile ranges, and outliers.

Free and total serum cortisol concentrations correlated well (Fig. 13).

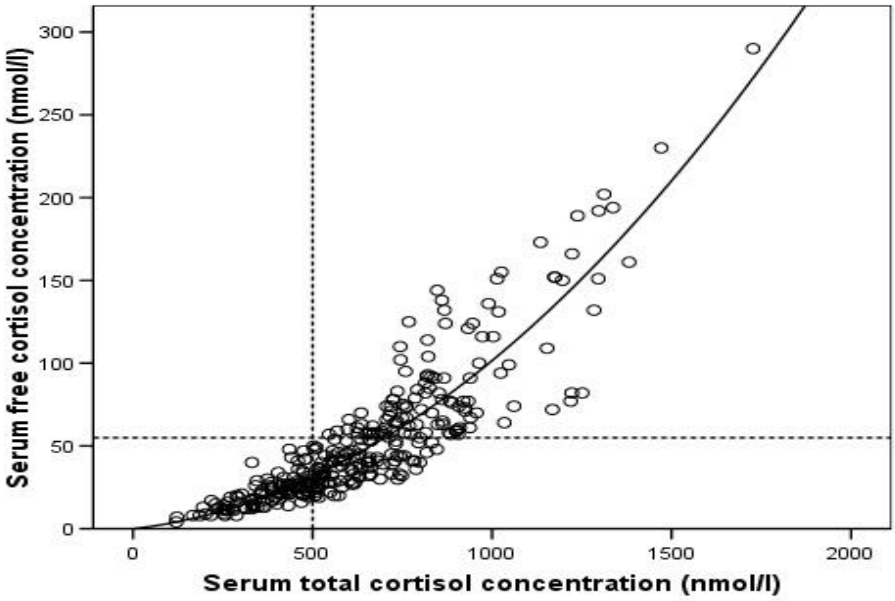


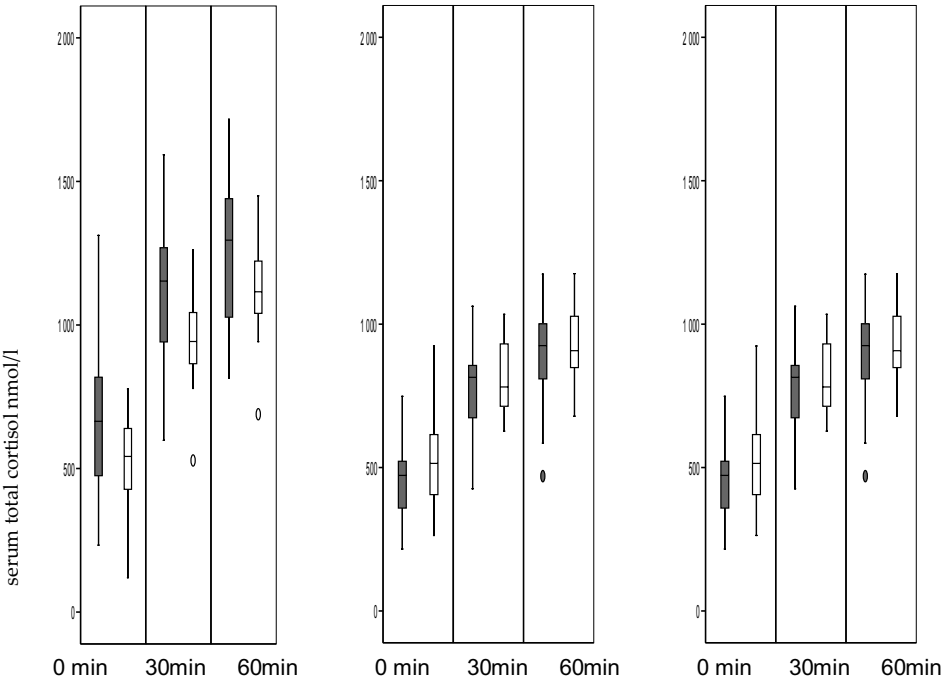
Figure 13. Pooled data and quadratic regression analysis was used to produce this figure. The equation from quadratic regression analysis for free serum cortisol concentration was 0.024 × total serum cortisol concentration + 0.0000772 × total cortisol concentration^2. The Pearson correlation coefficient was 0.88, $p<0.001$. The dependence of free cortisol on total cortisol shows the expected hyperbolic increase of free cortisol with total cortisol until CBG is saturated, when the relation becomes linear.

The GCS status, Hunt & Hess grade, Fisher grade, norepinephrine treatment, hydrocephalus, hypoalbuminemia, and hyponatremia did not affect the free or total serum cortisol concentration. The ACTH concentrations were similar in patients with aSAH and in the control group. In this study, two patients were susceptible to secondary AI due to low ACTH and free and/or total serum cortisol on the first and seventh day. Additionally, two patients had isolated low free serum cortisol and normal total cortisol but low ACTH.

