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Hormonal response following hemorrhage after severe trauma: an observational prospective study

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Abstract

Background Following severe trauma, activation of the autonomic and neuroendocrine systems is key in the response to hemorrhage by triggering vasopressor secretion, sodium and water reabsorption to maintain blood pressure and organ perfusion. However, these adaptative mechanisms remain not yet well described in this setting. The main goal of this study was to explore hypothalamic-posterior-pituitary-vasopressin, hypothalamic–pituitary–adrenal and renin–angiotensin–aldosterone system responses to severe trauma.

Methods This is a single-centre prospective observational study among adult severe trauma patients (Injury Severity Score (ISS) ≥ 9) in a French level-1 trauma center.

Results Sixty-five patients were included with a mean age of 46 (± 20) years old and a median ISS of 25 (19–30). Twenty-eight (43%) patients presented with a hemorrhage (transfusion of at least one pack of red blood cells (pRBC) in the 6 first hours), and 15 (23%) of them had a severe hemorrhage (> 3 pRBC in the first 6 h). Evolution of copeptin level, reflecting vasopressin secretion, was significantly different over the 48 h between transfused and non-transfused patients (interaction; $P < 0.001$) and regarding hemorrhage severity (no transfusion, 1–3 pRBC, > 3 pRBC) (interaction; $P < 0.001$). Copeptin was maximum at admission and higher in transfused than in non-transfused patients (486 ± 433 pmol/L vs.208 ± 206 pmol/L; $P < 0.001$). It rapidly decreased without significant difference anymore between groups from 6 h after admission. Renin (time effect, $P = 0.001$; transfusion effect, $P = 0.02$; interaction, $P = 0.04$) and aldosterone (time effect, $P < 0.001$; transfusion effect, $P = 0.7$; interaction, $P = 0.08$) were significantly different over the first 48 h regarding hemorrhage severity. There was no difference between transfused and non-transfused patients regarding levels of cortisol ($P = 0.06$). Twenty-two patients presented a relative corticosteroid insufficiency and 44 presented mineralocorticoid deficiency (aldosterone/renin < 2) over the first 48 h.

Conclusions The vasopressin and renin–angiotensin–aldosterone systems are key pathways in the response to hemorrhage following severe trauma, and their response is quickly exhausted with its severity. This study strengthens the pathophysiological rationale for exploring personalized vasopressor management, including the timely addition of vasopressin and/or angiotensin II in addition to norepinephrine during the resuscitation of traumatic hemorrhage.

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Keywords Severe trauma, Hemorrhage, Vasopressin, Cortisol, Renin, Biomarkers, Intensive care unit

Background

Severe trauma is the leading cause of death among patients aged 16–50 years and ranks third in disability-adjusted life years [1]. Although trauma care has improved over the last decades, hemorrhage and hemorrhage-related multiorgan failure (MOF) still account for more than 40% of mortality in severe trauma patients [2, 3]. Traumatic hemorrhage leads to hypovolemia and vasoplegia that cause hypoperfusion thereby promoting organ failure [4]. Autonomic and neuroendocrine system activation are known to be key in response to hypovolemic shock by triggering vasopressor secretion and water reabsorption to maintain blood pressure and organ perfusion [5]. Thus, sympathetic system through norepinephrine and adrenaline secretion, hormonal pathways with hypothalamic-posterior-pituitary-vasopressin (HPPV) and hypothalamic–pituitary–adrenal (HPA) axis with vasopressin and cortisol together with the renin-aldosterone-angiotensin system (RAAS) are the major adaptative pathways activated in response to hypovolemia and shock. Mainly studied in septic shock, their respective implications remain incompletely explored in the pathophysiology of hemorrhagic shock [6].

The HPPV axis is activated in response to hypovolemia and hypotension, sensed via decreased stretch in atrial and vascular baroreceptors, stimulating the hypothalamus to produce pre-provasopressin. This precursor is cleaved into arginine vasopressin (AVP), neurophysin II, and copeptin; copeptin is released in equimolar amounts with AVP and serves as a stable and reliable surrogate biomarker for AVP activity during hemorrhagic shock, since direct AVP measurement is unstable in plasma [7]. AVP induces potent systemic vasoconstriction and promotes water reabsorption at the kidney level [8]. Early secreted in response to severe trauma [9], AVP is correlated with injury severity [10]. HPA axis activation resulting in cortisol secretion is involved in hemodynamic homeostasis by regulating norepinephrine and angiotensin II secretion and water reabsorption. Adrenal response following severe trauma is usually high [11] but some patients also experience a sustained impairment of adrenal reserve [12]. In addition, following sympathetic nerve activation, hypotension and decreased sodium delivery to the distal tubule, RAAS system is activated with a release of renin by juxtaglomerular cells. It cleaves angiotensinogen in angiotensin I, a precursor of angiotensin II, a vasoconstrictive peptide that contributes in maintaining blood pressure and fluid homeostasis [13]. The only study in trauma patients [14] has shown that RAAS response was involved in hemorrhagic shock response with common dysfunction, presenting as hyperreninemic hypoaldosteronism as observed in septic shock [15–17]. Finally, the dysfunction of these three axes, has been shown to be involved in catecholamine resistant vasodilatory shock (CRVS) following septic shock, a complication also observed in most-severe trauma patients even when bleeding source is controlled.

A better understanding of pathways involved in vasopressor responses to severe trauma could lead to improvement in the management of vasopressor therapy in hemorrhagic shock following trauma and consequently patients' outcome. The main goal of this study was to assess the activation of the hypothalamic-posterior-pituitary-vasopressin, the hypothalamic–pituitary–adrenal axis and renin-angiotensin aldosterone system responses to severe trauma over the first 48 h of care. Other goals were to assess the occurrence of dysfunction in these axes over the same time frame and the relationship between these axis and organ failure, especially acute kidney injury (AKI).

