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# Perturbations rénales chez le patient traumatisé crânien : approche physiopathologique

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**THÈSE**

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**Perturbations rénales chez le patient traumatisé crânien :  
Approche physiopathologique**

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## LISTE DES ABBRÉVIATIONS

ACSOS = Agressions cérébrales secondaires d'Origine Systémique

ACR = Augmentation de la Clairance Rénale

AKI = Acute Kidney Injury

ANP = Atrial Natriuretic Peptide (Peptide Natriurétique Atrial)

BNP = Brain Natriuretic Peptide

CL<sub>CR</sub> = Clairance de la créatinine

CL<sub>PAH</sub> = Clairance de l'acide p-aminohippurique

CSW = Cerebral Salt Wasting

DFG = Débit de Filtration Glomérulaire

DSR = Débit Sanguin Rénal

FEUrate = Fraction Excrétée d'Urate

FF = Fraction de Filtration

IL-6 = Inter-Leukine 6

IRM = Imagerie par Résonance Magnétique

MCP-1 = Monocyt Chemoattractant Protein

NGAL = Neutrophil Gelatinase-Associated Lipocalin

NO = Monoxyde d'azote

PIC = Pression Intracrânienne

RBP = Retinol Binding Protein

RFR = Réserve Fonctionnelle Rénale

SDRA = Syndrome de Détresse Respiratoire Aigüe

SIADH = Syndrome de Sécrétion Inappropriée d'Hormone Anti-Diurétique

SPS = Syndrome de Perte de Sel

SRIS = Syndrome de Réponse Inflammatoire Systémique

VEC = Volume Extra-Cellulaire



En Europe, le traumatisme crânien représente environ 260 cas /100 000 habitants/an (1). Celui-ci représente un enjeu sociétal majeur car il conduit à 15% de mortalité et 50 à 60% de handicap (2). Les patients cérébrolésés pris en charge en réanimation présentent fréquemment des perturbations de la fonction rénale, notamment une augmentation de la clairance rénale (ACR) ou un syndrome de perte en sel (SPS). Ces deux syndromes peuvent avoir des conséquences délétères sur le pronostic du patient. Cependant, la physiopathologie expliquant de telles perturbations reste peu explorée et méconnue.

### **1. Augmentation de la clairance rénale**

L'augmentation de la clairance rénale (ACR) correspond à un état supra-physiologique du débit de filtration glomérulaire (DFG), définie par une clairance de la créatinine supérieure à 130 ml/min/1,73m<sup>2</sup>(3). Admise par consensus, cette définition se base sur la limite supérieure du DFG normal variable en fonction du sexe, de l'ethnie et de la surface corporelle, estimée entre 120 et 130 ml/min/1,73m<sup>2</sup> (4). **Chez le patient traumatisé crânien, l'ACR a également été définie par un DFG supérieur à 150ml/min/1,73m<sup>2</sup> chez la femme et supérieur à 160ml/min/1,73m<sup>2</sup> chez l'homme (5). Udy Anest Analg 2010**

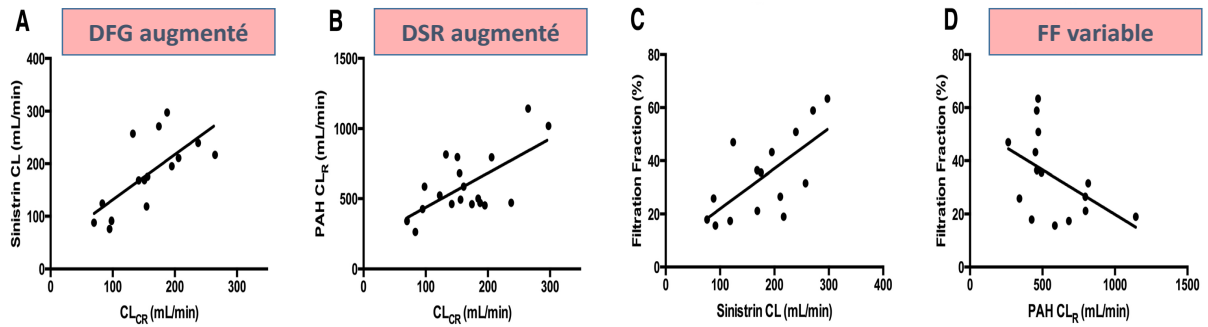
Des études observationnelles récentes montrent une grande variabilité d'incidence de l'ARC en réanimation polyvalente allant de 20 à 65% (6)(7). Celle-ci varie en fonction du motif d'admission ; les populations les plus à risque sont les patients polytraumatisés, les brûlés, les parturientes, les patients en post-opératoire d'une chirurgie majeure et dans certains cas le sepsis (8)(9)(10). En outre, l'incidence paraît encore plus importante chez les patients cérébrolésés, de 65 à 85% (11). Une incidence de 100% a même été décrite dans une population de 20 hémorragies sous arachnoïdiennes avec des clairances moyennes de 325ml/min/1,73m<sup>2</sup> (12).

L'ACR conduit à une augmentation de l'élimination des substances hydrophiles à élimination rénale, pouvant engendrer une diminution de leurs concentrations plasmatiques (12). Cette modification de la fonction rénale a été reconnue comme l'un des principaux facteurs de risque de sous dosage en  $\beta$ -lactamine (4)(13)(6). Dans ce contexte, une étude réalisée en réanimation chirurgicale retrouvait une association significative entre ARC, sous dosage en  $\beta$ -lactamine et échec thérapeutique (14). Dans une autre étude rétrospective utilisant le même protocole d'antibiothérapie, l'ACR était associé à un risque accru de récurrence de PAVM (OR = 4,4 [1,2-1,6] ;  $p = 0,03$ ). Ces échecs de traitement n'ont pas à ce jour d'effet démontré sur la mortalité (15).

A ce jour, les mécanismes physiopathologiques à l'origine de ce phénomène ne sont pas complètement élucidés. A notre connaissance, une seule étude s'est intéressée à la physiopathologie de l'ACR à l'aide de biomarqueurs rénaux chez 20 patients à risque (16). Les résultats de cette étude suggèrent :

- Une association significative entre clairance de la créatinine ( $CL_{CR}$ ) et clairance de la sinistrine, confirmant l'augmentation du DFG chez les patients en ACR (**Fig 1.A**).
- Une association significative entre  $CL_{CR}$  et clairance de l'acide p-aminohippurique ( $CL_{PAH}$ ), suggérant une augmentation du débit sanguin rénal (DSR) chez les patients en ACR (**Fig. 1.B**).
- D'importantes variations de la fraction de filtration pour une même valeur de  $CL_{PAH}$ , soulevant l'hypothèse d'une inhibition de la vasomotricité artériolaire rénale pour expliquer les changements de pression intra-glomérulaire (**Fig 1.D**)
- Cette étude retrouve en outre, une augmentation significative de la sécrétion tubulaire d'anions, bien que les mécanismes physiopathologiques de cette dysfonction tubulaire ne soient pas expliqués.

**Figure 1.** Exploration des mécanismes physiopathologiques à l'origine de l'ACR d'après Udy (16)



Les facteurs déclenchants restent à ce jour méconnus, bien que le rôle du syndrome inflammatoire systémique, des facteurs natriurétiques et de la réserve fonctionnelle rénale aient été évoqués.

- Le syndrome de réponse inflammatoire systémique (SRIS) est l'une des causes les plus fréquemment évoquées. Il pourrait être à l'origine d'une vasodilatation artériolaire et d'une augmentation du débit cardiaque (17)(18)(52).
- Certains auteurs ont également suggéré que l'augmentation des taux d'ANP pourrait participer à l'augmentation du DFG chez le traumatisé crânien, bien qu'une étude récente n'ait pas permis de retrouver de corrélation en CL<sub>CR</sub> et taux d'ANP plasmatique (19)
- Enfin, l'ACR est retrouvé dans certaines situations physiologiques comme la grossesse ou l'obésité. Un sujet sain ne solliciterait que 30 à 50% de ses capacités fonctionnelles rénales. La différence entre le DFG max et le DFG basal représente la réserve fonctionnelle rénale, cette RFR apparaît alors comme la capacité du rein à s'adapter afin de maintenir l'homéostasie (20)(21)

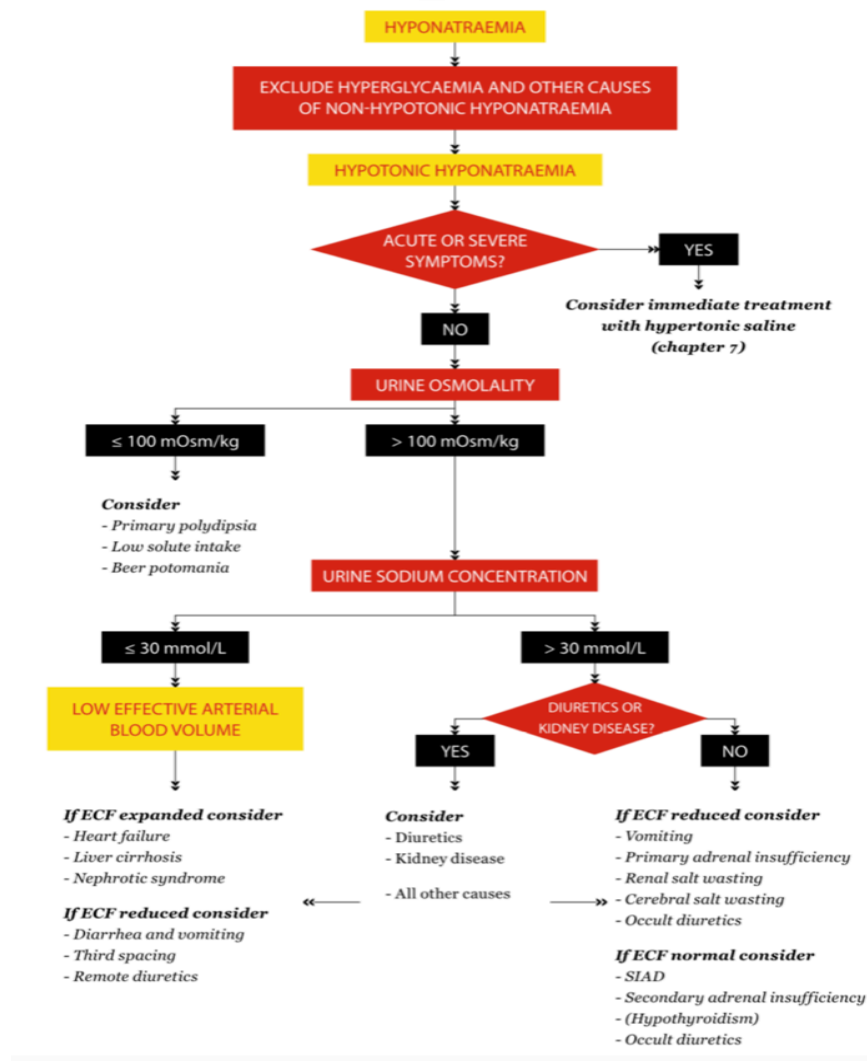
**Au total, l'ACR est une entité fréquente chez le traumatisé crânien, potentiellement responsable de sous-dosage en antibiotiques à élimination urinaire, entraînant un risque d'échec accru. Malgré cette forte incidence, la physiopathologie de l'hyperclairance rénale est mal connue. L'hypothèse d'une inhibition de la vasomotricité artériolaire, bien que probable, reste à confirmer.**



