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Abstract: Context: Glucocorticoids regulate hemostatic and endothelial function, and they are critical for adaptive functions during surgery. No data regarding the impact of adrenal function on hemostasis and endothelial function in the perioperative setting are available. Objective: We assessed the association of adrenal response to adrenocorticotropic hormone (ACTH) and markers of endothelial/hemostatic function in surgical patients. Methods: This prospective observational study, conducted at a tertiary care hospital, included 60 patients (35 male/25 female) undergoing abdominal surgery. Adrenal function was evaluated by low-dose ACTH stimulation test on the day before, during, and the day after surgery. According to their stimulated cortisol level (cutoff 500 nmol/L), patients were classified as having normal hypothalamic-pituitary-adrenal (HPA)-axis function (nHPA) or deficient HPA-axis function (dHPA). Parameters of endothelial function (soluble vascular cell adhesion molecule-1, thrombomodulin) and hemostasis (fibrinogen, von Willebrand factor antigen, factor VIII [FVIII]) were measured during surgery. Results: Twenty-one patients had dHPA and 39 had nHPA. Compared with nHPA, patients with dHPA had significantly lower peak cortisol before (median 568 vs 425 nmol/L, P < 0.001) and during (693 vs 544 nmol/L, P < 0.001) surgery and lower postoperative hemoglobin levels (116 g/L vs 105 g/L, P = 0.049). FVIII was significantly reduced in patients with dHPA in uni- and multivariable analyses; other factors displayed no significant differences. Coagulation factors/endothelial markers changed progressively in relation to stimulated cortisol levels and showed a turning point at cortisol levels between 500 and 600 nmol/L. Conclusions: Patients with dHPA undergoing abdominal surgery demonstrate impaired hemostasis which can translate into excessive blood loss. Keywords: Adrenal insufficiency; abdominal surgery; endothelial function; hemostasis.

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Impact of Adrenal Function on Hemostasis/Endothelial Function in Patients Undergoing Surgery

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Abstract

Context: Glucocorticoids regulate hemostatic and endothelial function, and they are critical for adaptive functions during surgery. No data regarding the impact of adrenal function on hemostasis and endothelial function in the perioperative setting are available.

Objective: We assessed the association of adrenal response to adrenocorticotropic hormone (ACTH) and markers of endothelial/hemostatic function in surgical patients.

Methods: This prospective observational study, conducted at a tertiary care hospital, included 60 patients (35 male/25 female) undergoing abdominal surgery. Adrenal function was evaluated by low-dose ACTH stimulation test on the day before, during, and the day after surgery. According to their stimulated cortisol level (cutoff ≥ 500 nmol/L), patients were classified as having normal hypothalamic-pituitary-adrenal (HPA)-axis function (nHPA) or deficient HPA-axis function (dHPA). Parameters of endothelial function (soluble...
vascular cell adhesion molecule-1, thrombomodulin) and hemostasis (fibrinogen, von Willebrand factor antigen, factor VIII [FVIII]) were measured during surgery.

**Results:** Twenty-one patients had dHPA and 39 had nHPA. Compared with nHPA, patients with dHPA had significantly lower peak cortisol before (median 568 vs 425 nmol/L, \( P < 0.001 \)) and during (693 vs 544 nmol/L, \( P < 0.001 \)) surgery and lower postoperative hemoglobin levels (116 g/L vs 105 g/L, \( P = 0.049 \)). FVIII was significantly reduced in patients with dHPA in uni- and multivariable analyses; other factors displayed no significant differences. Coagulation factors/endothelial markers changed progressively in relation to stimulated cortisol levels and showed a turning point at cortisol levels between 500 and 600 nmol/L.

**Conclusions:** Patients with dHPA undergoing abdominal surgery demonstrate impaired hemostasis which can translate into excessive blood loss.