Location (anterior communicating artery vs. other artery) did not affect serum ACTH or free or total serum cortisol concentrations. Patients with a Hunt & Hess grade of IV–V had higher ACTH concentrations at days 1 (10.7 ± 7.1 pmol/l) and 5 (8.2 ± 7.7 pmol/l) compared to patients with Hunt & Hess grade I–III (day 1, 3.8 ± 2.0 pmol/l, $p = 0.002$; day 5, 4.7 ± 1.8 pmol/l, $p = 0.04$). The GCS (<8 or >8), Fisher grade (I–II vs. III–IV), and presence of hydrocephalus did not affect ACTH concentrations.

The 24-hour free urinary cortisol concentration was 4896 ± 5342 nmol/l in patients with aSAH and 1641 ± 1601 nmol/l in the control group on day 2 (p = 0.001). On day 6, the 24-hour free urinary cortisol concentration was 3276 ± 3710 nmol/l in patients with aSAH.

The response to exogenous ACTH is shown in Figure 14.



= aSAH patients

= control patients

Figure 14. Response to exogenous ACTH in aSAH and control patients. No significant differences were found between the groups. The percentage of patients with a serum cortisol response of less than 248 nmol/l was also not different between the groups. On day 1, 8 (33%) patients with aSAH and 8 (50%) control patients had a cortisol response of less than 248 nmol/l (p =0.11). At day 5 and 3 months, one patient with aSAH and no control patients had a cortisol response of less than 248 nmol/l (not significant). The patient with a failed Synachten test at 3 months also failed the first and second test. Test 1=day 1; test 2=day 5 (control) or day 7 (aSAH); test 3 = 3 months. Data are presented as median, interquartile ranges, and outliers.

On day 1, a higher proportion of patients with aSAH had free and total serum cortisol concentrations of less than 55 nmol/l or 500 nmol/l, respectively (Fig. 15).

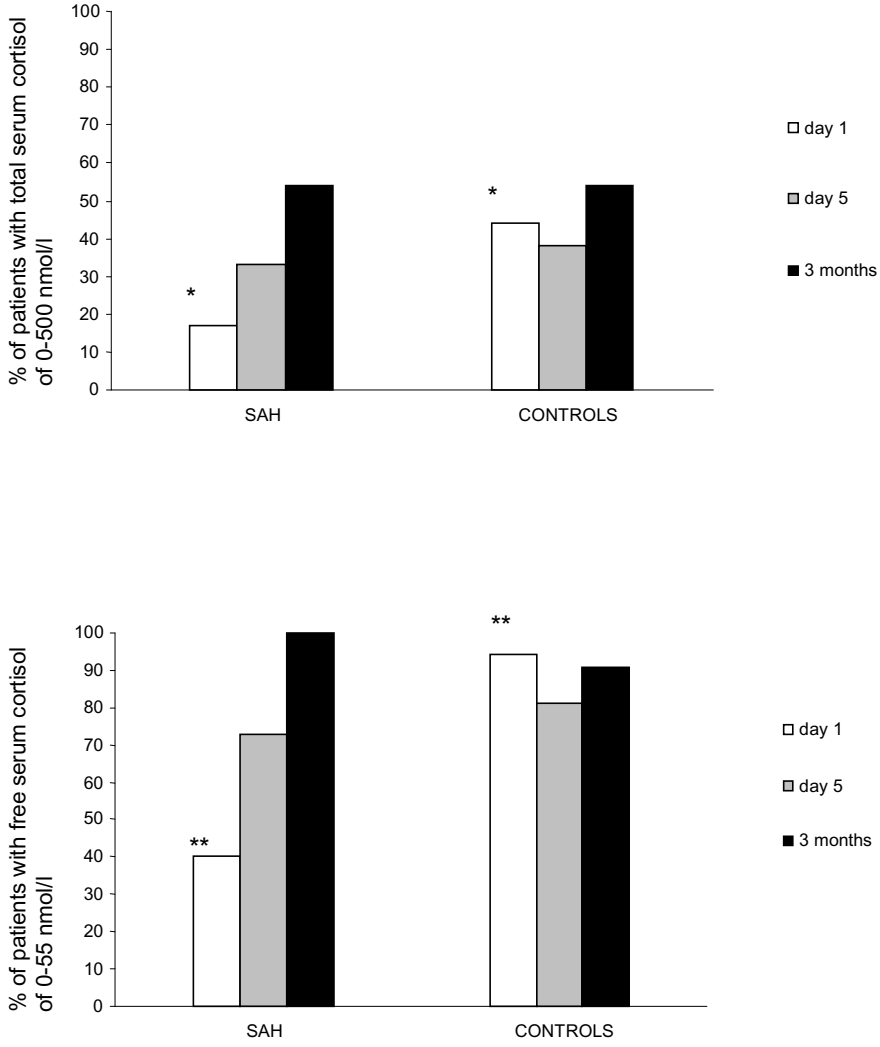


Figure 15. Percentage of patients with a baseline free serum cortisol concentration < 55 nmol/l or total serum cortisol concentration <500 nmol/l. *p=0.046 for difference between the groups on day 1. **p<0.001 for difference between the groups on day 1.