## 2. Hyponatrémie et « syndrome de perte de sel »

L'hyponatrémie est fréquente chez les patients cérébrolésés et son incidence varie entre 10 et 50 % (22-25). Elle constitue l'une des agressions cérébrales secondaires d'origine systémique (ACSOS) et pourrait avoir des conséquences délétères sur le pronostic (25-27). Chez les patients traumatisés crâniens, les étiologies principales des hyponatrémies sont la iatrogénie (mannitol, desmopressine ...), le syndrome de perte de sel (SPS) et le syndrome de Sécrétion Inappropriée d'Hormone Antidiurétique (SIADH) (23) (**Figure 2**).

**Figure 2.** Algorithme proposé par les recommandations européennes de 2014 pour le diagnostic étiologique d'une hyponatrémie (28)



Historiquement, le diagnostic de SPS a été soumis à de nombreuses controverses concernant son existence et sa prévalence, car possédant de critères diagnostiques non spécifiques, souvent communs avec le SIADH (29,30). Le diagnostic différentiel entre le SPS et le SIADH réside dans l'appréciation difficile du volume extracellulaire (**Tableau 1**). Le SPS se présente classiquement comme une perte rénale de sodium non expliquée par une pathologie endocrinienne, responsable d'une hyponatrémie hypo-osmolaire à volume extracellulaire diminué (31,32). L'incidence du SPS est variable entre 0,8% à 34,6% selon la définition utilisée (33).

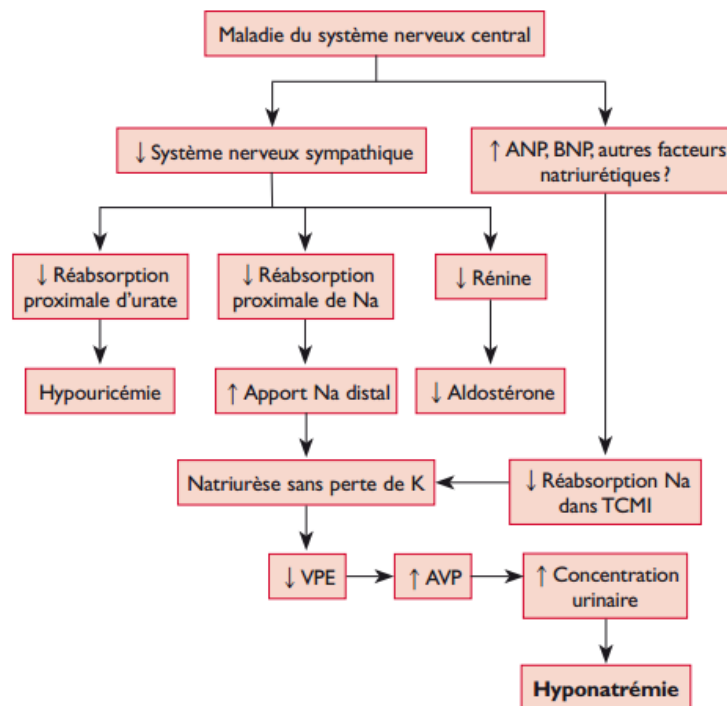
**Tableau 1. Diagnostic différentiel entre SIADH et SPS d'après Maesaka et coll. (31)**

Association with intracranial diseases
Hyponatremia
Concentrated urine
Urinary [Na] usually >30 mEq/l
Normal renal/adrenal/thyroid function
Nonedematous
Hypouricemia, increased FEurate
Only difference is volume status

La détermination du volume extracellulaire est donc d'une importance capitale mais son évaluation est reconnue comme inexacte selon les critères cliniques habituels (34). En utilisant des radio-isotopes, Audibert et coll. ont retrouvé une réduction significative du volume extracellulaire chez les patients atteints d'hémorragie sous-arachnoïdienne. La baisse du volume extracellulaire due à une perte rénale en sel pourrait être le mécanisme à l'origine d'une sécrétion en ADH malgré une baisse de l'osmolalité plasmatique (31) (35).

La physiopathologie du SPS demeure aujourd'hui encore hypothétique. Les deux mécanismes habituellement retenus et responsables de la perte rénale de sodium sont, d'une part, l'activation inappropriée du système des peptides natriurétiques et, d'autre part, la diminution de la stimulation sympathique rénale (**Figure 3**) (29) (36). Cette théorie reste cependant très controversée, d'autres mécanismes également évoqués dans la littérature impliqueraient une natriurèse de pression (via une hyperadrénergique ou l'administration de catécholamines) (35) et un hypoaldostéronisme secondaire (34). Certains auteurs ont également défini le SPS par la persistance d'une Fraction excrétée d'urate > 11% après correction de l'hyponatrémie, évoquant la possibilité d'un trouble de la réabsorption tubulaire proximale comme origine possible à cette perturbation (31).

**Figure 3. Physiopathologie du syndrome de perte en sel d'origine cérébrale, d'après Deslarzes et coll. [29]**



ANP: atrial natriuretic peptide; AVP: arginine vasopressine; BNP: brain natriuretic peptide; K: potassium; Na: sodium; TCMI: tubule collecteur médullaire interne; VPE: volume plasmatique efficace.

Le diagnostic étiologique d'une hyponatrémie est indispensable pour guider la prise en charge thérapeutique :

- Le SPS nécessite la correction de la volémie et la perfusion de soluté hypertoniques. En effet, la perfusion de solutés hypo- ou isotoniques (dont l'osmolarité est inférieure à celle de l'urine) entraîne une rétention d'eau libre via la sécrétion d'ADH et favorise l'hyponatrémie(28). Ce phénomène est décrit comme le « dessalement » ou *dessalation*, où le sodium et le chlorure apportés sont excrétés sous forme d'osmoles tandis que l'eau exempte de sodium est réabsorbée grâce à l'action de l'ADH au niveau du tube collecteur (45).
- L'administration orale d'urée (15-30 g par jour) est une stratégie alternative efficace pour corriger l'hyponatrémie dans le SIADH qui peut être envisagée chez les patients moins graves ou comme traitement de deuxième ligne (46). Cependant, la diurèse osmotique se produit en second lieu avec une perte d'eau libre sans électrolyte conduisant à une augmentation de la concentration de sodium sérique (c'est-à-dire que plus l'osmolarité de l'urine est faible, plus la perte d'eau libre sans électrolytes et l'augmentation du sodium sérique seront élevées), ce qui la rend inappropriée dans le SPS (32).
- Pour finir, la fludrocortisone est souvent utilisée pour traiter les hyponatrémies des patients présentant un syndrome de perte de sel. La fludrocortisone a une action minéralo-corticoïde prédominante, « *aldosteron-like* ». Elle va augmenter la réabsorption distale du sodium et favoriser l'excrétion du potassium. Une récente étude randomisée contrôlée a été réalisée chez des patients présentant un syndrome de perte de sel avec hyponatrémie. Chez ces patients atteints de méningite tuberculeuse, l'administration de fludrocortisone permettait de corriger plus rapidement l'hyponatrémie, avec une augmentation des épisodes d'hypokaliémies sévères et d'hypertension artérielle (47).

**Au total, le SPS est désormais une cause reconnue d'hyponatrémie chez le cérébrolésé, justifiant un traitement spécifique urgent. La compréhension des mécanismes physiopathologiques pourrait orienter une prise en charge plus spécifique, notamment pour le diagnostic, la prévention et/ou le suivi du SPS.**

### 3. Problématiques et hypothèses

Les perturbations de la fonction rénale sont fréquentes chez le patient traumatisé crânien, et potentiellement responsables d'effets délétères. De manière étonnante, les mécanismes physiopathologiques responsables de ces perturbations ne sont pas démontrés et restent peu explorés. Or la compréhension des mécanismes physiopathologiques est un prérequis indispensable pour le diagnostic, la prévention et la prise en charge des patients de réanimation.

**Ce travail a donc pour objectif principal d'explorer les mécanismes physiopathologiques des perturbations de la fonction rénale (augmentation de la clairance rénale et syndrome de perte en sel) chez le patient traumatisé crânien en utilisant des marqueurs accessibles en pratique clinique.**

#### **Plusieurs hypothèses de travail ont été élaborées :**

1. L'inhibition de la vasomotricité artériolaire serait le mécanisme principal de l'ACR chez le patient de traumatologie. La perte d'autorégulation rendrait le DSR et le DFG dépendant des changements hémodynamiques systémiques.
2. L'hyponatrémie chez le cérébrolésé serait la conséquence d'un bilan sodé négatif dans le cadre d'une natriurèse inadaptée. L'augmentation de la clairance rénale pourrait être un mécanisme explicatif à une natriurèse accrue. Une étiologie tubulaire pourrait être explorée par le biais de la fraction excrétée d'urate.