Methods

Study design

This observational, prospective and single-centre study was conducted in the surgical Intensive Care Unit of Bicêtre Hospital, an academic level-1 trauma center. This hospital provides 24-h availability of all essential trauma specialties, staff and equipment for trauma patient care. This study is an ancillary study [18] which was approved by the ethics committee ("Comité de Protection des Personnes") of the hospital (SC13-014 RCB: 2013-A01171-44) with waiver of participant consent. Patients or relatives were informed and we obtained confirmation of non-objection to data use.

Study population

Patients over 18 years old, directly admitted from the trauma scene to the ICU, with an Injury Severity Score (ISS) greater than 9, and for whom initial management in the trauma room required the insertion of an arterial and a venous catheter at the femoral site, were included. Pregnant women, patients with NYHA III or IV heart failure or chronic kidney disease (clearance < 30ml/min) and patients with lower limb amputation or severe crush injury on the same side the femoral catheters were inserted were not included in the study.

Clinical management

Following the emergency call, a physician-staffed mobile intensive care unit was sent to the trauma scene. After clinical assessment and medical care adjusted to trauma severity, patients were transported to the study center.

Upon arrival in the trauma room, the insertion of femoral catheters was decided based on the patient's history, clinical examination, and FAST ultrasound results, at the discretion of the clinician in charge as detailed elsewhere [19]. The decision to transfuse was made by the physician in charge, based on his evaluation of the patient's clinical situation using standard parameters (including clinical signs of shock, positive FAST ultrasound or obvious external hemorrhage and bed-side measurement of hemoglobin).

Data collection

For each patient, demographics, past medical history, trauma characteristics, pre-hospital management data such as time to hospital admission, initial Glasgow Coma Scale (GCS) score, minimum systolic blood pressure, peripheral oxygen saturation, maximum heart rate, need for mechanical ventilation, volume of fluid resuscitation, catecholamines use were collected. We also reported the following scores: Injury Severity Score (ISS) [20], details of injuries for each organ (Abbreviated Injury Scale 2015, AIS) [21] and simplified acute physiology score (SAPS II) [22]. Severe organ injury was defined if the AIS for the given organ was 3 or more. At each time point of blood sampling, mean blood pressure, heart rate, peripheral oxygen saturation and biological data were reported. Fluid administration, dose of catecholamines (in norepinephrine equivalent), transfusion therapy (type of product and amount) and hemostatic procedures were collected during the first 48 h of admission. The following outcome variables were also reported: length of mechanical ventilation, length of intensive care unit (ICU) stay and hospital mortality.

Samples collection and hormonal measurements

A standardized blood test, including an arterial blood gas and two 5-ml Ethylene Diamine Tetra Acetic acid (EDTA) tubes of whole blood, was taken from the catheters on admission (H0), at six hours (H6), twelve hours (H12), twenty-four hours (H24) and forty-eight hours (H48) after admission. The tubes were centrifuged at 2500 g at 4 °C for 10 min. The supernatant plasma was then aliquoted and stored at −80°C. Plasma copeptin reflecting AVP concentration [7, 9] was determined using the TRACE (Time Resolved Amplified Cryptate Emission) sandwich immunofluorescence method on a KRYPTOR compact PLUS (BRAHM-STM Thermo Fisher Scientific, Germany). Plasma total cortisol was determined by chemiluminescence immunoassay on an Immulite 2000 (Siemens, France). Plasma renin concentrations were determined by chemiluminescence immunoassay (CLIA) on Liaison XL (DiaSorin, France). Plasma aldosterone was measured by a solid-phase competition radioimmunoassay (ALDO-RIACT, CisBio Bioassays, France).

Outcome

The primary outcome of interest was the copeptin concentrations during the first 48 h of admission after severe trauma. The secondary outcomes were cortisol, renin and aldosterone concentrations during the first 48 h of admission.

Definitions and groups of interest

Due to the lack of accepted guidelines and the heterogeneity of hemorrhagic shock definitions in the literature, patients were categorized based on the occurrence of hemorrhage [23]. Hemorrhage was defined as the transfusion of at least one pack of red blood cells (pRBC) during the first six hours after ICU admission. Moderate hemorrhage was defined as the transfusion of 1–3 pRBC during the first 6 h after admission and severe hemorrhage was defined as the transfusion of more than 3 pRBC during the first 6 h after admission. Hemorrhagic shock severity was assessed through norepinephrine requirement and blood lactate kinetic over the 48 h. Norepinephrine tartrate formulation was used in our ICU and high doses were defined as ≥ 0.2 µg/kg/min [24].

Acute kidney injury (AKI) was defined and classified according to the "Kidney Disease: Improving Global Outcome" (KDIGO) criteria [25]. As baseline serum creatinine was not available for these patients, we calculated it backwards from MDRD backwards (Modification of Diet in Renal Disease Study) equation set to an estimated glomerular filtration rate (eGFR) of 75 $ml.min^{-1}$ per 1.73 m^2 as recommended by KDIGO guidelines [25]. Maximal creatinine value over the ICU stay was used to classify AKI. Patients were split in two groups according to their KDIGO: moderate to severe AKI (KDIGO 2 or 3) and normal to mild AKI (no AKI or KDIGO 1).

Absolute glucocorticoid deficiency was defined as a plasma total cortisol below 100 ng/ml and relative deficiency was defined as plasma total cortisol below 250 ng/ml [26, 27]. Mineralocorticoid deficiency (MD) was defined as an aldosterone/renin ratio lower than 2 [14]. As described in previous study [16], patients were also described according to median renin in the population.

Statistical analysis

There are few data regarding hormonal concentrations in trauma patients and this is an exploratory study so sample size calculation was not indicated. Since trauma patients present a wide variety of traumatic injuries, we considered that a sample over 60 patients would be representative for this exploratory study. Patients were included in the analysis if they have at least two hormonal measurements over the 48 h.