**Key Words:** Adrenal insufficiency, hemostasis, endothelial function, abdominal surgery

Surgery represents a major stress to the body, leading to a variety of homeostatic responses to defend and protect the organism in this setting. Apart from effects on volume, electrolyte, and pH balance, surgical interventions may have an impact on hemostasis (ie, by increasing coagulation proteins and platelet reactivity and by decreasing coagulation inhibitors and fibrinolysis) [1-3] and arterial endothelial function [4, 5]. Some of these adaptive reactions are mediated through stress hormones (ie, glucocorticoids and catecholamines) [6].

Glucocorticoids are critical for vascular function/reactivity and they exert a permissive function on catecholamine release and action during the stress response [7], effects that are promoted through genomic and nongenomic pathways [8, 9]. Glucocorticoids act on the coagulation system in various ways. Their impact is mainly known from states with endogenous cortisol excess or exogenous therapeutic administration of glucocorticoids [10]. Glucocorticoids promote an increase in clotting factors (ie, factor VIII [FVIII], von Willebrand factor antigen [vWF]) [11], thrombin/antithrombin complexes, plasminogen activator inhibitor-1 [PAI-1] and fibrinogen levels [12].

Apart from their well-known effects on the vasculature, catecholamines also stimulate clotting factors (ie, FVIII and vWF) and fibrinolytic molecules (ie, tissue plasminogen activator) [13] and they represent important cofactors for platelet activation/aggregation [14, 15]. Adrenocortical and adrenomedullary function are closely linked together by a complex system of paracrine regulation [16]. For example, glucocorticoids induce enzymes for catecholamine biosynthesis and stimulate the release of catecholamines [17].

Therefore, the integrity of the adrenocortical and adrenomedullary unit in the form of an adequate response of the hypothalamic-pituitary-adrenal (HPA) axis to stress (ie, the rapid increase of the cortisol secretion and a sufficient catecholamine secretion capacity) is critical to maintain volume/electrolyte balance and to control inflammatory cascades, vascular tone, endothelial function, and homeostatic functionality in the peri- and postoperative period.

Surgery is a potent activator of the HPA axis [18, 19], with the degree of the activation being dependent on several factors, including severity of surgical stress [20], administered medications [21-23], and type of anesthesia [24]. Untreated adrenocortical insufficiency in the perioperative setting is associated with increased morbidity and mortality, mainly due to arterial hypotension and volume-refractory shock [25, 26]. Furthermore, the perioperative regulation of the volume balance and the amount of blood loss correlate with the adequacy of the adrenal function. Patients with adrenal insufficiency undergoing coronary artery bypass graft procedures show altered perioperative outcomes, such as increased blood loss and impaired volume balance [27].

Currently, no data are available regarding the impact of adrenal function on hemostasis and platelet function in the perioperative setting. Therefore, the aim of this study was to evaluate the association of the adrenal response to adrenocorticotropic hormone (ACTH) and markers of endothelial and hemostatic function in patients undergoing abdominal surgery. Based on the assumption that patients with deficient HPA-axis function (dHPA) have impaired adrenal catecholamine secretion, we hypothesize that

a) Glucocorticoid and catecholamine deficiency are associated with lower levels of coagulation factors (ie, FVIII and vWF) and probably lower levels of markers of endothelial function.

b) Combined glucocorticoid and catecholamine deficiency may have the profoundest impact on coagulation markers whose secretion is dependent on glucocorticoid and catecholamine action (FVIII and vWF).

**Methods**

**Participants**

This prospective observational study was conducted at the Luzerner Kantonsspital, a large urban hospital. Consecutive
patients scheduled for various types of abdominal surgery were recruited (Fig. 1). We excluded patients with a history of glucocorticoid treatment (topical, inhaled, intraarticular, or systemic application during the last 6 months), endocrine diseases (ie, Cushing disease, thyroid dysfunction), acute illness, and induction of anesthesia with etomidate.

The study conformed to the declaration of Helsinki and was specifically approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz). Written informed consent was obtained from all patients.