Dans cette optique, nous avons créé une base de données chez tous les patients polytraumatisés et traumatisés crâniens admis en réanimation chirurgicale au cours d'une période de 6 mois. Tous les patients bénéficiaient d'un ionogramme urinaire quotidien. Les données cliniques, biologiques et échographiques collectées au cours des 7 premiers jours du séjour étaient reportées **Tableau 2**. Le calcul de l'apport en sodium intraveineux ou per os a été réalisé chez tous nos patients de façon quotidienne (**Tableau 3**). Nous avons estimé que l'absorption du sodium était complète et nous avons négligé les pertes sodées autres qu'urinaires (digestives et insensibles comme la sueur et les larmes).

**Tableau 2. Recueil des données cliniques et paracliniques au cours du temps (en jour).**

	Jour 1	Jour 2	Jour 3	Jour 4	Jour 5	Jour 6	Jour 7
Poids							
Apports hydriques (ml/24h)							
Balance hydrique (ml/24h)							
Apports sodés (mmol/24h)							
Balance sodée (mmol/24h)							
Créatinine plasmatique (µmol/L)							
Natrémie (mmol/L)							
Kaliémie (mmol/L)							
Phosphate (mmol/L)							
Glycémie (mmol/L)							
Urée plasmatique (mmol/L)							
Hématocrite (%)							
Protidémie (g/L)							
Acide urique (mmol/L)							
Osmolarité plasmatique (mmol/L)							
Diurèse (ml/24h)							
Créatininurie (mmol/L)							
Urée urinaire (mmol/L)							
Urate urinaire (mmol/L)							
Phosphaturie (mmol/L)							
Natriurèse (mmol/L)							
Glycosurie (mmol/l)							
Kaliurèse (mmol/L)							
Chlore urinaire (mmol/L)							
FeNa (%)							
FeUrée (%)							
FeUrate (%)							
FePhosphate (%)							
Osmolarité urinaire (mmol/24h)							
Osmolarité urinaire (mmol/L)							
Clairance de l'eau libre							
CrCL mesurée (ml/min)							
Ventilation mécanique (1/0)							
Sédation (MDZ/PROPO)							
Noradrénaline (1/0)							
Noradrénaline (moyenne/24h, en µg/kg/min)							
Inotrope (1/0)							
Mannitol (1/0)							
HSHC (1/0)							
AINS (1/0)							
IEC (1/0)							
Fludrocortisone (1/0)							
Urée (1/0)							
Acétazolamide (1/0)							
Diurétiques de l'anse (1/0)							
PAM moyennée (mmHg)							
FC moyennées (bpm)							
ITV sous-aortique (ETT)							
Débit cardiaque (ETT)							
Index de résistivité rénal (échographie rénale)							
BNP (pg/ml)							
Aldostérone (pmol/L)							
Cortisol (noml/L)							
TSH (UI/L)							

**Tableau 3. Calcul apport sodé quotidien**

Par jour	Na (mmol/unité)	0-6	6-12	12-18	18-24	Total	Bilan hydrique (ml/24h)	Bilan sodé (mmol/24h)
<b>Réhydratation (ml)</b>								
<b>Remplissage (ml)</b>								
<i>NaCl 0,9% (par ml)</i>	0,15							
<i>Isofundine (par ml)</i>	0,15							
<i>Albumine (4 ou 20%)</i>	0,15							
<i>Ringer (par ml)</i>	0,13							
<i>PG5 (par ml)</i>	0,07							
<i>Bicarbonates 4,2%</i>	0,50							
<i>Bicarbonates 1,4%</i>	0,17							
<i>Dextrion</i>	0,03							
<i>Parentérale (par ml)</i>	0,04							
<b>Per os (ml)</b>								
<i>Nutrison (par ml)</i>	0,04							
<b>SE (ml)</b>								
<b>IV (ml)</b>								
<i>NaCl 10% (par ml)</i>	1,71							
<i>NaCl 3% (par ml)</i>	0,51							
<i>SE dilués (par ml de NaCl 0,9%)</i>	0,15							
<i>IV dilués (par ml de NaCl 0,9%)</i>	0,15							
<i>Thiopental (par flacon de 1g)</i>	4,60							
<i>Amoxicilline / Augmentin (par flacon de 2g)</i>	5,48							
<i>Céfazoline (par flacon de 2g)</i>	4,40							
<i>Ceftriaxone (par flacon de 2g)</i>	7,20							
<i>Cefotaxime (par flacon de 2g)</i>	4,20							
<i>Pipéracilline ± Tazobactam (par flacon de 4g)</i>	11,35							
<i>Ceftazidime (par flacon de 2g)</i>	4,50							
<i>Méropéném (par flacon de 2g)</i>	7,80							
<i>Ciprofloxacine (par poche de 200mg/100ml)</i>	30,80							
<i>Lévofloxacine (par poche de 500mg/100ml)</i>	15,80							
<i>Linézolide (par poche de 600mg/300ml)</i>	4,95							
<i>Métronidazole (par poche de 500mg/100ml)</i>	14,76							
<i>Lévétyracétam (par flacon de 500 mg)</i>	0,80							
<i>Paracétamol (par poche de 1g/100ml)</i>	0,17							
<b>TOTAL</b>								

**Augmented renal clearance in critically ill trauma patients:  
a pathophysiologic approach using renal vascular index.**

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## ABSTRACT

**BACKGROUND:** In critically ill trauma patients, augmented renal clearance (ARC) is common and may result in subtherapeutic antibiotic exposure. The aim of the present study was to explore the relationship between creatinine clearance ( $Cr_{CL}$ ), cardiac output (CO) and renal Doppler vascular index (RVI) in order to assess the potential mechanisms driving ARC in this population.

**METHODS:** This study involves a retrospective review of a prospectively collected database of every trauma patients consecutively admitted to a 25-bed Surgical and Trauma Intensive Care Unit (ICU) over a 3-month period. Were included every trauma patients who underwent cardiac and renal ultrasound measurements over three consecutive days during their initial ICU management. ARC was defined by a 24-hr urinary measured  $Cr_{CL} > 130$  ml/min

**RESULTS:** Thirty patients, contributing for 86 coupled physiologic data, were retrospectively analyzed. There was an inverse correlation between  $Cr_{CL}$  and RVI values ( $\rho = -0.501$ ;  $p < 0.0001$ ). The best threshold value for RVI to predict ARC was 0.65 (sensitivity 76% [62 – 86]; specificity 72% [56 - 84]). There was only a slight correlation between  $Cr_{CL}$  and CO values ( $\rho = 0.219$ ;  $p = 0.05$ ). There was no statistical correlation between RVI and MAP ( $\rho = -0.09$ ;  $p = 0.41$ ), whether in patients with or without ARC.

**CONCLUSION:** The combination of an inhibition of arteriolar vascular tone coupled with an increased cardiac output in patients with a greater physiological reserve should be accepted as the leading mechanism for ARC.

**KEY WORD:** Augmented renal clearance; Renal vascular index; Renal ultrasound; Trauma; Critical illness

## BACKGROUND

For several years, augmented renal clearance (ARC) has been increasingly investigated in critical care practice, currently defined by an increased urinary creatinine clearance ( $Cr_{CL}$ ) exceeding 130 mL/min/1.73m<sup>2</sup> [1]. ARC has been reported in approximately 30-65% of patients during the first week in the intensive care unit [2]. At-risk populations of ARC included those with sepsis, burns, major trauma and brain injury [3, 4]. This is a major concern as ARC has been recognized as one of the leading causes of subtherapeutic antibiotic exposure, potentially responsible for poor clinical outcome in septic patients [4-9].

The pathophysiologic mechanisms responsible for ARC in critically ill patients remain mainly unknown, although alterations in both glomerular filtration and renal tubular function have been observed [10]. The most widespread theory involves an increase in cardiac output, resulting in an increased renal blood flow (RBF) and therefore an increased glomerular filtration rate (GFR) [11]. However, most trials failed to establish a significant relationship between cardiac index and ARC, suggesting that the underlying mechanisms are likely more complex [1]. Other authors thus hypothesized that changes in vasomotor tone and intra-glomerular filtration pressure were potentially the main mechanism underlying ARC in critically ill patients [10].

Renal Doppler vascular index (RVI) has been used to reflect regulation of renal vascular tone in the critical care settings [12, 13]. A recent meta-analysis suggested that abnormally high RVI was associated with further renal impairment in septic critically ill patients [14]. In addition, RVI seems to be of interest in evaluating changes in renal perfusion as a consequence of therapeutic interventions [15-17]. The ability of RVI to monitor renal perfusion remains, however, questionable and still needs to be demonstrated [18].

The main objective of this study was thus to investigate the relationship between 24-hr urinary creatinine clearance ( $Cr_{CL}$ ), renal Doppler vascular index (RVI) and cardiac output (CO) in critically ill trauma patients. We hypothesized that ARC should be driven by an inhibition of arteriolar tone responsible for a loss of renal autoregulation, RBF and GFR becoming dependent of changes in systemic hemodynamics.

## **METHODS**

### **1. Design, population and settings**

This study is a retrospective analysis of our local database (declared to the French Data Protection Authority: declaration number 2166637v0) prospectively collected in a 25-bed Surgical and Trauma Intensive Care Unit (ICU) over a 3-month period (May to July 2018). Ethical approval for this analysis was obtained from the Ethics Committee of the French Society of Anesthesiology and Intensive Care (IRB number: CERAR 00010254-2018-089). The patients and/or next of kin were informed about the inclusion of their anonymized health data in the database, and none declined participation.