5.4 Effect of aneurysmal subarachnoid haemorrhage on the GH-IGF-I response

The patient population from study III was used in study IV. Serum GH and IGF-I concentrations are presented in Table 9 and in Figure 16. IGF-I levels were significantly lower in patients with aSAH compared to control patients on days 1-5 (p=0.01), but no difference was found at 3 months. Serum GH concentrations were similar in aSAH and control patients.

Table 9. Serum GH and IGF-I concentrations. Data are presented as mean ± SD.

	GH			**IGF-I**		
	aSAH	Control	p	aSAH	Control	p
Day 1	3.4 ± 5.5	1.6± 2.7	0.18	8.2 ± 3.1	10.5 ± 2.7	0.04
Day 2	3.5 ± 5.5	4.5 ± 5.3	0.48	8.4 ± 3.6	11.9 ± 3.1	<0.01
Day 3	3.0 ± 5.3	1.8 ± 1.6	0.37	8.1 ± 4.2	11.4 ± 4.2	<0.01
Day 4	2.4 ± 4	3.5 ± 4.5	0.54	7.8 ± 3.9	10.9 ± 3.8	0.01
Day 5	2.0 ± 2.1	2.4 ± 3.7	0.72	8.0 ± 4.4	11.1 ± 4.1	<0.01
Day 6	2.1 ± 2.4			7.8 ± 4.0		
Day 7	1.6 ± 2.4			7.7 ± 4.0		
3 months	2.0 ± 5.1	3.7 ± 5.0	0.23	9.7 ±3.1	10.4 ± 2.4	0.9

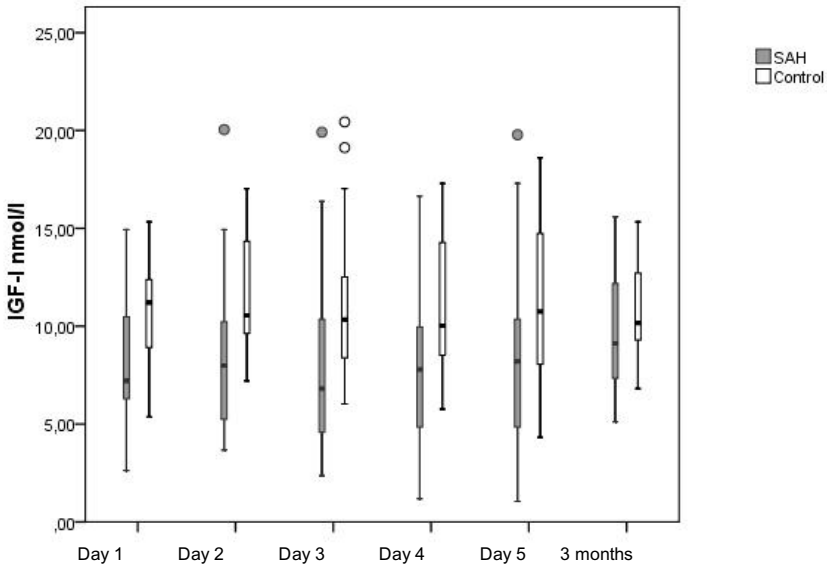


Figure 16. Serum IGF-I concentrations in aSAH and control patient. p=0.01 for the difference between groups on days 1-5 and p=0.9 for the difference at 3 months.

The mean IGF-I concentration in aSAH patients for days 1-5 was 8.1 ± 3.5 nmol/l and 11.2 ± 3.1 nmol/l in the control group. Ten patients in the aSAH group had a GOS of 4 or less, and the others had a GOS of 5. Patients with a GOS ≤4 had a lower quality of life than patients with a GOS=5 (0.7 vs.0.88, p=0.003).

Figure 17 represents the distribution of IGF-I in respect to different cut-off levels. No statistically significant differences were found in the proportion of having lower than age related IGF-I reference values between patients with aSAH or controls.

Hunt and Hess grade, Fisher grade, and the presence of hydrocephalus or vasospasm were not associated with the level of IGF-I concentration, either < 11 nmol/l or > 11 nmol/l.