Qualitative variables were expressed as counts (proportions). Quantitative variables were expressed as mean (SD) or median (25th-75th interquartile range)

according to their distributions. Quantitative variables were compared by a Student t-test or a Mann–Whitney test (according to data distribution) and qualitative variables by a Chi-square test or a Fisher test. Copeptin, cortisol, renin and aldosterone concentrations measured over the first 48 h of admission were analyzed using a two-way repeated measures analysis with factors "group" and "time", and the analysis of their interaction (P group x time) set as fixed effect and patient as random effect. These analyses were performed on absolute values (for variables expressed as mean) or on rank (for variables expressed as median). Groups were defined according to the presence of hemorrhage (no transfusion versus transfusion), hemorrhage severity (no transfusion, 1 to 3 pRBC and > 3 pRBC) and the presence of AKI (normal to mild AKI versus moderate-severe AKI) as described below. If the interaction between the two factors was significant (P group x time < 0.05), multiple comparisons between-group were made at each time point and p values were adjusted using Holm-Sidàk post-test. Two-sided level of significance was fixed at 5%. Data were analyzed using Prism (GraphPad Software, San Diego, California, USA).

Results

Population characteristics

Seventy-five patients were enrolled in the study. Ten patients were secondarily excluded: 3 had an ISS lower than 9, 6 had insufficient blood samples for hormonal dosages and 1 had his file lost. Among the 65 patients included in the final analyses, 47 (72%) were men, with a mean age of 46 (± 20) years, admitted for blunt injury (97%). The median ISS was 25 (18–30).

Thirty-seven patients had no transfusion over the first 6 h of admission. Twenty-eight patients presented with hemorrhage, from which 13 were transfused with 1 to 3 pRBC and 15 had severe hemorrhage requiring transfusion with 4 or more pRBC over the 6 first hours of admission. There were no significant differences between non-transfused and transfused patients regarding demographic characteristics, ISS, type of trauma, pre-hospital management and mortality. None of the patients received pre-hospital transfusion. At admission, transfused patients had a more severe hemodynamic status than those who were not transfused. Moreover, they presented more often severe abdominal or pelvic injuries but had less often severe trauma brain injury (TBI). Characteristics of the study population are presented in Table 1.

Copeptin response

The evolution of copeptin level, reflecting AVP secretion, was statistically different between transfused and non-transfused patients over the 48 h of admission with an interaction between time and groups (transfusion effect x time; $P < 0.001$). Copeptin concentration was maximum on admission with a significantly higher concentration in transfused than in non-transfused patients (468 (136–737) pmol/L vs. 122 (52–288) pmol/L; $P = 0.003$) and decreased rapidly in both groups, without difference between transfused and non-transfused patients from 6 h after admission (135 (56–273) pmol/L vs. 73 (53–184) pmol/L; $P = 0.1$) (Fig. 1A). Regarding hemorrhage severity, copeptin concentration was significantly different between the three groups (no transfusion, 1–3 pRBC, > 3 pRBC) with an interaction between time and groups (transfusion effect x time; $P < 0.001$). Copeptin concentration at admission was significantly higher in patients receiving greater amount of pRBC (no transfusion: 122 (52–288) pmol/L vs. 1–3 pRBC: 268 (123–608) pmol/L; $P = 0.04$, vs. > 3 pRBC: 585 (332–922) pmol/L; $P = 0.006$). This difference was no longer observed from 6 h of admission (no transfusion: 73 (184–53) pmol/L vs. 1–3 pRBC: 152 (48–304) pmol/L; $P = 0.4$, vs. > 3 pRBC: 119 (56–323) pmol/L; $P = 0.4$) (Fig. 1B).

Hemorrhagic shock severity

Norepinephrine concentration was statistically different between the three groups over the first 48 h with an interaction between time and groups (time x transfusion effect, $P = 0.004$). In the group of transfused patients with more than 3 pRBC, norepinephrine infusion was maximum at 12 h with an infusion rate of 0.5 (0.1–0.7) µg/kg/min whereas in the two other groups norepinephrine infusion was maximum at 6 h and decreased thereafter (Table 2) (Additional file 1A-B). Lactate was statistically different between the three groups over the first 48 h with an interaction between time and groups (time x transfusion effect, $P = 0.019$) (Additional file 1C-D). In the group of transfused patients with more than 3 pRBC, lactate remained higher than 2.0 mmol/L at 12 h for 53% of patients (Additional file 2). Though bleeding was controlled by 6 h and copeptin level decreased from 6 h after admission, norepinephrine requirement and lactate remained high, particularly in the severe hemorrhage group. Adjunctive AVP was not administered to any patient.

Glucocorticoid response

Cortisol measurements were obtained for 63 patients, 2 patients in the non-transfused group had no measurement because of technical issues. Cortisol concentrations were not statistically different between transfused and non-transfused patients or within 48 h of admission (transfusion effect; $P = 0.3$, time effect; $P = 0.6$, transfusion effect x time; $P = 0.09$). Cortisol concentration on admission was 208 (153–246) ng/ml in patients transfused with at least 1pRBC within the first 6 h of admission and 205 (113–280) ng/ml in non-transfused patients and

Table 1 Demographics and clinical characteristics in the overall cohort and in both transfused and non-transfused patients