During the study period, every trauma patients who underwent cardiac and renal ultrasound over three consecutive days during their initial ICU management were included. Indications for performing the ultrasound measurements were at the discretion of the attending physician. Non-inclusion criteria were pregnancy, age < 18 years, end-stage renal failure or indication for renal replacement therapy, known renal artery stenosis, cirrhosis, congestive heart failure, atrial fibrillation or arrhythmia.

## 2. Data collection and ultrasound measurements

Our local database includes daily metabolic, hemodynamic and ultrasound measurements prospectively collected as part of a standard care in every trauma patient. Serum creatinine was measured using a standardized enzymatic method with Isotope Dilution Mass Spectrometry (IDMS). Measured  $Cr_{CL}$  was calculated as follows: 24-hr urinary volume (ml/day) x urinary creatinine (mmol/L) / plasma creatinine ( $\mu$ mol/L), converted in ml/min. Excretion fraction of sodium ( $FE_{Na}$ ) was calculated as follows: (urinary sodium [mmol/L] x plasma creatinine [ $\mu$ mol/L]) / (urinary creatinine [mmol/L] x Natremia [mmol/L]). For data analysis, ARC was defined by a measured  $Cr_{CL} > 130$  ml/min. For population analysis, patients were considered in ARC when the mean  $Cr_{CL}$  was above 130 ml/min over the three consecutive days.

All cardiac and renal ultrasound measurements were performed using a General Electric Vivid S6 machine (GE Healthcare, Wauwatosa, WI, USA) by an experienced physician unaware of the measured  $Cr_{CL}$ . As previously described, renal Doppler vascular index was obtained from the most representative proximal interlobar arteries [19]. The peak systolic velocity ( $V_{max}$ ) and the minimal diastolic velocity ( $V_{min}$ ) were determined by pulse wave Doppler, and RVI was calculated as  $(V_{max} - V_{min})/V_{max}$ . The results from three consecutive similar-appearing waveforms were averaged for each kidney (**Supplementary Data**). Using echocardiography, stroke volume (SV) was calculated as the product of the aortic valve area ( $\pi/\text{diameter}^2/4$ ) by the area under the envelope of the pulsed-wave Doppler measured at the aortic annulus and averaged over three consecutive measurements. Cardiac output was calculated as the product of heart rate (HR) and stroke volume.

The intra-observer and interobserver reproducibility of VTI and RI measurements were assessed in ten patients before the study. Intra-observer variability coefficient was  $5 \pm 3\%$  for RVI and  $4 \pm 3\%$  for VTI. Inter-observer variability was  $4 \pm 3\%$  for RVI and  $4 \pm 4\%$  for VTI. The least significant change was 9.8 for RVI and 7.8 for VTI.

### 3. Statistical analysis

Results are expressed as mean  $\pm$  standard deviation or median (25% to 75% interquartile range) for continuous variables and as numbers (percentages) for categorical variables. The data distribution was analyzed by a Kolmogorov-Smirnov test. Comparisons between continuous variables were performed using the Student *t* test or the Mann–Whitney test and categorical variables were compared using the chi-square test or Fisher’s exact test as appropriate.

Relationships between RVI, CO and Cr<sub>CL</sub> were assessed using Spearman’s correlation coefficient and differences over time were assessed by repeated-measures ANOVA procedure. The reliability of each variable was estimated by intraclass correlation coefficients. The accuracy of RVI and CO to predict ARC was assessed using a receiving operator curve (ROC) analysis. The best threshold values were chosen to maximize Youden index. These thresholds were subsequently adopted to define higher and lower RVI and CO values. Finally, the correlation between RVI and MAP was assessed to estimate renal autoregulation using logistic regression procedure [13, 20].

A *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2017 for Windows (Addinsoft Paris, France).

## RESULTS

### 1. Population

During the study period, 63 trauma patients were admitted for multiple trauma, brain trauma or both. Only thirty patients met the inclusion criteria (lack of ultrasound data over 3 consecutive days, N = 30; end-stage renal failure or indication for renal replacement therapy, N = 3). Most of them were included the first day of ICU admission (73%); others were included the second (17%) or the third day (10%) of ICU admission. The characteristics of the population are resumed **Table 1**. Over the three consecutive days, 18 patients (60%) presented ARC (mean  $Cr_{CL} > 130$  ml/min) and 4 (13%) presented renal failure (mean  $Cr_{CL} < 60$  ml/min).

Finally, 86 coupled data of  $Cr_{CL}$ , RVI and CO were analysed (missing  $Cr_{CL}$  value in 4 patients). Representation of  $Cr_{CL}$ , RVI and CO over time is showed in **Figure 1**. The intra-patient variability coefficients were  $15 \pm 10\%$  for  $Cr_{CL}$ ,  $6 \pm 4\%$  for RVI and  $19 \pm 9\%$  for CO without significant difference over the three consecutive days. The intraclass correlation coefficients were 0.93 [0.87 – 0.97] for  $Cr_{CL}$ , 0.83 [0.68 – 0.92] for RVI and 0.51 [0.06 – 0.76] for CO.

## 2. Relationship between Cr<sub>CL</sub>, RI and systemic hemodynamic data

Mean values for Cr<sub>CL</sub> was  $139 \pm 56$  ml/min over the three consecutive days, and ARC was found in 52/86 urinary samples (60%). There was an inverse correlation between Cr<sub>CL</sub> and RVI values ( $r = -0.501$ ;  $p < 0.0001$ ). There was only a weak correlation between Cr<sub>CL</sub> and CO values ( $r = 0.219$ ;  $p = 0.05$ ) (**Figure 2**). There was no statistical correlation between Cr<sub>CL</sub> and MAP values or norepinephrine dosages.

The best threshold values for RVI and CO to predict ARC were respectively 0.65 (sensitivity 76% [62 – 86]; specificity 72% [56 - 84]) and 5.5 L/min (sensitivity 44% [32 – 58]; specificity 80% [64 - 90]). Those values were used to define lower and higher values for both CI and RVI measurements. The ROC curves (0.74 [0.64 – 0.84],  $p < 0.001$  and 0.6 [0.48 – 0.72],  $p = 0.106$  respectively) are displayed in **Figure 3**. Representation of Cr<sub>CL</sub> measurements according to various values of CO and RVI is depicted **Figure 4**. Percentages of ARC according to various values of RVI and CO are depicted in **Supplementary Data**.

We found no statistical correlation between RVI and MAP ( $r = -0.09$ ;  $p = 0.41$ ), whether in patients with or without ARC. For a given MAP, lower RVI values were observed in ARC patients (**Supplementary data**). There was no relationship between RVI and norepinephrine dose.

## DISCUSSION

In critically ill patients, augmented renal clearance is common and may result in subtherapeutic antibiotic exposure when standard dosing regimens are used [1-9]. On the other hand, evidence regarding the pathophysiological mechanism underlying ARC is uncommon, and the hypothesis put forward to date remain to be confirmed.

Our results suggested an inverse correlation between RVI and  $Cr_{CL}$  in critically ill trauma patients without renal impairment. The weak but statistical association between CO and  $Cr_{CL}$  suggested that increased cardiac output is not the main mechanism responsible for ARC. In another physiological study using exogenous markers of renal function in 20 critically ill patients with ARC, Udy et al. observed a strong correlation between  $Cr_C$ , Sinistrin clearance and PAH clearance, demonstrating elevated glomerular filtration and high renal plasma flow in ARC patients [10]. On the other hand, considerable variations in filtration fraction, supporting the hypothesis that changes in intra-glomerular filtration pressure were probably the key mechanism underlying ARC in critically ill patients. In agreement with these data, we can assume that 1) lower RVI for a given MAP should reflect the inhibition of arteriolar tone responsible for ARC in critically ill patients; 2) the sustained vasodilatation may contribute to kidney autoregulation impairment, 3) RBF and GFR becoming dependent of changes in systemic hemodynamics.

Nevertheless, we observed a considerable overlap in RVI and CO values between patients with or without ARC, suggesting a significant inter-individual variability. Under normal conditions, renal functional reserve reflects the ability of the kidney to respond to an increased physiological demand through a combination of nephron recruitment, increase in renal blood flow and/or glomerular hyperfiltration [21]. Renal functional reserve seems to be significantly lower in the elderly than in young and healthy individuals, potentially explaining the demographic characteristics of ARC patients [1]. Moreover, the key mechanism leading to this reduced arteriolar tone remains unknown. Trauma, sepsis and systemic inflammation may result in afferent vasodilation and increased renal blood flow [22, 23]. In brain damaged patients, the implication of a specific plasma mediator of a “brain-kidney” crosstalk remains an attractive theory. In this context, experimental data have suggested a right shift of cerebral autoregulation curve after inhibition of NO synthesis



[24]. Although speculative, the role of natriuretic factors, endothelin and relaxin has also been advocated [11, 25, 26]. Further studies are needed to explore the association between cerebral reactivity and renal autoregulation in this specific population at risk for ARC [27].

The aim of our work was to study the possible involvement of renal vascular tone (studied using Doppler vascular index) in ARC physiopathology in critically ill patients. We did not use RVI as a screening marker for ARC, the considerable overlap between patients with and without ARC precluding the use of this index in daily practice. Indeed, determinants of RVI are multiple, including renal vascular resistances (RVR) and compliance, renal interstitial pressure, ureteral pressure or systemic arterial pressure [28]. Although RVI is not a valuable reflect of renal blood flow, Lerolle et al. previously demonstrated a negative relationship between MAP and RVI, without correlation with the dose of norepinephrine. Higher RVI values were observed in patients with acute kidney injury, consistent with the physiological increase in RVR in hypoperfusion situations [13]. This assessment was however challenged by Dewitte et al. in which such a relationship was only observed in patients without persistent AKI, suggesting that RVI could only reflect renal autoregulation before the occurrence of renal vascular or tubular damage [20]. The statistical association between  $Cr_{CL}$ , RVI and MAP was not observed in the current study, although ARC patients displayed lower RVI for a given MAP, suggesting a shift in renal autoregulation.