In patients with aSAH, there were no differences in IGF-I or GH concentrations between the patients in respect to aneurysm location (anterior communicating artery versus others), treatment modality (clip vs. coil), Hunt-Hess grades (I-III versus IV-V), Fisher grade (I-II versus III-IV), GCS (< 8 or >), symptomatic vasospasm and/or need for

norepinephrine (n=9), or hydrocephalus on admission. Gender or BMI did not affect IGF-I or GH concentrations. Age was negatively correlated with IGF-I (r=-0.31, p=<0.001).

The mean 15D HRQoL sum in patients with aSAH was 0.81 ± 0.16 and in control patients 0.86 ± 0.09 (p=0.24). Quality of life was moderately low (<0.8) in 6 patients with aSAH and in 5 control patients (p=0.75). In addition, 3 patients with aSAH and none of the control patients had poor quality of life (<0.6). The HRQoL dimensions of speech (p=0.04) and eating (p=0.03) were lower in patients with aSAH than in the control group; otherwise, no statistically significant differences were observed in the scores between the groups. Ten patients in the aSAH group had 4 or less on the Glasgow outcome scale (GOS), and the others had GOS 5. Patients with GOS ≤ 4 had lower quality of life than patients with GOS 5 (0.7 vs.0.88, p=0.003). Additionally, patients with GOS ≤ 4 had lower mean IGF-I concentrations than patients with GOS 5 (8.3 ± 2.6 nmol/l vs. 12.7 ± 5.1 nmol/l, p=0.02). Patients with Hunt & Hess grades IV-V had similar HRQoL than patients with Hunt & Hess grades I-III (0.73 ± 0.2 vs. 0.84 ± 0.13, p=0.12). aSAH patients with low HRQoL (<0.8) had lower mean IGF-I concentrations than patients with good HRQoL (5.7 ± 2.1 nmol/l vs. 8.7 ± 3.4 nmol/l). Mean IGF-I for days 1-7 was mildly associated with HRQoL by a Pearson's correlation coefficient 0.36, p=0.08).

In the Bayesian model, use of statins prior to aSAH, hyponatremia, SOFAmax, and the sum of IGF results for days 1-7 after the aSAH were associated with poor HRQoL. This model was accurate in 78.6% of cases in leave-one-out cross validation (corresponding log-score 0.57, compared to 53.6% accuracy for the biggest class (i.e., default or educated guess), log-score 0.69,). When the model was tested by putting the total material into the model, an accuracy of 89% was reached. The sensitivity was 0.86 and specificity 0.93. The results indicate that a low IGF level in the days following aSAH may be associated with poor HRQoL or death.

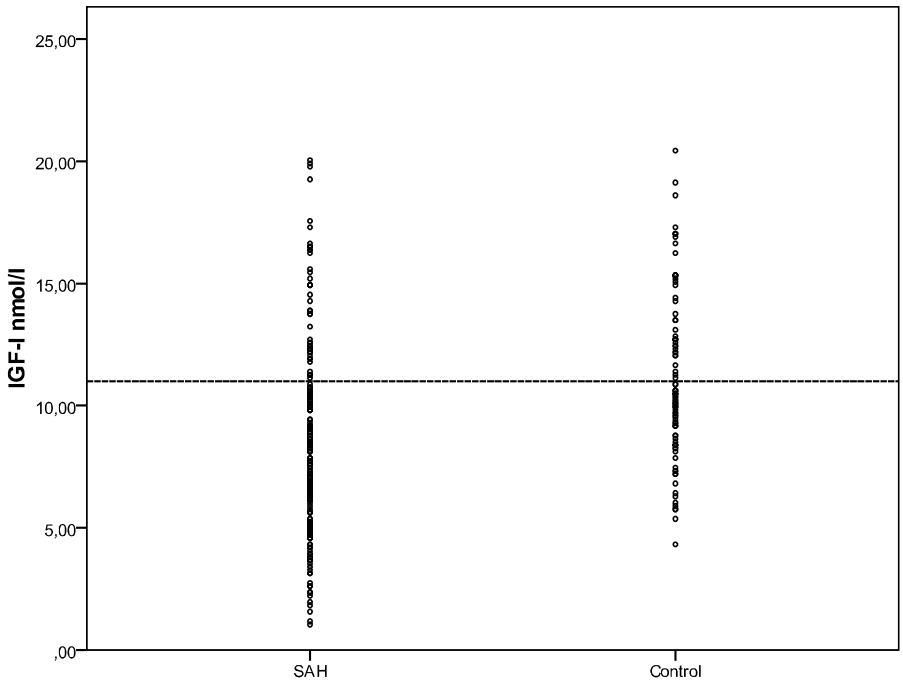


Figure 17. IGF-I concentrations in aSAH and control patients. The line represents the cut-off level of 11 nmol/l.