	All	Non-transfused	Transfused[ε]
	n = 65	n = 37	n = 28
Characteristics			
Age—years	46 (20)	46 (21)	47 (21)
Women—n (%)	18 (28)	10 (27)	8 (29)
Hypertension	10 (16)	6 (17)	4 (14)
ACE inhibitor/ARB	4 (6.3)	2 (5.7)	2 (7.1)
Diuretics	5 (7.8)	1 (2.8)	4 (14)
Type of trauma—n (%)			
Blunt injury	63 (97)	36 (97)	27 (96)
Penetrating trauma	2 (3.1)	1 (2.7)	1 (3.6)
ISS	25 (7, 18–29)	25.0 (7, 20–29)	25.0 (7, 18–29)
AIS[ϕ] Head—n (%)	27 (42)	21 (57)	6 (21)
AIS Face – n (%)	1 (1.5)	0 (0)	1 (3.6)
AIS Chest—n (%)	33 (51)	20 (54)	13 (46)
AIS Abdomen—n (%)	15 (23)	3 (8.1)	12 (43)
AIS Pelvis—n (%)	24 (37)	10 (27)	14 (50)
AIS Extremities – n (%)	3 (4.7)	1 (2.8)	2 (7.1)
SAPS II	40 (16)	39 (14)	42 (18)
Prehospital			
Time from trauma to hospital admission—min	87.0 (49.4)	87.9 (51.2)	85.6 (47.9)
GCS	14 (9–15)	14 (6–15)	15 (13–15)
SBP—mmHg	103 (32)	102 (37)	105 (24)
HR—bpm	101 (28.9)	94 (30.1)	110 (24.8)
Intubation – n (%)	34 (52)	23 (62)	11 (39)
Fluids—ml	1000 [500–1250]	1000 [500–1255]	750 [500–1200]
Catecholamines—n (%)	17 (26)	9 (24)	8 (29)
Admission			
SBP—mmHg	118 (30)	125 (29)	109 (31)
HR—bpm	94.0 (23.1)	87 (18.8)	102 (26)
Hb—g/dl	11.8 (2.3)	12.9 (1.7)	10.3 (2.2)
Lactate – mmol/l	2.1 [1.4–3.7]	1.7 [1.3–3.0]	2.5 [2.0–5.4]
Catecholamines—n (%)	26 (40)	14 (38)	12 (67)
Creatininemia—µmol/min/1.73m^2	82.0 [61.0–108]	74.0 [59.0–98.0]	87.5 [70.0–111]
Outcomes			
Crystalloids administration H6 – ml	1750 [875–3438]	1000 [642–1902]	3125[1525–4000]
Transfusion of RBC in the first 6 h – number of pRBC	0 [0; 3]	0 [0; 0]	4 [2; 5]
Transfusion of RBC between 6 and 12 h – number of pRBC	0 [0–0]	0 [0–0]	0 [0–0]
Hemostatic procedure – n (%)	23 (35)	2 (5.4)	21 (75)
Etomidate°	37 (66)	22 (67)	15 (65)
Acute kidney injury			
KDIGO 1	11 (17)	5 (14)	6 (21)
KDIGO 2	6 (9.2)	4 (11)	2 (7.1)
KDIGO 3	3 (4.6)	1 (2.7)	2 (7.1)
Lenght of mechanical ventilation – days	3.0 [1.0–6.0]	3.0 [1.0–6.5]	2.0 [1.0–5.5]
In-hospital mortality – n (%)	14 (22)	10 (27)	4 (14)

Data are reported as mean (SD) or median [Q1-Q3]. [ε] Patient transfused with red blood cells over the first 6 h of admission. [#] Non-transfused patients were compared with transfused patients. * Two-sided level of significance was fixed at 5%

ACE angiotensin-converting enzyme. AIS abbreviated injury score. ARB angiotensin receptor blocker. GCS Glasgow Coma Scale. Hb hemoglobin. HR heart rate. H6 Over the first 6 h after admission. ISS injury severity score. KDIGO Kidney Disease: improving Global Outcome. MBP mean blood pressure. PT prothrombin time. pRBC packed red blood cells. SAPS Simplified Acute Physiology Score. SD standard deviation. SBP systolic blood pressure

AIS[ϕ] is the number of patients with an AIS > 2. Hemostatic procedure was defined as performing angioembolization or hemostatic surgery within the first six hours of management from admission. ° Injection of etomidate during the first 48 h of ICU hospitalization

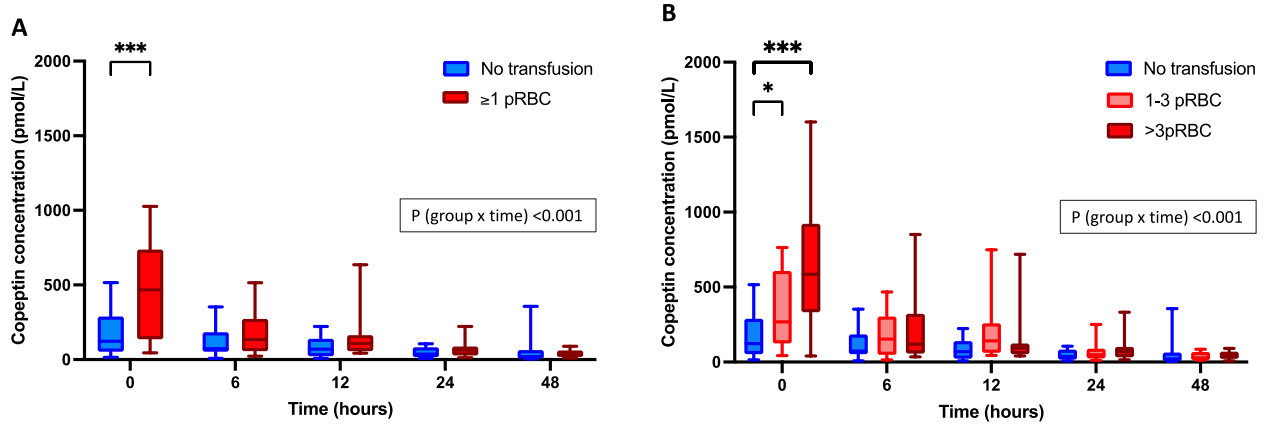

Fig. 1 Evolution of vasopressin secretion assessed by copeptin concentration over 48 h following severe trauma admission. **A** According to the presence or not of hemorrhage **B** According to hemorrhage severity (blue = no transfusion, pink = transfusion of 1–3 pRBC, red = transfusion of > 3 pRBC, in the 6 first hours of admission). Hemorrhage was defined as the transfusion of at least one pack of red blood cells (pRBC) during the first 6 h after admission. Comparison between groups at admission are presented. * indicates P < 0.05, ** indicates P < 0.01, *** indicates P < 0.001. All values are presented as the median, interquartile range and 10-90th percentile