Study Procedures

The adrenal function was evaluated by low-dose (1 µg) ACTH stimulation test in all patients on the day before surgery (8 AM), during surgery (30 minutes after the first incision, the time of the stimulation test depending from the time of scheduled surgery) and on the first postoperative day (8 AM). Dehydroepiandrosterone sulfate (DHEA-S) as an additional parameter for adrenal function was measured before surgery. Parameters of endothelial function and hemostasis were measured during surgery (30 minutes after the first incision).

Study Measurements

Evaluation of adrenal function: low-dose ACTH stimulation test, measurement of DHEA-S

For the low-dose (1 µg) ACTH stimulation test, a bolus intravenous injection of 1 µg (1–24)-corticotropin (tetracosactrin, Synacthen, Novartis Pharma, Berne, Switzerland) was administered. One vial of 250µg tetracosactrin was diluted in sterile saline solution to a concentration of 1µg/mL, filtered in plastic syringes, and stored at 4 °C as described elsewhere [28]. Blood was taken immediately before (basal cortisol level) and 30 minutes after (stimulated cortisol level) injection of the corticotropin bolus. A stimulated cortisol level of ≥500 nmol/L [29] was defined as a normal adrenal response to corticotropin and normal HPA-axis function (nHPA).

Parameters of endothelial function and hemostasis: soluble vascular cell adhesion molecule-1, thrombomodulin, fibrinogen, vWF, FVIII

Soluble vascular cell adhesion molecule-1 (sVCAM-1) and thrombomodulin were measured as markers of endothelial function. Fibrinogen, vWF, FVIII, and thrombocytes were measured to evaluate hemostasis.

Statistical Analysis

Baseline characteristics and laboratory measurements were analyzed descriptively using medians and interquartile ranges for continuous variables or numbers and percentages for categorical variables. Comparisons were performed between groups of persons with nHPA and dHPA, respectively, using the Kruskal-Wallis (continuous variables) or Chi-square (categorical variables) tests. Of note, 3 persons had missing measurements of preoperative hemoglobin (all in the nHPA group, and there were 14 postoperative hemoglobin measurements (6 in the dHPA group and 8 in the

Figure 1. Patient flow chart depicting the number of patients included in the study and in the final analysis, respectively.
nHPA group). Persons with missing laboratory parameters were excluded from the respective univariable analysis.

Multivariable linear regression analyses were performed to test for differences between the nHPA and dHPA groups, using the parameters of endothelial function and hemostasis as outcomes, adjusted for a priori determined confounders of age, sex, weight, intraoperative volume balance, and intubation time. Because some persons had missing information for weight (deficient group n = 1, normal group n = 3), intubation time (deficient group n = 2, normal group n = 5), and volume balance (deficient group n = 4, normal group n = 7), the missing values were replaced by the overall means of the respective variables in order to maintain them in regression analyses. Regression assumptions were visually checked using residual-versus-fitted plots (not shown).

Additionally, the binary classification of preoperative, stimulated cortisol into deficient and normal in the main analysis was scrutinized in an exploratory analysis. Based on the multivariable linear regression models described above, the “deficient or normal” groups were replaced by a restricted cubic spline transformation of preoperative stimulated cortisol levels with 3 knots. Next, we plotted model-predicted coagulation parameters as a function of stimulated cortisol values, without making any assumptions regarding the shape of the association (plotting marginal effects with all other values fixed at the mean).

Analyses were performed using Stata 13 (Stata Corp., College Station, TX, USA). Statistical significance was defined as P values < 0.05 (2-tailed). We did not adjust the analysis for multiple comparisons.

Results
Baseline Characteristics
A total of 60 patients (35 male / 25 female) were included in the study; median age was 66 years. A deficient adrenal response to ACTH on the day before surgery was diagnosed in 21 patients (35%, dHPA group), whereas 39 patients (65%, nHPA group) had intact adrenocortical function. The 2 groups were well balanced with respect to sex, age, surgery type and characteristics (ie, open vs laparoscopic procedure, elective vs urgent procedure), use of intraoperative noradrenalin and pre-/postoperative systolic blood pressure. However, the dHPA group tended to be heavier, have a shorter intubation time, and a higher blood volume balance, although differences did not reach statistical significance (Table 1).