The current study has some limitations. First, the design was monocentric with a retrospective analysis over a relatively short period (3 months), which limits the generalizability of the results. Moreover, we included only trauma patients who underwent at least three consecutive renal and cardiac ultrasound measurements, which excluded half of the patients admitted over the period. However, ultrasound measurements were standardized, prospectively collected and blinded for  $Cr_{CL}$  values. Moreover, we acknowledge a limited number of patients, although contributing for numerous physiologic data without statistical differences over time using repeated-measures ANOVA procedure. Third, RVI, MAP and CO levels were measured once per day whereas  $Cr_{CL}$  was recorded from the 24-hr urinary samples. As those parameters may vary widely over 24h in ICU patients, it is uncertain that  $Cr_{CL}$  data correspond to the actual  $Cr_{CL}$  at the time of other physiologic parameters measurements. This limitation could explain the poor correlation between CO and 24-hr  $Cr_{CL}$  when compared to other studies assessing continuous CO measurements [11]. The day of inclusion is also heterogeneous, which

could be a limiting factor if we consider that the hyperkinetic phase at risk of ARC occurs mainly in the initial phase. Finally, 24-hr measured  $Cr_{CL}$  is known to overestimate glomerular filtration rate and RVI is far from being the most valuable marker of renal vascular resistance or plasma renal flow [18, 21]. On the other hand, the clinical evaluation of renal autoregulation is restricted because of the lack of non-invasive RBF assessment at the bedside [27]. Standardized and valuable measurements of GFR and RPF by exogenous markers, contrast-enhanced ultrasound and/or magnetic resonance imaging might be necessary to corroborate the hypothesis pertaining to this study.

## **CONCLUSION**

Increased cardiac output is not the main mechanism responsible for ARC. The combination of an inhibition of arteriolar vascular tone coupled with an increased renal blood flow in patients with a greater physiological reserve should be accepted as the leading mechanism for ARC. Further studies are though necessary to comfort this hypothesis.

## LIST OF ABBREVIATIONS

- ARC = augmented renal clearance
- CO = cardiac output
- $Cr_{CL}$  = creatinine clearance
- GFR = glomerular filtration rate
- HR = heart rate
- ICU = Intensive Care Unit
- RBF = renal blood flow
- RVI = renal vascular index
- ROC = receiving operator curve
- SV = stroke volume
- $V_{max}$  = peak systolic velocity
- $V_{min}$  = minimal diastolic velocity

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## TABLES AND FIGURES LEGEND

**Table 1:** Characteristics of the population

**Figure 1:** Variations of creatinine clearance  $Cr_{CL}$  (ml/min), cardiac output CO (L/min) and renal Doppler vascular index RVI over three consecutive days in 30 critically ill trauma patients.

**Figure 2:** Relationship between creatinine clearance  $Cr_{CL}$  (ml/min) and (A) renal Doppler resistivity index RVI or (B) Cardiac Output CO (L/min) and (C) Mean Arterial Pressure (MAP) in 88 pooled physiologic data over three consecutive ICU-days.

**Figure 3:** Receiver operating characteristic (ROC) showing the ability of resistivity index (continuous line; area under the curve = 0.74 [0.64 – 0.84],  $p < 0.001$ ; best cut-off value  $RI \leq 0.65$ ) and cardiac output (dotted line; area under the curve = 0.6 [0.48 – 0.72],  $p = 0.106$ ; best cut-off value  $CO > 5.5$  L/min) to predict ARC defined by a 24-hr urinary creatinine clearance  $> 130$  ml/min.

**Figure 4:** Representation of creatinine clearance ( $Cr_{CL}$ ) measurements according to different values of cardiac output (CO) and renal Doppler resistivity index (RI).



## SUPPLEMENTARY DATA

**Appendix 1:** Principles of measurements of renal Doppler vascular index (RVI). (A) Visualization of proximal interlobar arteries in color-Doppler mode. (B) Peak systolic velocity ( $V_{max}$ ) and minimal diastolic velocity ( $V_{min}$ ) determined by pulsed Doppler from three consecutive similar-appearing waveforms. *RVI calculated as  $(V_{max} - V_{min})/V_{max}$  [19].*

**Appendix 2:** Percentages of ARC according to various values of cardiac output (CO) and renal Doppler vascular index (RVI).

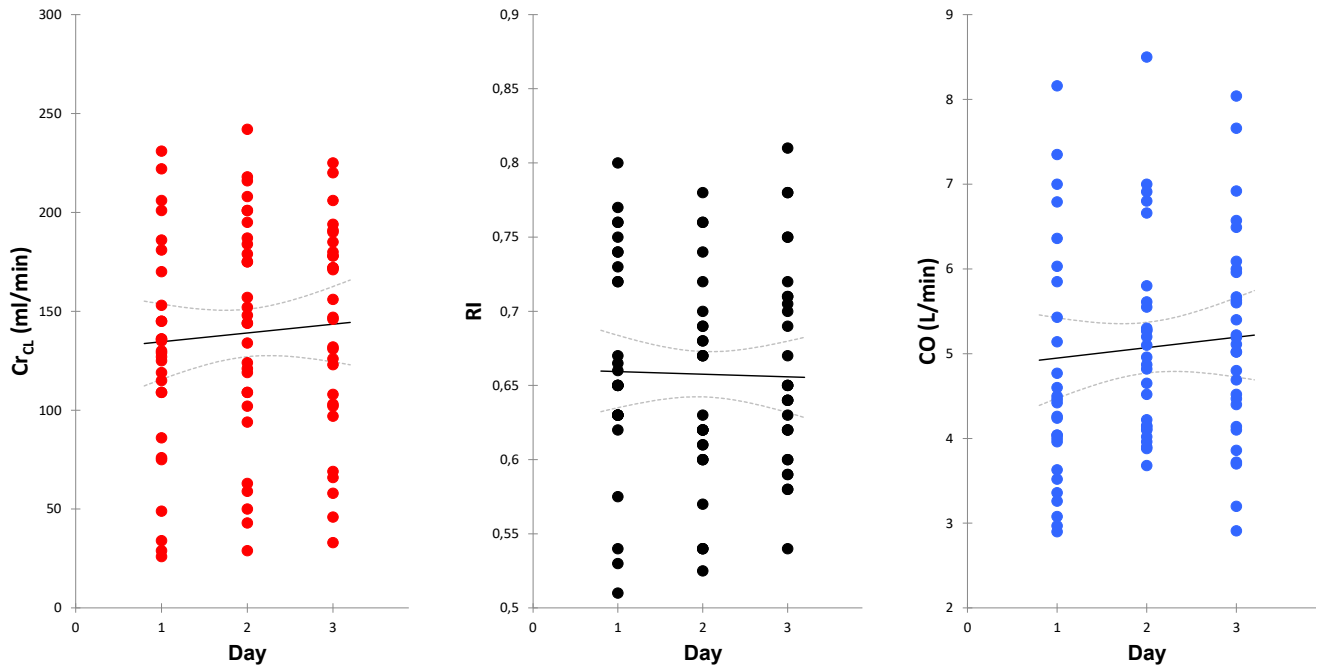
**Appendix 3:** Relationship between Renal Vascular Index (RVI) and Mean Arterial Pressure (MAP) with (continuous line) and without (dotted line) Augmented Renal Clearance (ARC).