6 Discussion

We found that a single dose of etomidate suppresses cortisol synthesis for less than 24 hours in patients admitted for elective cardiac surgery due to severe aortic stenosis. Etomidate was haemodynamically more stable than propofol. In addition, measuring free serum cortisol in patients with severe sepsis, septic shock, or aSAH did not show any advantages over total serum cortisol. We also showed that aSAH may cause secondary AI, and IGF-I concentrations are low in patients with acute aSAH, which may have impact on outcome.

6.1 Critical illness-related corticosteroid insufficiency

Generally, one of the major stress responses is the activation of the HPA axis by increasing cortisol production (Aron 2007). Corticoids regulate inflammation, impair the vasomotor tone of the vasculature, affect the distribution of body fluids, and sensitize the catecholamine receptors (Rhen 2005). Early studies in critically ill patients showed that high dose corticoid treatment increases morbidity and mortality. In studies published before 1989, mortality seemed to increase, whereas mortality seemed to decrease in studies published after 1997 (Minneci 2009). The main difference among these studies was the steroid dose used and tapering the steroid treatment. Since the study by Annane in 2000 (Annane 2000) that showed increased morbidity and mortality in patients with AI, several studies attempted to determine the relevancy of possible AI in septic patients. Septic patients are generally thought to need corticoid replacement therapy, but much is to be discussed regarding why, for whom, and on what basis this supplementary anti-inflammatory drug should be administered. Because most of the critically ill patients are faced with enormous stress, other patient categories have been evaluated for an inadequate cortisol response, including patients with aSAH, TBI, coronary artery disease (Henzen, 2003), liver failure (Marik 2005), and acute pancreatitis (Peng 2009).

CIRCI is defined as an inadequate response to corticosteroids in regards to meeting the needs of a patient. Following this definition, the earlier concept of AI should be avoided. However, most of the studies done on this subject have been done in patients with sepsis; thus, the CIRCI definition may not be adequate for patients with, for example, aSAH. As shown in our study, secondary AI may predominate in aSAH. The adequacy of the cortisol response in relation to disease severity remains unclear and needs to be studied further.

There are three main methods of defining adequate serum cortisol concentrations in critically ill patients: random serum cortisol concentration, a response to ACTH stimulation, and clinical judgement and vital parameters, such as hypotension. Obviously, the incidence of possible AI due to cortisol deficiency varies greatly depending on which criteria are used to define the problem (Bernard 2006). Several random serum cortisol definitions are used to determine AI in critical illness (Bernard 2006; Cooper 2003; Lipiner 2007; Marik 2003), and we showed that one individual patient can be categorized as having AI and not having AI depending on whether free or total serum cortisol concentrations are used.

Although timing of cortisol measurements is essential in critical illness, the circadian rhythm of serum cortisol concentration variation may be disturbed (Voerman 1992). Moreover, morning cortisol samples are not standardised. Typically, major nursing procedures with potentially high stress stimuli, may precede cortisol sampling. From this perspective, an ACTH stimulation test could have some advantages over random serum cortisol sampling.

Our study did not show any difference in the absolute values of free or total serum cortisol concentrations in severe sepsis or septic shock. However, the ratio of free/total cortisol was elevated as a result of low CBG. Free serum cortisol was not helpful in diagnosing the adequacy of serum cortisol production in patients with severe sepsis, septic shock, or aSAH. This finding was also reported by Annane et al.(2006), but Hamrahian et al. (2004) suggested that measuring free serum cortisol may be superior to measuring total serum cortisol, especially if patients have hypoproteinemia. Low serum albumin did not affect our serum cortisol measurements in patients with aSAH. Free and total cortisol concentrations correlated well in patients with sepsis or aSAH. In sepsis, both the free and total serum cortisol concentration was lower in survivors than nonsurvivors. The free serum cortisol concentration was not helpful for distinguishing between survivors and nonsurvivors. To achieve a morbidity or mortality difference, patients with higher initial serum cortisol levels should be given low dose hydrocortisone. The possible effect of additional glucocorticoids in these patients may be explained by down-regulation of glucocorticoid receptors (Molijn 1995). Thus, new recommendations for hydrocortisone treatment in sepsis are based on clinical parameters. Although our study showed increased cortisol levels after aortic valve surgery, we do not know if this was adequate. Corticoids may have some other additional benefits, such as reducing the risk of atrial fibrillation after CABG surgery (Halonen 2007).

More severe sepsis resulted in higher total and free serum cortisol concentrations, which is in agreement with other studies (Annane 2000; Lipiner, 2007; Marik 2003). Interestingly, aSAH severity did not affect free or total serum cortisol concentrations. Our study is the first to report this observation in the acute phase of aSAH, but other studies have demonstrated this in the chronic phase of aSAH (Aimaretti 2005; Dimopoulou 2004a; Kreitschmann-Andermahr 2004). We found some individuals with low ACTH and total and free serum cortisol concentrations, reflecting secondary AI, which could theoretically explain this finding. Definitive reference values would be needed for an adequate cortisol response in aSAH compared to other diseases.