Impact of Adrenal Function on Hemostasis
Univariable analyses of cortisol levels indicated that—compared to patients with normal HPA-axis function—patients with deficient HPA-axis function had a significantly lower peak cortisol level after stimulation with ACTH before (median 425 vs 568 nmol/L, P < 0.001) and during (median 544 vs 693 nmol/L, P < 0.001) surgery. Stimulated cortisol levels in the postoperative setting also tended to be higher in the nHPA-axis group, but the difference did not reach statistical significance (median 566 vs 650 nmol/L, P = 0.066) (Fig. 2/Table 2).

Patients in both groups had similar preoperative hemoglobin levels (median of 139 g/L in both groups), but patients in the dHPA group had lower postoperative levels (median 105 vs 116 g/L in the deficient and normal groups, respectively, P = 0.049) suggesting greater blood loss (Table 3). The higher operative blood loss is also reflected by the nominally higher amount of infused solutions in the dHPA group (median 2500 mL vs 2350 mL in the normal group, P = 0.136) (Table 1).

The univariable analysis of biochemical and coagulation parameters during surgery revealed that patients with deficient HPA-axis function had significantly reduced concentrations of FVIII (median 125% vs 184% in the normal HPA-axis group, P = 0.000). In contrast, there were no significant group differences in concentrations of vWF, thrombomodulin, sVCAM-1, and fibrinogen during surgery (Table 3). FVIII was also significantly lower in the multivariable regression analysis adjusted for age, sex, weight, intraoperative volume balance, and intubation time (Fig. 3).

The exploratory, restricted cubic spline analyses suggest that most coagulation parameters do indeed show a turning point around the cutoff at around 500 (indicated by black line in Fig. 4) to 600 nmol/L, thus validating our initially chosen cutoff for deficient vs normal cortisol. The only exception was thrombomodulin, which exhibited a linear association with stimulated preoperative cortisol.

Discussion
An insufficient response of plasma cortisol to ACTH is common in patients undergoing abdominal surgery and the rate in our study is comparable to other studies [27]. However, the reasons for this high proportion of patients with a deficient HPA-axis function remain unclear. We have excluded patients with possible causes (ie, history of treatment with glucocorticoids or induction of general anesthesia with etomidate) of primary or secondary/tertiary adrenal insufficiency. There seems to be a dynamic in cortisol secretion patterns: Patients with deficient HPA-axis function had significantly lower peak cortisol levels in the postoperative setting also tended to be higher in the nHPA-axis group, but the difference did not reach statistical significance (median 566 vs 650 nmol/L, P = 0.066) (Fig. 2/Table 2).

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It could be assumed that patients with deficient HPA-axis had subnormal stimulated cortisol levels only by chance or confounding factors (ie, altered binding protein levels) interfered with the cortisol assay leading to false low values. However, patients with deficient HPA-axis function demonstrated (1) distinct alterations in the coagulation system, even after correction for multiple confounders (age, sex, weight, intraoperative volume balance, and intubation time) and (2) coagulation factors and endothelial markers changed progressively in relation to stimulated serum cortisol levels (as could be shown in the restricted cubic spline transformation). Most of these parameters show a turning