**Table 1: Characteristics of the population**

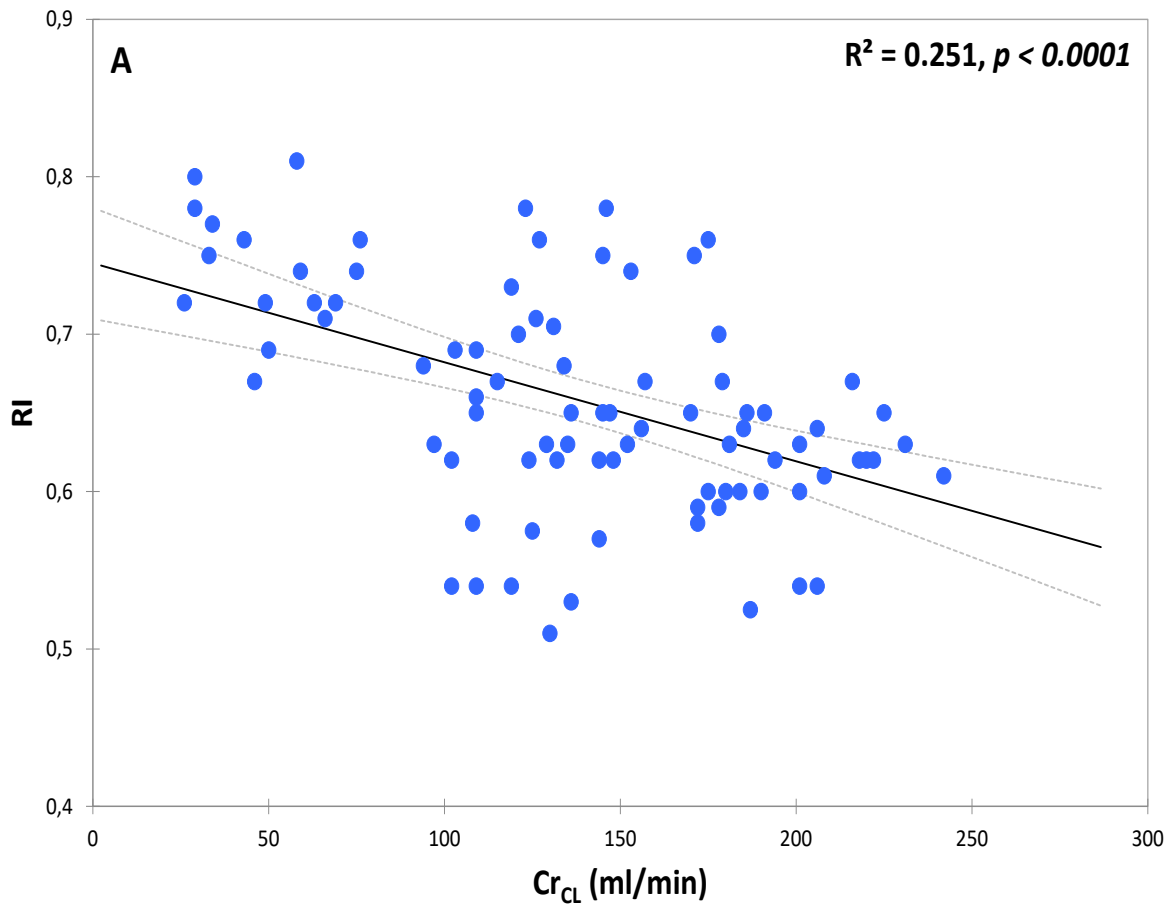
	Overall (N = 30)	No ARC (N = 12)	ARC (N = 18)	<i>p</i>
<b>Demographic data</b>				
• Age	48 [32 – 67]	67 [57 – 75]	36 [28 – 56]	0.002
• Male sex	27 (90)	11 (92)	16 (89)	0.804
• Body Mass Index	26 [22 – 29]	27 [22 – 29]	27 [22 – 29]	0.882
<b>Reason for admission</b>				
• Multiple trauma with brain trauma	13 (43)	5 (42)	8 (44)	0.880
• Isolated brain trauma	9 (30)	5 (42)	4 (22)	0.255
• Multiple trauma without brain trauma	8 (27)	2 (17)	6 (33)	0.312
<b>SAPS II at ICU admission</b>	42 [23 – 49]	50 [46 – 55]	31 [18 – 42]	0.001
<b>ISS</b>	34 [29 – 50]	46 [29 – 57]	32 [27 – 40]	0.125
<b>Norepinephrine at ICU admission</b>	18 (60)	8 (67)	10 (56)	0.54
Median duration for norepinephrine infusion	5 [0 – 8]	1 [0 – 2]	1 [0 – 2]	0.930
<b>Mechanical ventilation at ICU admission</b>	22 (73)	9 (75)	13 (72)	0.866
Median duration for mechanical ventilation	5 [0 – 8]	8 [2 – 10]	2 [0 – 6]	0.035
<b>Median values from day 1 to 3</b>				
• Serum creatinine (µmol/L)	56 [53 – 79]	83 [54 – 105]	56 [53 – 61]	0.054
• Diuresis	1858 [1275 – 2700]	1787 [1228 – 2183]	1997 [1228 – 2183]	0.397
• Urine creatinine (mmol/L)	6.8 [4.9 – 9.8]	6.2 [4.4 – 7.2]	7.5 [5.2 – 11.6]	0.062
• 24-hr urinary Cr <sub>CL</sub> (ml/min)	148 [114 – 169]	105 [51 – 115]	168 [160 – 187]	< 0.0001
• Natremia (mmol/L)	140 [137 – 142]	143 [139 – 151]	138 [137 – 140]	0.029
• Natriuresis (mmol/L)	90 [54 – 120]	89 [61 – 110]	91 [51 – 144]	0.719
• Excreted fraction of sodium (%)	0.77 [0.30 – 1.19]	0.98 [0.63 – 1.13]	0.69 [0.23 – 0.88]	0.066
• RVI	0.64 [0.62 – 0.70]	0.70 [0.65 – 0.74]	0.63 [0.61 – 0.65]	0.025
• CO (L/min)	4.9 [4.2 – 5.9]	4.7 [4.1 – 5.1]	5.2 [4.4 – 6.2]	0.363
• MAP (mmHg)	89 [83 – 94]	90 [87 – 100]	88 [82 – 89]	0.122
• Doses of norepinephrine (µg/kg/min)	0.02 [0 – 0.19]	0.07 [0 – 0.25]	0 [0 – 0.16]	0.205
<b>Length of stay in ICU</b>	12 [8 – 17]	16 [10 – 17]	11 [8 – 14]	0.203
<b>Death in ICU</b>	3 (10)	3 (25)	0 (0)	0.025

*Results expressed in numbers (percentages) or median [25% to 75% interquartile range]. ARC = Augmented Renal Clearance (mean Cr<sub>CL</sub> > 130 ml/min over 3 consecutive days); CO = Cardiac Output; Cr<sub>CL</sub> = Creatinine Clearance; ICU = Intensive Care Unit; ISS = Injury Severity Score; MAP = Mean Arterial Pressure; RVI = Renal Vascular Index; SAPS = Simplified Acute Physiologic Score*

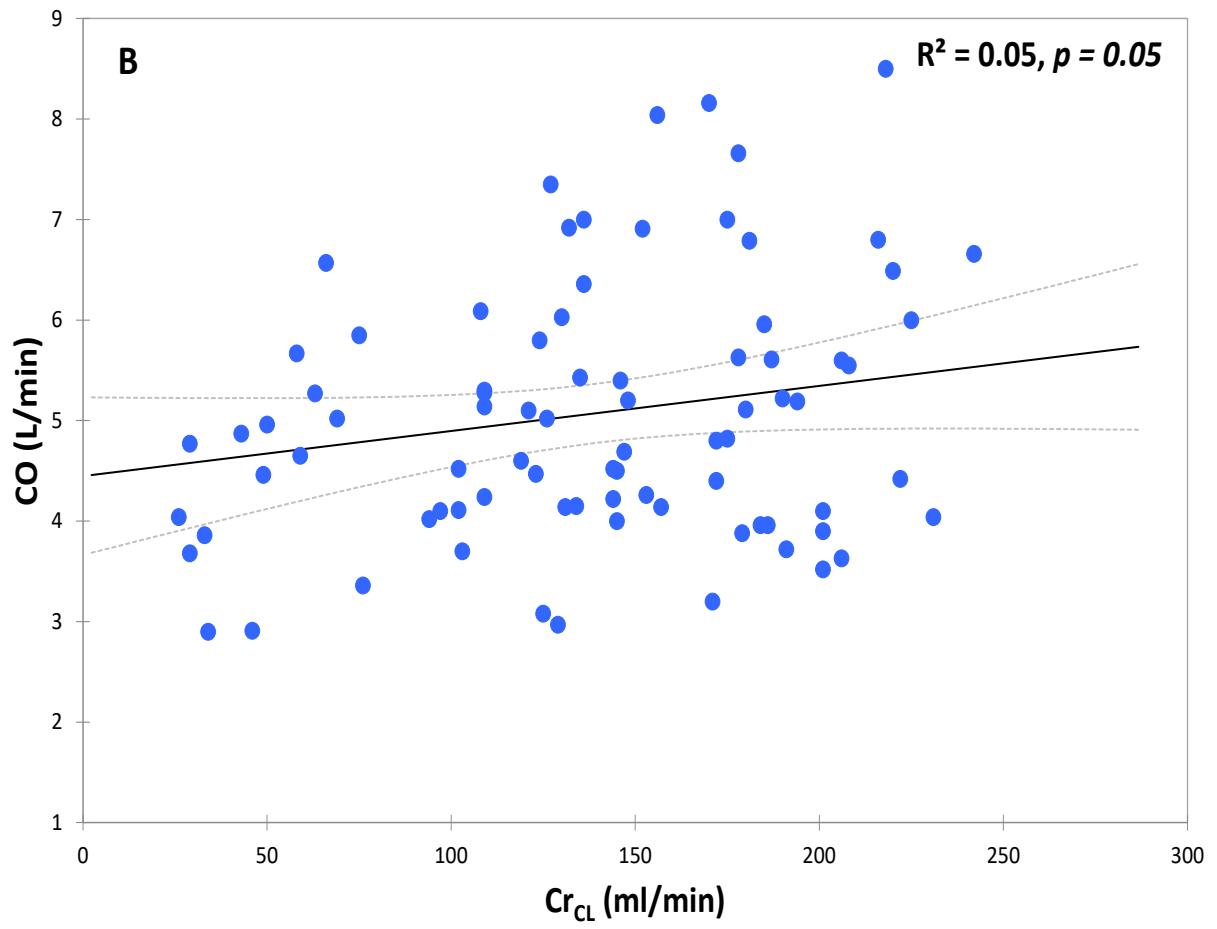
**Figure 1:** Variations of creatinine clearance  $Cr_{CL}$  (ml/min), cardiac output CO (L/min) and renal Doppler vascular index RVI over three consecutive days in 30 critically ill trauma patients.