Table 2 Norepinephrine requirement over the 48 h of ICU admission

Norepinephrine	No-transfusion	1–3 pRBC	> 3 pRBC
	n = 37	n = 13	n = 15
ICU admission—(µg/kg/min)	0 [0.0–0.19]	0 [0.0–0.43]	0.32 [0.0–0.69]
N (%)	13 (35)	7 (54)	9 (60)
6 h of admission—(µg/kg/min)	0.15 [0.0–0.39]	0.10 [0.0–0.32]	0.39 [0.21–1.04]
N (%)	24 (64)	7 (54)	13 (87)
12 h of admission—(µg/kg/min)	0.29 [0.0–0.49]	0 [0.0–0.14]	0.52 [0.12–0.71]
N (%)	19 (51)	5 (38)	14 (93)
24 h of admission—(µg/kg/min)	0 [0.0–0.24]	0 [0.0–0.0]	0.31 [0.0–0.82]
N (%)	13 (35)	3 (23)	9 (60)
48 h of admission—(µg/kg/min)	0 [0.0–0.10]	0 [0.0–0.0]	0 [0.0–0.16]
N (%)	10 (27)	2 (15)	5 (33)

Norepinephrine requirement is reported median [Q1-Q3] doses in (µg/kg/min) and number (percentage) of patients receiving the treatment at each time point. pRBC packed red blood cells

Table 3 Glucocorticoid and mineralocorticoid deficiencies over the first 48 h following ICU admission for trauma

	H0	H6	H12	H24	H48
Cortisol*	n = 63	n = 56	n = 50	n = 46	n = 27
< 100 ng/ml	7	11	3	5	5
100–250 ng/ml	38	31	31	27	12
Aldosterone/Renin ≤ 2°	n = 54	n = 49	n = 45	n = 41	n = 25
Overall population	27	33	31	31	17
Not transfused patients	15	19	16	15	8
Patients transfused 1–3 pRBC	6	6	7	6	3
Patients transfused > 3 pRBC	6	8	8	10	6

Data are reported as number of patients. n = represent the number of patients with available measurement of *cortisol or °renin and aldosterone.

remained stable over the 48 h of admission. (Additional file 3 A).

Twenty-two patients (35%) presented an absolute corticosteroid insufficiency with total plasma cortisol < 100ng/ml at least once within the first 48 h, 12 (35%) in the non-transfused group and 10 (36%) in the transfused group with no difference between group ($P = 0.9$). Fifty-five (87%) patients presented an altered corticosteroid response to stress with total plasma cortisol between 100 and 250 ng/ml at least once over the first 48 h, 28 (80%) in the non-transfused group and 27 (96%) in the transfused group. Evolution of insufficiencies over the 48 h is shown in Table 3. Etomidate use was not different between the two groups (22 (67%) vs.15 (65%) $P = 0.91$) (Table 1).

Minerolocorticoid response

Renin and aldosterone concentrations were obtained for 56 patients, 5 patients in the non-transfused group and 4 in the transfused group had no measurement at any time point due to technical issues or insufficient sample volumes. Evolution of renin concentration was statistically different over the 48 h of admission between non-transfused and transfused patients without interaction between time and groups (time effect, $P = 0.002$; transfusion effect, $P = 0.04$; time x transfusion effect, $P = 0.2$) (Additional file 3B). Renin was higher at admission in

transfused patients as compared to non-transfused patients (102 (59–254) pg/ml vs. (27 (11–82) pg/ml; $P=0.005$) and peaked in both groups at 12 h (158 (59–351) pg/ml vs. 58 (10–117) pg/ml). Regarding hemorrhage severity, evolution of renin concentration was statistically different over the 48 h of admission between the three groups with an interaction between time and groups (time effect, $P=0.001$; transfusion effect, $P=0.02$; time x transfusion effect, $P=0.04$). Renin concentration at admission was significantly greater in patients receiving > 3 pRBC (no transfusion: 22 (11–82) pg/ml vs. 1–3 pRBC: 87 (18–254) pg/ml; $P=0.5$, vs. > 3 pRBC: 103 (82–378) pg/ml; $P=0.005$) (Fig. 2B).

In the overall population, the median renin concentration at admission was 69.5 (17.4–122.7) pg/ml. Results were available for 54 patients which were dichotomized by median renin concentrations at admission (Additional file 4). Patients with high renin concentration presented more frequently with hemorrhage (6 (22%) vs. 17 (63%); $P<0.01$) and a higher severity of hemorrhagic shock, with higher proportion of patients requiring norepinephrine ($P=0.002$) and elevated blood lactate ≥ 2mmol/L ($P=0.002$) (Additional file 5). MD was also more frequent in this subgroup of patients (9 (33%) vs. 18 (67%); $P=0.01$) but, in-hospital mortality was lower (11 (41%) vs. 2 (7.4%); $P<0.01$).

Finally, over the 48 h period, in transfused patients, higher norepinephrine needs were associated with significantly higher renin level (Additional file 6).

Aldosterone concentrations were maximum on admission and decreased significantly over the 48 h of admission with a different evolution over the first 48 h between transfused and non-transfused patients with an interaction between time and groups (time effect, $P<0.001$; transfusion effect, $P=0.8$; time x transfusion effect, $P=0.02$) (Additional file 3 C). Similar results were found regarding hemorrhage severity (time effect, $P<0.001$; transfusion effect, $P=0.7$; time x transfusion effect, $P=0.08$) (Fig. 2C).