| Parameter                                      | dHPA          | nHPA          | P value |
|------------------------------------------------|---------------|---------------|---------|
| Male, n (%)                                    | 13 (61.9%)    | 22 (56.41%)   | 0.681   |
| Caucasians, n (%)                             | 21 (100%)     | 37 (94%)      | 0.924   |
| Age, years                                    | 66 [59; 72]   | 69 [53; 76]   | 0.914   |
| Weight, kg                                    | 78 [67; 85]   | 73 [64; 80]   | 0.118   |
| BMI, kg/m²                                     | 26.7 [24.9; 27.6] | 25.9 [23.3; 27.0] | 0.068   |
| **Characteristic of surgery**                 |               |               |         |
| Laparoscopic, n (%)                            | 13 (62%)      | 24 (61%)      | 0.977   |
| Open surgery, n (%)                            | 8 (38%)       | 15 (39%)      | 0.977   |
| Elective surgery, n (%)                        | 18 (85%)      | 34 (88%)      | 0.873   |
| Emergency operation, n (%)                     | 3 (14%)       | 5 (12%)       | 0.873   |
| **Type of abdominal surgery**                  |               |               |         |
| Cholecystectomy lap.-scop./open                | 4/1           | 6/1           |         |
| Sigma resection                                | 0             | 7             |         |
| Ileostomy reversal                             | 1             | 5             |         |
| Hernioplasty                                   | 6             | 6             |         |
| Rectum amputation                              | 3             | 2             |         |
| Hemicolecotomy                                 | 3             | 4             |         |
| Gastrectomy                                    | 2             | 2             |         |
| Esophagus resection                            | 0             | 1             |         |
| Pancreas resection                             | 0             | 2             |         |
| Adhesiolysis                                   | 1             | 3             |         |
| **Preoperative medication (n)**                |               |               |         |
| Alpha blocker                                  | 0             | 1             |         |
| Beta blocker                                   | 2             | 5             |         |
| Calcium antagonists                            | 2             | 3             |         |
| ACE-inhibitors/sartans                         | 3             | 6             |         |
| NSAID                                          | 1             | 4             |         |
| Antidepressants                                | 1             | 1             |         |
| ASA class I; II; III; IV (n)                   | 7; 10; 3; 1   | 13; 16; 7; 2  |         |
| **Perioperative anesthesia drugs (n)**         |               |               |         |
| Etomidate                                      | 0             | 0             |         |
| Propofol                                       | 16            | 34            |         |
| Thiopentone                                    | 5             | 5             |         |
| Isoflurane in air                              | 21            | 39            |         |
| Volume balance (mL)                            | 2500 [2250; 3000] | 2350 [1200; 3450] | 0.136 |
| Intubation time (min)                          | 150 [115; 245] | 202.50 [125; 282] | 0.194 |
| Use of intraoperative noradrenaline (n)        | 2             | 5             | 0.704   |
| Systolic blood pressure preop. (mmHg)          | 131 [122; 142] | 124 [110; 131] | 0.061   |
| Diastolic blood pressure preop. (mmHg)         | 78 [70; 94]   | 70 [63; 80]   | 0.007   |
| Systolic blood pressure postop. (mmHg)         | 130 [117; 145] | 130 [120; 140] | 0.729   |
| Diastolic blood pressure postop. (mmHg)        | 80 [76; 84]   | 80 [70; 84]   | 0.580   |

Baseline characteristics in patients undergoing abdominal surgery with deficient (n = 21, dHPA) and normal HPA-axis function (n = 39, nHPA). Apart from gender, data are represented as median [IQR].

Abbreviations: ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index; dHPA, deficient hypothalamic-pituitary-adrenal; IQR, interquartile range; nHPA, normal hypothalamic-pituitary-adrenal; NSAID, nonsteroidal anti-inflammatory drug; postop., postoperative; preop., preoperative.
point at cortisol levels between 500 and 600 nmol/L which corresponds to the generally accepted cutoff for the classification of HPA-function (normal vs deficient). With these points taken together, we conclude that these patients had a clinically existent and relevant dysfunction of the adrenal gland.

In the postoperative setting, levels of basal and stimulated cortisol demonstrated no difference between the 2 groups. Therefore, the deficiency of the adrenal function in the setting of acute illness/surgery could be a temporary phenomenon reflecting a delayed response to stress with downstream effects on the hemostasis system. This finding is supported by the fact that levels of DHEA-S, which are a sensitive indicator for the presence of chronic adrenal insufficiency [30-32], were not different in patients with nHPA and dHPA.