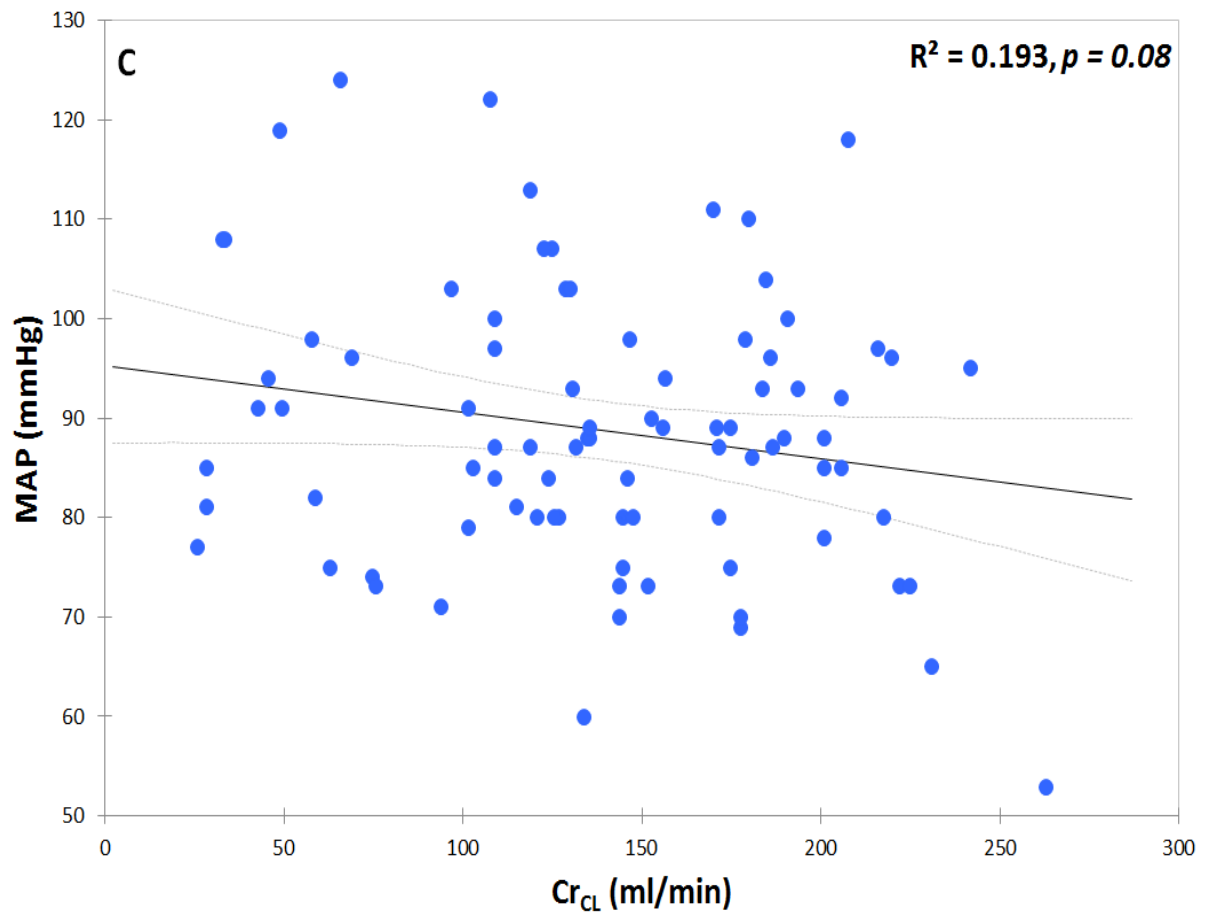
**Figure 2:** Relationship between creatinine clearance  $Cr_{CL}$  (ml/min) and (A) renal Doppler resistivity index RVI or (B) Cardiac Output CO (L/min) and (C) Mean Arterial Pressure (MAP) in 88 pooled physiologic data.



*Correlations were assessed using Spearman correlation coefficient.*

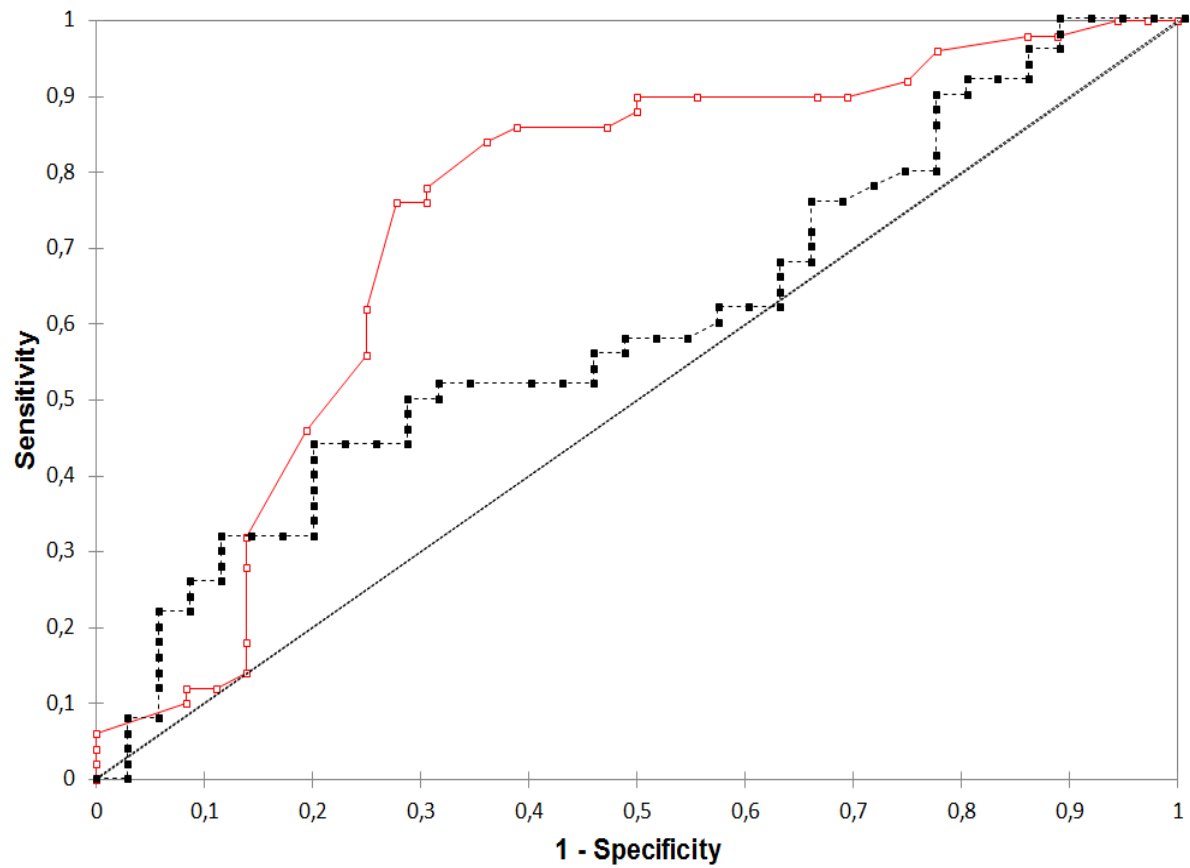


*Correlations were assessed using Spearman correlation coefficient.*

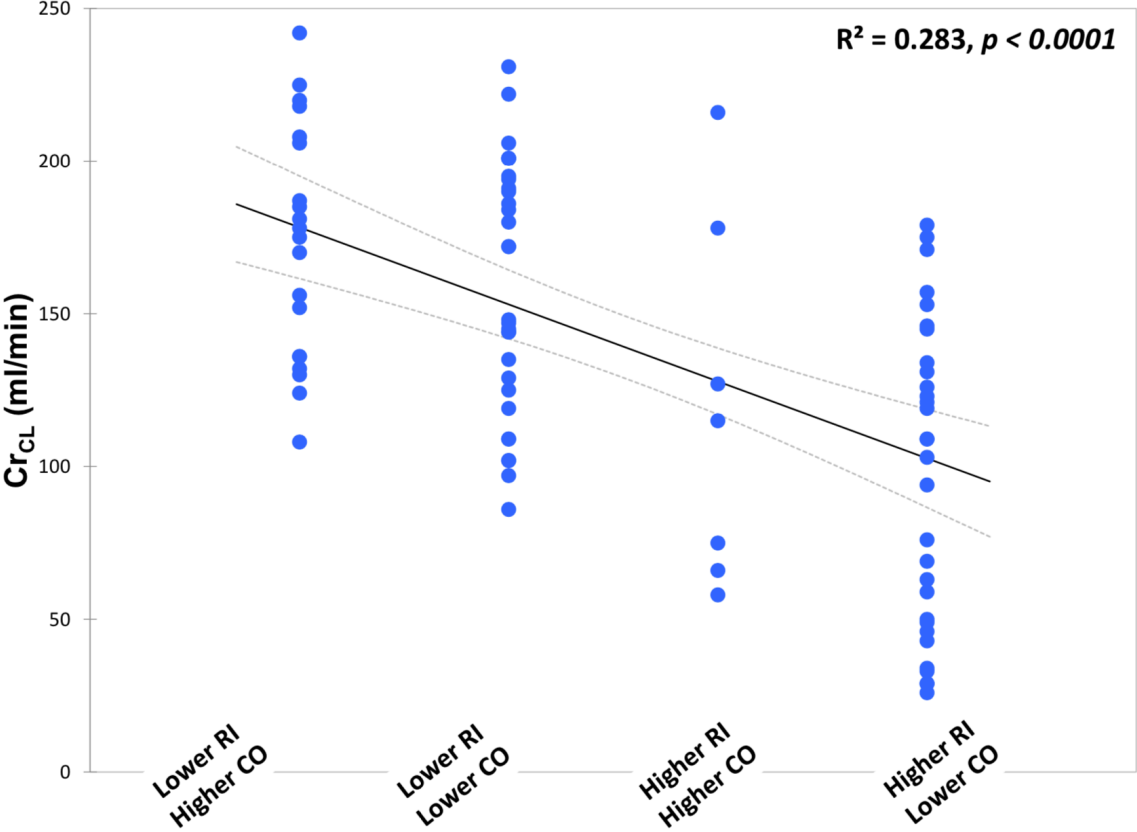


*Correlations were assessed using Spearman correlation coefficient.*

**Figure 3:** Receiver operating characteristic (ROC) showing the ability of resistivity index (continuous line; area under the curve = 0.74 [0.64 – 0.84],  $p < 0.001$ ; best cut-off value  $RI \leq 0.65$ ) and cardiac output (dotted line; area under the curve = 0.6 [0.48 – 0.72],  $p = 0.106$ ; best cut-off value  $CO > 5.5$  L/min) to predict ARC defined by a 24-hr urinary creatinine clearance  $> 130$  ml/min.



**Figure 4:** Representation of creatinine clearance ( $Cr_{CL}$ ) measurements according to different values of cardiac output (CO) and renal Doppler resistivity index (RI).