Relationship with AKI

Twenty patients (30%) presented an AKI during ICU stay following severe trauma; 11 (16.9%) patients experienced AKI KDIGO stage 1, 6 (9.2%) AKI KDIGO stage 2 and

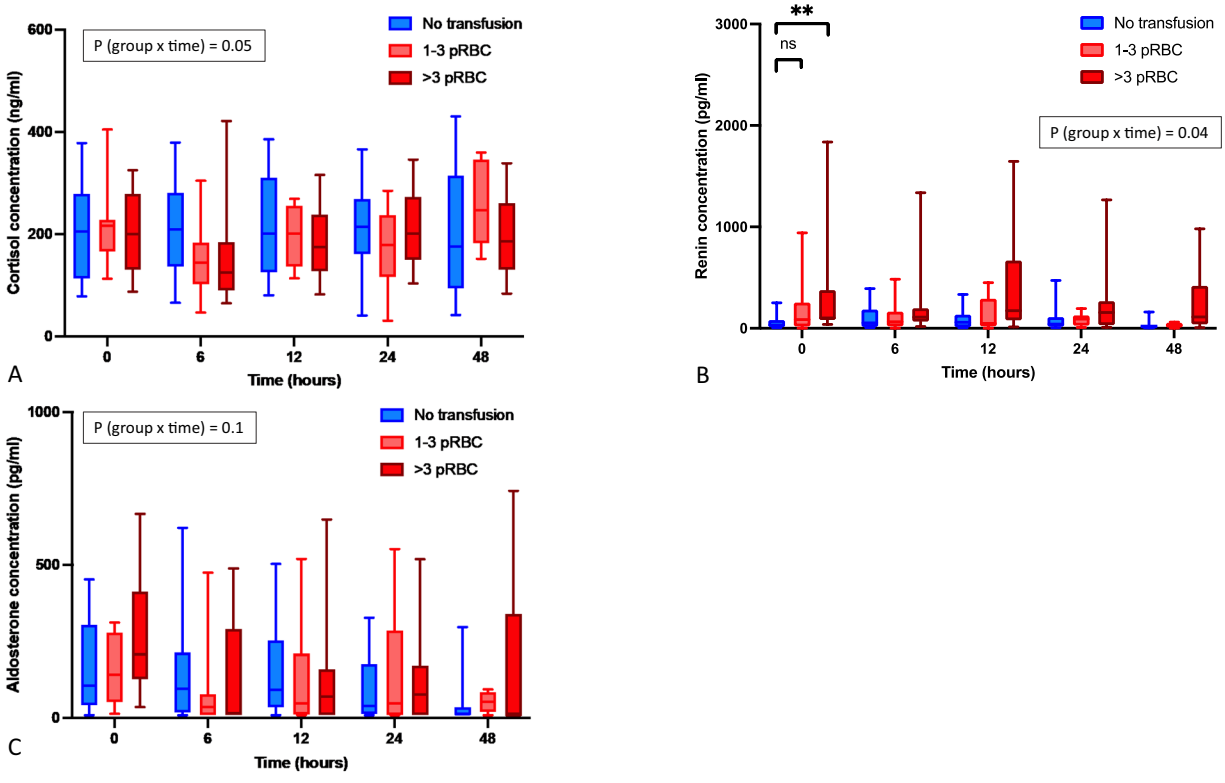

Fig. 2 Evolution over the first 48 h of admission according to hemorrhage severity of (**A**) Cortisol concentrations, (**B**) Renin concentrations and (**C**) Aldosterone concentrations (blue = no transfusion, pink = transfusion of 1–3 pRBC, red = transfusion of > 3 pRBC in the 6 first hours of admission). Comparison between groups at admission are presented. ns indicates P > 0.05, * indicates P < 0.05, ** indicates P < 0.01, *** indicates P < 0.001. All values are presented as median, interquartile range and 10-90th percentile. Over the 48 h of admission, up to 44 (78%) patients presented MD, 25 (78%) in the non-transfused group, 7 (64%) in the 1–3 pRBC group and 12 (92%) in the > 3pRBC group. Nineteen (34%) patients had MD at all the time measured and only 12 (22%) patients never presented it (Table 3). MD was more frequent between H6 and H24 of admission, particularly in transfused patients. Prevalence of MD was not different between the three groups of transfusion over the 48 h ($P=0.26$)

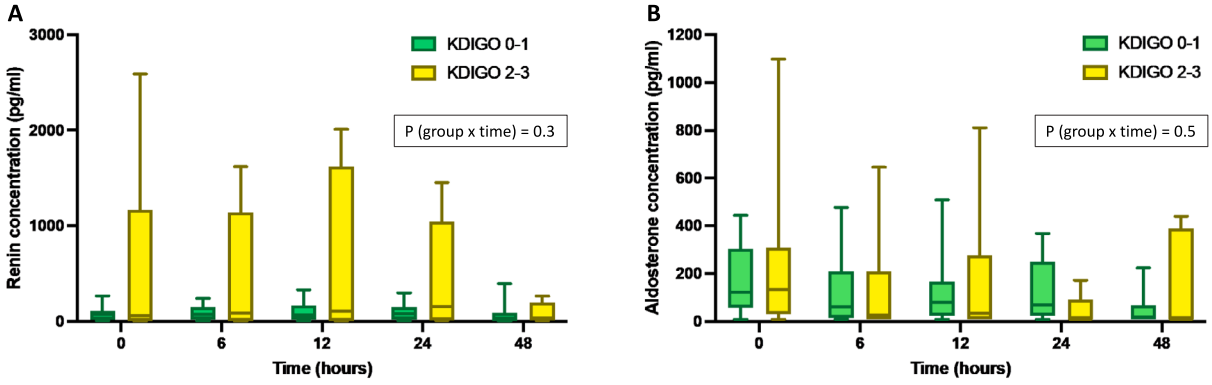

Fig. 3 Evolution of renin and aldosterone according to AKI status over 48 h following severe trauma admission. **A** Renin plasma concentration, **B** Aldosterone plasma concentration are shown in patients with normal to mild AKI (green) and with moderate-severe AKI (yellow). Normal to mild AKI was defined as KDIGO stage 0 or 1 and moderate-severe AKI was defined as KDIGO stage 2 or 3. AKI: Acute Kidney Injury. All values are presented as the median, interquartile range and 10-90th percentile

3 (4.6%) AKI KDIGO stage 3 without difference between transfused and non-transfused groups ($P=0.7$). Renin peaked at 24 h at 156 (12–1045) pg/ml in the moderate-severe AKI group vs. 81 (19–152) pg/ml in the normal to mild AKI group but concentrations were not statistically different between groups (time effect, $P=0.002$; AKI effect, $P=0.2$; time x AKI effect, $P=0.3$) (Fig. 3A). Aldosterone concentrations were not different between AKI groups (time effect, $P<0.001$; AKI effect, $P=0.5$; time x AKI effect, $P=0.5$) (Fig. 3B). There was no difference regarding MD prevalence between AKI groups ($P=0.7$).