Our main finding is that the lack of an adequate adrenal response is associated with alterations in the coagulation system: patients with a deficient HPA-axis displayed significantly lower levels of FVIII during surgery, whereas other parameters remained unchanged (vWF antigen, thrombomodulin, and sVCAM-1).

On a clinical basis, these alterations in hemostasis translated to an increased intraoperative blood loss, probably an increased amount of infusions, and a lower postoperative hemoglobin level. By analogy, an increased rate of bleeding complications is seen in patient with congenital (hemophilia A) and acquired FVIII deficiency, and, historically, epinephrine, although not norepinephrine, was used to stimulate FVIII clotting activity in patients with hemophilia [33]. Reduced permissive action of cortisol on catecholamine release during surgery could thus be one explanation for...
why patients with dHPA mounted a relatively lower FVIII response. FVIII increase during stress is mediated by beta-adrenergic receptors [34], which are also involved in vWF antigen release from endothelial cells during the stress response [35]. Indeed, compared to patients with nHPA, those with dHPA showed also lower absolute levels of VWF antigen. However, FVIII seems to show a relatively stronger stress response than VWF antigen [36], which together with limited statistical power, likely prevented the group difference in VWF antigen from becoming statistically significant. In turn, to our knowledge, it is currently unknown to what extent and by which mechanisms catecholamines are involved in the human stress response of sVCAM-1 and thrombomodulin, which may explain the absence of a group difference.

The hemostasis/coagulation system is a complex and balanced system simultaneously protecting the body against excessive blood loss and preventing hypercoagulability and thrombosis. It involves several key components: endothelial function, cellular factors (ie, platelet aggregation and activation), a coagulation cascade (ie, vWF, coagulation factors) that itself is regulated by proteins (protein C, protein S, antithrombin), fibrinolysis, and inhibition of fibrinolysis respectively (ie, by PAI-1). The crosstalk between the endocrine system and hemostasis/coagulation is well known and supported by a plethora of data from ex vivo and in vivo studies in healthy persons, patients with endocrine diseases, and patients taking exogenous glucocorticoids [37]. For example, acquired vWF disease and decreased FVIII levels can occur with hypothyroidism [38] and are described in patients with hypopituitarism [39]. Endogenous Cushing syndrome—the “pathologic counterpart” of adrenal insufficiency—is associated with a hypercoagulable state and increased risk of thromboembolic complications [40, 41]. Endogenous Cushing syndrome affects every component of the hemostatic system: increased platelet count [42, 43] and activation/aggregation [44], increased thrombin/antithrombin complexes [12, 45], and increased PAI-1 and fibrinogen levels [11, 12, 43, 46]. Alterations in the coagulation cascade have also been described. In all studies, FVIII consistently seems to be elevated in endogenous Cushing syndrome [10, 11, 46-50]. There is an increase in vWF levels [11, 12, 45, 47, 48, 51, 52] in patients with endogenous Cushing syndrome, as well as a positive correlation between serum cortisol levels and vWF concentrations [52], and patients present usually with large vWF multimers [48].

Elevated levels of glucocorticoids stimulate the endothelial production of vWF, probably by a direct effect of

| Parameter | dHPA       | nHPA       | P value |
|-----------|------------|------------|---------|
| Hemoglobin preoperative (g/L) | 139 [125; 146] | 139 [132; 143.50] | 0.843 |
| Hemoglobin postoperative (g/L) | 105 [93; 114] | 116 [105; 128] | 0.049 |
| Thrombocytes (g/L) | 221 [191; 258] | 213 [179; 284] | 0.110 |
| DHEA-S (µmol/L) preoperative | 1.73 [0.97; 3.49] | 1.78 [0.99; 3.70] | 0.914 |
| High-sensitive CRP (mg/L) preoperative | 0.77 [0.43; 2.24] | 1.58 [0.89; 3.71] | 0.079 |
| Albumin (g/L) preoperative | 29 [23; 32] | 29 [24; 33] | 0.658 |
| Fibrinogen Clauss (g/L) during surgery | 2.51 [1.92; 2.76] | 2.31 [2.07; 2.96] | 0.895 |
| Factor VIII (%) during surgery | 125 [98; 140] | 184 [135; 244] | 0.000 |
| vWF antigen (%) during surgery | 115 [95; 148] | 139 [97; 177] | 0.215 |
| sVCAM1 (ng/mL) during surgery | 350 [270; 431] | 377 [299; 473] | 0.577 |
| Thrombomodulin (ng/mL) during surgery | 29.20 [25.30; 34.60] | 28.20 [24; 32.50] | 0.271 |