In the clinical point of view, corticoids exert many fast beneficial effects, such as a diminished need for norepinephrine infusions, by sensitizing catecholamine receptors (Rhen 2005). In patients with aSAH, corticoids may be used to treat vasospasm for the same reason, but it also may be used in some situations to treat hyponatremia (Katayama 2007). These regimens are not definitively proven in the case of aSAH. In practice, we face a situation in which only recommendations for the diagnosis of CIRCI in septic patients exist. Taken literately, the diagnostic criteria for CIRCI and AI should be used for critically ill patients in general. No scientific evidence is provided for this aspect because many disease entities are not well studied.

Our study in patients with aSAH is the first to describe the behaviour of free and total serum cortisol concentrations in the acute phase of the disease. Describing the typical pattern of cortisol response in aSAH is important before judging patients as having an inadequate response. As discussed above, the critical care

environment and nursing procedures, sedative agents, antibiotics, body composition (Klose 2007), contraceptive agents (Klose 2007), and cortisol assessment methods (Arafah 2006) have not been standardised in studies investigating CIRCI or AI in critically ill patients. We may be in a situation that is described as follows: "CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness"; and further studies are needed to carefully define adequacy of human stress response in different diagnosis categories.

6.2 Effects of common sedative agents used in critical illness on serum cortisol concentrations

Critically ill patients require sedatives for various indications, and continuous infusions are most commonly applied to keep the patient adapted to ventilatory support therapy. In neurological critical care, sedatives enable adaptation to mechanical ventilation and play an essential role in treating patients with high intracranial pressure and/or decreased consciousness. In addition to long-lasting sedation in the ICU environment, short procedural sedation is needed for, for example, wound care and cannulation.

Critically ill patients typically receive multiple drugs with sedative properties. Other drugs, such as antifungals, that affect the endocrinological axis may also occasionally be used. This context makes the interpretation of endocrinological test results a challenge.

Etomidate is an old drug that raised concerns among intensivists in 1983 (Ledingham 1983) in regards to increased mortality due to an inhibition of cortisol production in patients with multiple trauma. However, in that particular study, etomidate was used as an infusion; since then, etomidate infusions have not been used.

Etomidate is haemodynamically stable (Gooding 1979; Reich 2005), making it an attractive drug for facilitating intubation in critically ill patients. The haemodynamic profile has also made etomidate a drug of choice in emergency care medicine if sedation is needed for intubation (Jabre 2009; Zed 2006). These patients are typically suffering from various deceases that lead to ICU treatment.

The effects of a single dose of etomidate have been studied in different patient scenarios. A recent study of 479 acutely ill patients, ketamine was demonstrated to be an alternative to etomidate in these patients (Jabre 2009). This study is, thus far, the largest study comparing etomidate to another drug. This study had two important findings. First, etomidate can be replaced by another haemodynamically stable induction agent, ketamine. Second, etomidate use was not associated with increased morbidity or mortality. However, only 76 septic patients were recruited and the findings may be due to the small sample size in this subgroup. Jabres et al. (2009) study was not powered to detect possible effects of etomidate in patient subgroups. Jabre et al. (2009) also studied the adrenal axis and found that etomidate suppresses the effect of the ACTH stimulation test and the baseline total cortisol concentrations.

We must emphasize that patients with severe sepsis or septic shock may benefit from a normal functioning HPA axis and may need cortisol substitution (Annane 2000; Sprung 2008). Cuthbertson et al. (2009) showed that a septic patient who receives a single bolus of etomidate has a blunted response to the ACTH stimulation test, and they may have increased mortality. Other studies of septic patients have come to the conclusion that small single doses of etomidate may have detrimental effects (Mohammad 2006; Warner 2009), and it has been shown to be a

risk factor for developing AI (Malerba 2005). In patients with infections and sepsis, a very reluctant attitude towards etomidate should be expressed if it is considered as an anaesthetic agent (Annane 2005). Some authors have suggested cortisol replacement therapy for patients who have received etomidate (Fengler 2008; Vinclair 2008).

Interestingly, animal studies for a new anaesthesia agent, methoxycarbonyl-etomidate, have been published (Cotten 2009). Although based on very preliminary data, this etomidate analogue is very quickly metabolized, haemodynamically stable, and does not cause adrenal gland suppression.

The results mentioned above are similar to our study; etomidate suppresses cortisol production and has a stable haemodynamic profile. The causality of the negative effects on cortisol production and outcome in neuroanaethesia or neurocritical care has not yet been demonstrated. No studies of HPA function and etomidate in the context of aSAH or TBI have been published. Etomidate is used because of its minimal effects on ICP, but the question of HPA function, cortisol, morbidity, and mortality should be raised.