Discussion

Key findings

This study explored hypothalamic-posterior-pituitary-vasopressin, hypothalamic–pituitary–adrenal axis and renin-angiotensin aldosterone system in severe trauma patients and reported results contributing to the understanding of the involvement of these neuro-hormonal pathways in response to hemorrhage. First, HPPV and RAAS responses are key hormonal pathways with sympathetic system activated in the 48 h following severe traumatic hemorrhage. AVP secretion is early at the onset of hemorrhage and associated with its severity, but its secretion is short-lived with a rapid decrease in the first few hours of shock despite persistent vasoplegia and need for catecholamine (i.e., norepinephrine) infusion, indicative of an insufficient response. Cortisol is early secreted following trauma stress, and although the response is often dysregulated, its concentration appears independent of hemorrhage. Finally, RAAS activation is delayed during the first 12 h after trauma, correlating with hemorrhage and shock severity but often shows high renin with inappropriately low aldosterone concentrations, indicative of mineralocorticoid deficiency.

Relationship to previous studies

Consistently with the literature, secretion of AVP is early but short-lasting. Indeed, it was higher at admission but decreased rapidly in the first 6 h of admission [7, 9, 10]. As compared with previous studies, we included only severely injured patients from which 43% developed hemorrhage with an original approach enabling the study of copeptin kinetics. We showed that AVP secretion after severe trauma increases with hemorrhage severity, with copeptin response closely reflecting the degree of bleeding. In a previous study, it was observed that copeptin was initially more elevated in patients presenting subsequently AVP secretion insufficiency compared to those who did not [7]. Interestingly, we observed that in the three levels of hemorrhage severity (i.e., no transfusion, 1–3 pRBC, >3 pRBC over the first 6 h of admission), copeptin dropped early and drastically between admission and 6 h of admission no matter the need for vasopressors (i.e., hemorrhagic shock), with no difference any more in copeptin concentration between the groups. Despite bleeding control, transfused patients, and particularly patients transfused with more than 3 pRBC required high dose of infused norepinephrine until 24 h of admission. Thus, copeptin kinetics in transfused patients suggest early depletion of posterior pituitary AVP stores and a limited ability to maintain high AVP levels during ongoing hypovolemic and distributive shock. This may reflect the exponential rise of AVP below a critical MAP threshold and the subsequent decline in secretion once hypovolemia is corrected, compounded by pituitary depletion. This could enhance refractory hypoperfusion CRVS and subsequent risk of MOF. Sims et al. showed that adjunctive low-dose AVP reduced transfusion requirement in patients undergoing massive transfusion for blunt trauma (≥6 unit of blood product) [28]. In our study, we identified hormonal pattern suggestive of AVP deficiency not only in patients meeting

criteria for severe hemorrhagic shock, but also in those with less pronounced hypoperfusion (i.e., lower transfusion needs and lower norepinephrine requirements) and in patients displaying CRVS, characterized by persistent high norepinephrine doses at 12 h of admission. Compared with Sims et al. data, our findings suggest that earlier use of exogenous AVP during trauma resuscitation may help a wider spectrum of patients. Further research is needed to determine which trauma populations would benefit most and define optimal timing and safety of AVP administration.

Regarding glucocorticoid response we observed a suppression of cortisol pulsatile secretion following trauma as reported in a previous study [10]. Critical illness-related corticosteroid insufficiency (CIRCI) has been mostly studied in septic shock patients [27, 29, 30]. Our study showed that HPA impairment should be considered and needs to be addressed in the context of trauma. Indeed, we found that 87% of the study population presented an altered corticosteroid response and 35% a deep corticoid insufficiency, confirming that as in other critical diseases, adrenal reserve is altered in these patients [12, 31]. However, we did not find any statistical difference of secretion over 48 h or difference of CIRCI incidence between transfusion groups (transfused vs non-transfused patients) and regarding hemorrhage severity (i.e., no transfusion, 1–3 pRBC, > 3 pRBC over the first 6 h of admission). This observation is likely explained by stress, rather than hypovolemia, being the main trigger of cortisol secretion. Non-transfused patients were also severely injured (ISS 25 (20–30)) adrenal response is frequently activated and impaired in such patients in the absence of shock [32–34]. Finally, there are complexes interactions between HPPV and HPA axis, because AVP activates ACTH secretion via the V1b receptor but during CIRCI it has been observed that AVP was released as a compensatory mechanism [26].