Biochemical and coagulation parameters in patients with deficient (n = 21, dHPA) and normal HPA-axis function (n = 39, nHPA). Data are represented as median [IQR].

Abbreviations: CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulfate; sVCAM-1, soluble vascular cell adhesion molecule-1; vWF, von Willebrand factor antigen.

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**Figure 3.** Multivariable regression analysis (adjusted for age, gender, weight, volume balance, and intubation time) displaying differences in clotting factors and endothelial markers measured during surgery between groups with deficient and normal HPA-axis function. Data are displayed as model-derived predicted absolute differences and 95% confidence intervals.
glucocorticoids on vWF gene expression [53]. Higher vWF levels promote a rise in FVIII [54] in patients with Cushing syndrome. Thereby treatment of endogenous cortisol excess is associated with a decrease and normalization of vWF and FVIII [47, 48], indicating the dynamic impact of hypercortisolism on the coagulation system.

On the other side there is a paucity of data describing the direct impact of adrenal insufficiency on the hemostatic
system [37, 55]. It is well known that Addison disease can be associated with anti-phospholipid syndrome and recurrent thromboembolic events [56] and anti-phospholipid syndrome itself can lead to bilateral adrenal hemorrhage/infarction and acute adrenal insufficiency [57, 58].

Derex et al described the case of a young woman with previously undiagnosed primary adrenal insufficiency and a spontaneous intracerebral hemorrhage due to severe hypofibrinogenemia and a deficit of vitamin K-dependent coagulation factors [59]. The hemostatic abnormalities resolved after treatment with hydrocortisone. Peacey et al demonstrated that increased hydrocortisone doses in patients with hypopituitarism did not significantly affect levels of PAI-1, tissue plasminogen activator, and fibrinogen [60].

To the best of our knowledge, this study shows for the first time the consequences of a reduced cortisol secretion on FVIII. Referring to the above-mentioned mechanism of glucocorticoids on endothelial vWF production, we should expected lower levels of vWF in our HPA-axis deficient patients. These had a trend to lower vWF levels, but the difference was statistically not significant.

Our study has limitations: the number of studied subjects was rather small, and we evaluated only a part of the complex coagulation system addressing thrombocyte and endothelial function, respectively. Assuming a close relationship between cortisol and catecholamine effects on the coagulation system, measuring catecholamines perhaps would have elucidated further mechanisms. However, this was not done in this study. We did not assess hemostasis parameter before surgery, which would have allowed a more precise pathophysiological classification of low FVIII and vWF levels in patient with dHPA (preexisting factor deficiency vs inability to mount an adequate FVIII response). The definition of normal and deficient HPA-axis function was made solely on the low-dose ACTH stimulation test.

Therefore, we emphasize the need to extend the studies and to also include persons with established and chronic adrenal insufficiency, respectively, in comparison to persons with nHPA and dHPA.

In conclusion, our data indicate that persons undergoing abdominal surgery with subnormal secretion of cortisol and probably decreased sympatho-adrenal medullary function have reduced levels of clotting factors whose release may critically relate to catecholaminergic function, particularly FVIII. This may have important clinical consequences, such as excessive blood loss.

**Additional Information**

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**Disclosures:** The authors have nothing to disclose.

**Data Availability:** All datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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