However, etomidate is still commonly used worldwide, though its use is not popular in Finland. Etomidate's haemodynamic profile is constantly used as an argument for its use, and ketamine has been neglected, particularly because of its tendency to increase ICP in patients with acute brain catastrophes (Himmelseher 2005). However, this aspect was not supported in a systematic review, and it was pointed out that the haemodynamic profile of ketamine may be beneficial in patients needing sedation for intubation because of brain trauma (Himmelseher 2005). Ketamine does not cause decreases in serum cortisol concentrations. We showed that, although etomidate is more haemodynamically stable, blood pressure is easily corrected with small boluses of phenylephedrine if propofol is used as an iduction agent. Etomidate does not have enough advantages over commonly used small doses, carefully titrated propofol, and opioid induction, at least in a controlled environment and carefully monitored patients. The stress induced by major surgery may overcome the inhibitory effects of a single dose of etomidate on cortisol synthesis (Crozier 1994). However, propofol causes hypotension, which has been shown to be an independent risk factor for peri-operative complications (Arbous 2001).

Although etomidate has probably the most potent suppressive effect on cortisol synthesis among common sedative agents, almost all sedative agents used in ICUs have endocrinological effects. Propofol decreases catecholamine and cortisol concentrations after CABG (Plunkett 1997), but it does not have significant effects on steroidogenesis (Aitkenhead 1989), which is also supported by our study. Opioids have a depressant effect on serum cortisol concentrations (Oltmanns 2005), and benzodiazepines may also cause some cortisol synthesis depression (Crozier 1994), but it seems that midazolam does not inhibit adrenal gland function (Aitkenhead 1989; Plunkett 1997; Shapiro 1986).

Dexmedetomidine is a new α2-agonist used for sedation in ICU patients. Similar to etomidate, dexmedetomidine is an imidazole derivate, thus having the potential to inhibit cortisol synthesis. However, in short-term use, no suppression of cortisol synthesis was detected (Venn 2001).

The complex interactions of sedative agents and other drugs make it impossible to completely control for agents that may affect serum cortisol concentrations. With this perspective, large studies in different disease categories with morbidity and mortality endpoints must be carried out to really detect the clinical significance of sedative

agents on cortisol and/or other endocrinological abnormalities. Most importantly, reference values for serum cortisol concentrations should be published for the most common critical illness subgroups.

6.3 GH-IGF-I response in neurological critical illness

GH mediates its actions via IGF-I. Recent studies have shown that IGF-I plays an important role in neuronal growth, apoptotic cell death, and protection against brain ischemia (Kooijman 2009). IGF-I has an essential neuromodulatory role throughout the lifespan (Aleman 2009). In animal models of ischemic stroke, treatment with IGF-I was shown to possibly reduce areas of brain ischemia (Liu 2004). No studies have evaluated the role of IGF-I and the outcome in patients with aSAH. In prolonged critical illness GH-treatment increased mortality (Takala 1999)

GH insufficiency is the most vulnerable axis of brain trauma-induced pituitary insufficiency with a hypothetical explanation of the vulnerable location of the somatotrophs (Popovic 2005). The possible GH-IGF-I insufficiency in neurocritical illness can be approached in two ways: GH-IGF-I as an indicator of pituitary dysfunction or relative IGF-I insufficiency mirroring its role as a neuroprotective agent.

We showed that the blood IGF-I concentration is lower in patients with aSAH than control. Cumulative IGF-I concentration was associated with morbidity assessed by HRQoL and GOS. The IGF-I concentrations were under the cut-off levels given in other studies, more often in aSAH patients (Hartman 2002). No association between GH and IGF-I concentrations was detected. Single GH measurements are generally agreed to be of little value if no GH stimulation test is performed (Gasco 2008). However, the IGF-I concentrations were not low at 3 months in either aSAH or control patients. This finding is not in accordance with other studies in which low values were detected in the chronic phase of aSAH (Dimopoulou 2004; Tanriverdi 2007).

There are several cut-off limits for detecting somatotroph insufficiency that can be used if classical hypopituitarism is the target to be detected. On the other hand, focusing on the question of IGF-I and neuroprotection is interesting. In this context, no real cut-off limits exist in any neurological disease. An excess amount of IGF-I may be needed, and IGF-I could be used as a drug for acute neurological repair (Kooijman 2009). Bondanelli et al. (2006) reported that all patients with ischemic stroke in their study had normal age-related IGF-I values. However, patients with lower IGF-I values have worse outcomes than patients with higher IGF-I values. Also, in children with meningococcal sepsis, nonsurviving patients have low IGF-I values (de Groof 2002). We showed that patients with aSAH have lower IGF-I values than control patients. Further studies are needed to confirm these potentially clinically relevant findings.