RAAS response is activated during 12 h following admission and renin level is all the more significant that hemorrhage is severe. In contrast, aldosterone secretion was not significantly associated with hemorrhage severity and appeared inappropriately low relative to renin from 6 h after admission in patients with severe hemorrhage and higher renin. RAAS dysfunction can also be assessed through MD defined by PA/PR < 2 as proposed in Tolstoy's study on hemorrhagic shock patients following penetrating injury [14]. Consistent with their findings, we confirmed a high prevalence of MD after severe trauma peaking between 6- and 24-h following admission particularly in patients with high admission plasma renin and with hemorrhagic shock. This may be due to differences in trauma patterns: most patients in our cohort had blunt trauma with varied injuries and shock etiologies (e.g., distributive traumatic shock, thoracic injury, neurological injury). Additionally, MD may reflect not only angiotensin II insufficiency but also inhibition of 11ß-hydroxylase (required for aldosterone synthesis) by etomidate used in 66% of patients in both transfused and non-transfused groups, mostly in the pre-hospital setting. As angiotensin II levels were not measured, the precise location of RAAS disturbance was not identified and could vary between groups [17, 35]. Interestingly, the evolution of norepinephrine requirements was similar to renin kinetic in the three groups described and particularly in patients transfused with > 3 pRBC who had high renin and high norepinephrine requirement (up to 0.52 µg/kg/min) between 12 and 24 h of admission despite bleeding control. Transfused patients with higher doses of norepinephrine (i.e., ≥ 0.2 µg/kg/min) had higher renin concentrations over the 48 h of admission. Concomitantly they presented the highest prevalence of MD. This supports a role for RAAS dysfunction in post-hemorrhagic circulatory failure, potentially related to trauma-induced endotheliopathy and impaired ACE activity [16]. Renin assessment could thus help clinicians to detect patients with CVRS who would benefit from angiotensin II treatment [16]. In addition, we found no association between mortality and high renin as described in other conditions like septic shock [35]. This may be explained by the fact that, in our cohort, patients with normal or low renin levels were those with severe TBI and poorer outcomes, as compared to patients with high renin levels who primarily experienced hemorrhagic shock. Finally, we did not identify clearly the link between the development of traumatic AKI and RAAS activation as observed in other settings [35–37]. We observed a trend toward higher renin in patients developing moderate to severe AKI but this difference did not reach statistical significance compared to those with normal or mild AKI. Also, AKI may have been underestimated as KDIGO staging was based solely on creatinine due to missing urine output data and as, an eGFR of 75 $ml.min^{-1}$ per 1.73 m^2 was assumed given the unknown baseline creatinine whereas this is a young and healthy population with probably better eGFR [38]. More studies are needed to better understand the exact role of RAAS in traumatic AKI and to identify the target population who would benefit from RAAS modulation therapy.

Implications of study findings

Our study suggests that AVP and RAAS pathways are strongly activated in the early physiological response to traumatic hemorrhage, with patterns suggesting secretion insufficiency in injured patients with severe hemorrhage and CRVS. Although patients were compared according to hemorrhage severity, lactate kinetics and early norepinephrine requirements further highlight the severity of the cohort and confirm that most patients in the hemorrhage group exhibited circulatory failure

consistent with the pathophysiological definitions of traumatic hemorrhagic shock. While AVP and angiotensin II have been recently emphasized for the management of CVRS in septic shock as adjuncts to norepinephrine [13, 39], our findings support the assessment of plasma copeptin and renin levels to guide personalized resuscitation in severe trauma. Moreover, it raises the possibility that some patients may benefit from early AVP administration during the initial hours of hemorrhagic shock, and from angiotensin II in the most severe cases and, at a later stage, in patients with persistent CRVS, to help restore vascular tone and limit MOF progression.

Strength and limitations

This study has several strengths. This is the first study evaluating the responses of the three neuro-hormonal pathways involved in vasopressor secretion following blunt trauma. Second, this is a large-scale study with repeated samples collected within the first 48 h of admission. Third, the study provides a rational on new potential strategies for vasopressor use in hemorrhagic shock.

The study has also limitations. First, we did not measure endogenous AVP or other vasoactive hormone such as catecholamines due to their instability post-sampling, preventing a comprehensive understanding of hormonal response to hemorrhage. Second, steroid and RAAS response could be completed by important biomarkers of these cascades. Indeed, angiotensin I, II, ACE and non-traditional RAAS pathway markers could have added to the understanding of RAAS disturbances. Third, initial copeptin levels may have been underestimated in the non-transfused group, which included more patients with traumatic brain injury and possible neurohypophysis injury, potentially affecting endogenous copeptin secretion [40]. Then, RAAS implication in traumatic AKI is not fully understood yet, however, the study is underpowered to get a representative group of patients developing AKI. Finally, because of the difficulties to have samples on these patients some of them were missing at certain time points.

Conclusion

The vasopressin and renin–angiotensin–aldosterone systems are key pathways in the response to hemorrhage following severe trauma, and their responses, wear thin with hemorrhage severity. This study reinforces the pathophysiological rationale for personalized vasopressor management in the resuscitation of traumatic hemorrhage by supplementing at the most appropriate time severe trauma patients with vasopressin and/or angiotensin II in addition to norepinephrine.

Abbreviations

AIS	Abbreviated injury score
AKI	Acute kidney injury
AVP	Arginine vasopressin
CIRCI	Critical illness-related corticosteroid insufficiency
CRVS	Catecholamine resistant vasodilatory shock
eGFR	Estimated glomerular filtration rate
ICU	Intensive care unit
ISS	Injury severity score
KDIGO	Kidney disease: improving global outcome
MOF	Multiple organ failure
pRBC	Packed red blood cells
RAAS	Renin–angiotensin–aldosterone system
SAPS II	Simplified acute physiology score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05782-0.

Additional file 1

Additional file 2

Additional file 3

Additional file 4

Additional file 5

Additional file 6

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Author contributions

Idea, design, data acquisition, analysis, writing of manuscript: MW Idea, design, data acquisition, analysis, critical review: AHa Design, hormonal measurements, analysis, critical review: EP Idea, design, critical review: BV, JD Data acquisition, critical review: HJ, BB, PEL, LW, AHu.

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Thermo Fisher Scientific® has provided ELISA kits for copeptin measurements.

Data availability

All information and data and scripts are available upon request with the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee ("Comité de Protection des Personnes") of Bicêtre' hospital (SC13-014 RCB: 2013-A01171-44) with waiver of participant consent following our national regulations.

Consent for publication

Not applicable.

Competing interests

MW reports honoraria from Edwards. AH reports honoraria from Laboratoire du Biomédicament Français, Edwards and Octapharma. The other authors declare that they have no competing interest.

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