Decreased HRQoL after aSAH has been shown in several studies (Katati 2007; Kreitschmann-Andermahr 2007; Visser-Meily 2009). The symptoms of depressed quality of life may be similar to those caused by pituitary insufficiency: fatigue, depression, anxiety, and weakness (Schneider 2007), and these symptoms may be misinterpreted in some cases as normal neurological sequelae of aSAH. Our preliminary study shows that

neuroendocrinological changes may be associated with morbidity, and these findings should be investigated further in larger studies.

6.4 Limitations of the study

In this study, several different patient categories were studied. One may argue that patients admitted for elective cardiac surgery are very different from patients with sepsis or aSAH. However, all of these patients face major stress, inflammatory responses, and activation of the HPA axis. Disturbances in the stress-mediated endocrinological reactions may lead to increased morbidity. Typically, all the studied patient groups are admitted routinely to the ICU because of serious illness requiring intensive care.

In our sepsis study, cortisol sampling was not scheduled and no ACTH stimulation test was performed. Pituitary function is affected by complex negative feedback loops and several cytokines (Marik 2008). Thus, secondary AI may also play a role in septic patients (Prigent 2004), and this aspect requires further study. Although 125 blood samples were collected in the sepsis study, there might have been selection bias. The cohort in the Finnsepsis study (Karlsson 2007) was much larger, but blood samples were not available from all of the patients

Only study III had enough power to detect possible AI. Our study with aortic stenosis was had the power to detect haemodynamic changes between propofol and etomidate, not differences in cortisol synthesis. Because of this small sample size, no conclusion could be made concerning morbidity or mortality.

7 Conclusions

1. Etomidate transiently decreases the postoperative serum cortisol concentration. Propofol is twice as likely as etomidate to evoke hypotension when inducing anaesthesia in patients with severe aortic stenosis.

2. The behaviour of serum free and total serum cortisol was similar. Measuring free serum cortisol does not provide any advantages over measuring total serum cortisol, and it is not better at predicting hospital mortality in patients with severe sepsis or septic shock.

3. In the acute phase, some patients may have secondary AI. The severity of aSAH does not affect calculated free or total serum cortisol. Measuring free serum cortisol is not helpful in determining AI in patients with aSAH.

4. Serum IGF-I concentrations are low in patients with aSAH, which may contribute to poor outcome assessed by GOS and HRQoL.

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Appendix:

FISHER CT-SCALE

GLASGOW COMA SCALE

GLASGOW OUTCOME SCALE

HUNT & HESS SCALE

WOLRD FEDERATION OF NEUROSURGICAL SOCIETIES SCALE

ORIGINAL PUBLICATIONS I-IV

COMMENT ON STUDY III

Fisher CT-scale (Fisher 1980)

1= no blood

2= diffuse thin layer of blood, in vertical cisterns < 1mm

3= localized clot or thick layer of blood, in vertical cisterns > 1mm

4= intracerebral and/or intraventricular clot

Glasgow coma scale (Teasdale 1974)

Best Eye Response (4)

1= No eye opening.

2=Eye opening to pain.

3=Eye opening to verbal command.

4=Eyes open spontaneously.

Best Verbal Response (5)

1= No verbal response

2= Incomprehensible sounds.

3= Inappropriate words.

4= Confused

5= Orientated

Best Motor Response (6)

1= No motor response.

2= Extension to pain.

3= Flexion to pain.

4= Withdrawal from pain.

5= Localizing pain.

6= Obeys Commands.

Glascow outcome scale (Jennet 1975)

1= death

2= persistent vegetative state

3= severe disability (conscious but disabled)

4= moderate disability (disabled but independent)

5= good recovery

Hunt & Hess scale (Hunt 1968)

0= no SAH

1= asymptomatic or mild headache, mild nuchal rigidity

2= moderate to severe headache, nuchal rigidity, no neurological deficit, expect cranial nerve palsy

3= drowniness, confusion, or mild focal deficit

4= stupor or mild to moderate hemiparesis, possible early decerebrate rigidity

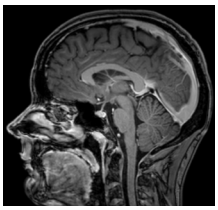
5= deep coma, decerebral posturing, moribund

World Federation of Neurosurgical Societies Scale (Report…1988)

		GCS	Motor deficit
Grade	0	15	Absent and no SAH
	1	15	Absent
	2	13-14	Absent
	3	13-14	Present
	4	7-12	Present
	5	3-6	Present or absent

Stepani Bendel

Pituitary and Adrenal Response to Critical Illness



Activation of the pituitary and adrenal axis is essential in modifying the stress response in critically ill patients. Inadequate stress response in critically ill patients may negatively affect outcome. In this study, pituitary and adrenal responses were evaluated in patients with severe aortic stenosis, severe sepsis and aneurysmal subarachnoid haemorrhage. This dissertation provides new information on acute hormonal response in these specific groups of critically ill patients.

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