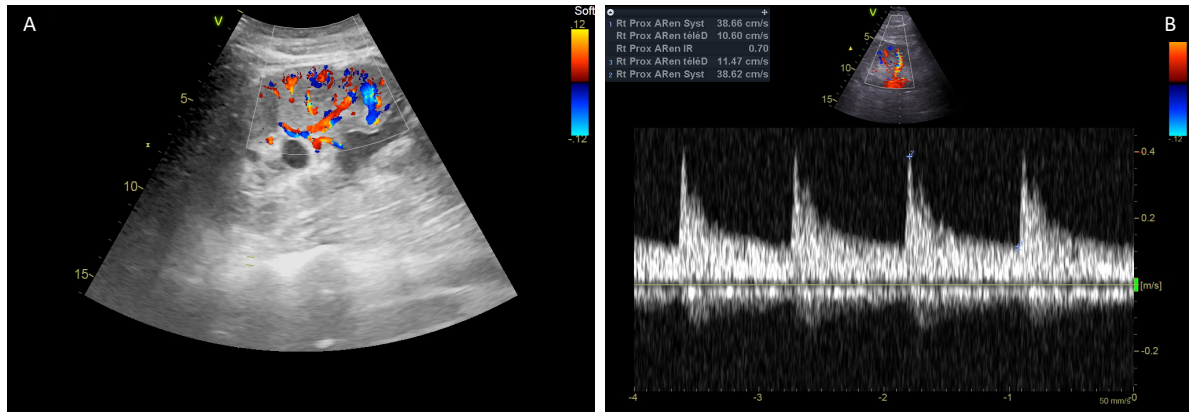


Correlations were assessed using Spearman correlation coefficient.

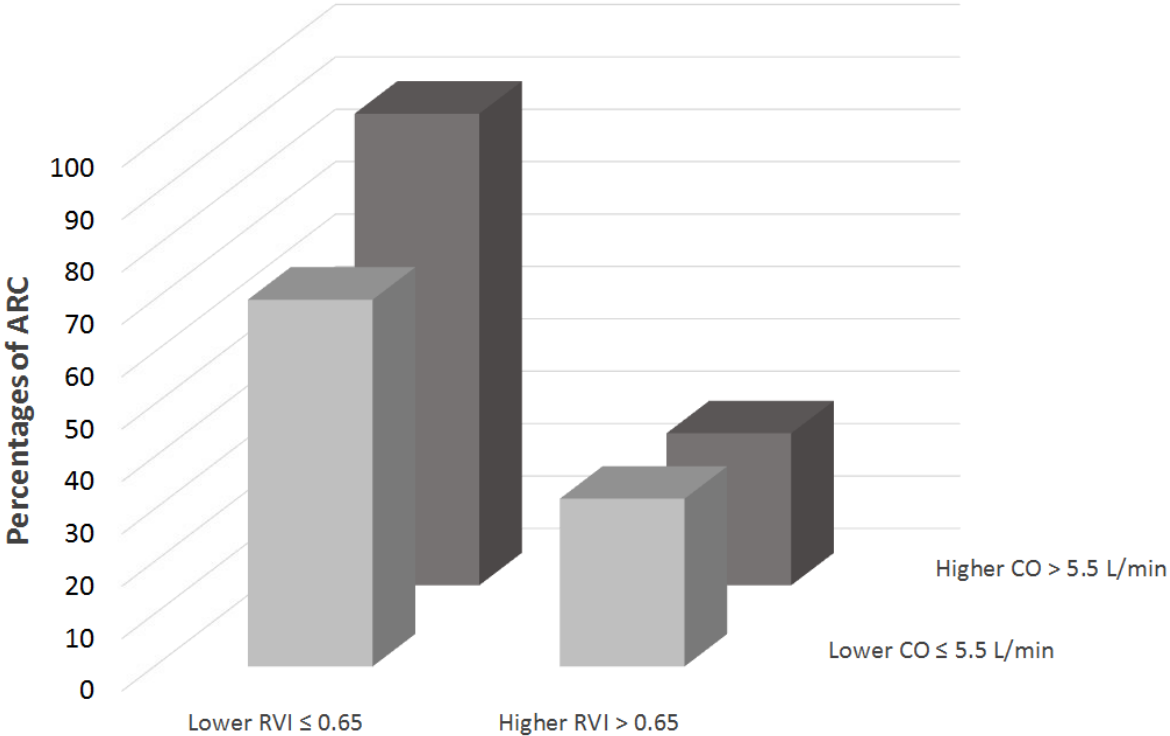
Lower CO  $\leq 5.5$  L/min; higher CO  $> 5.5$  L/min ; lower RI  $\leq 0.65$  and higher RI  $> 0.65$ .



**Appendix 1.** Principles of measurements of renal Doppler vascular index (RVI). (A) Visualization of proximal interlobar arteries in color-Doppler mode. (B) Peak systolic velocity ( $V_{max}$ ) and minimal diastolic velocity ( $V_{min}$ ) determined by pulsed Doppler from three consecutive similar-appearing waveforms. RVI calculated as  $(V_{max} - V_{min})/V_{max}$  [19].

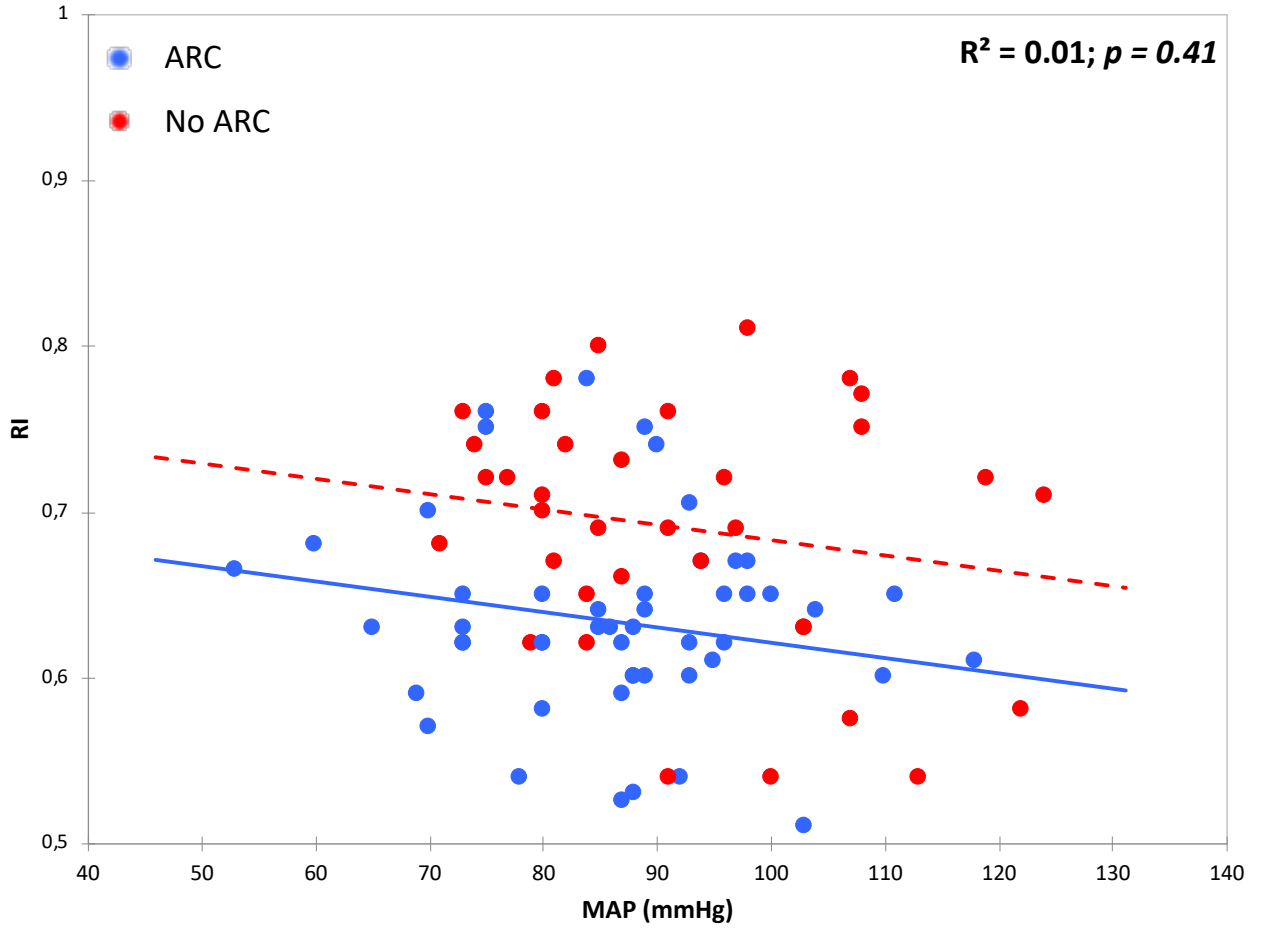


**Appendix 2:** Percentages of ARC according to various values of cardiac output (CO) and renal Doppler vascular index (RVI).



*Lower CO ≤ 5.5 L/min; higher CO > 5.5 L/min; lower RVI ≤ 0.65 and higher RVI > 0.65.*

**Appendix 3:** Relationship between Renal Vascular Index (RVI) and Mean Arterial Pressure (MAP) with (continuous line) and without (dotted line) Augmented Renal Clearance (ARC).



**Salt wasting syndrome in the brain-damaged patients:  
a pathophysiologic approach using sodium balance and urinary biochemical analysis**

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## ABSTRACT

**PURPOSE:** To explore the underlying mechanisms leading to the occurrence of hyponatremia and enhanced urinary sodium excretion in brain-damaged patients using sodium balance and urinary biochemical analysis.

**METHODS:** We conducted a retrospective analysis of a local database prospectively collected in 60 brain trauma patients without chronic renal dysfunction. Metabolic and hemodynamic parameters were averaged over three consecutive periods over the first seven days after admission. The main outcome investigated in this study was the occurrence of at least one episode of hyponatremia.

**RESULTS:** Over the study period, there was a prompt decrease in sodium balance ( $163 \pm 193$  vs.  $-12 \pm 154$  mmol/day,  $p < 0.0001$ ) and free water clearance ( $-0.7 \pm 0.7$  vs.  $-1.8 \pm 2.3$  ml/min,  $p < 0.0001$ ). The area under the ROC curves for sodium balance in predicting the occurrence of hyponatremia during the next period was 0.81 [95% CI: 0.64 – 0.97]. Variables associated with averaged urinary sodium excretion were sodium intake ( $R^2 = 0.26$ ,  $p < 0.0001$ ) and fractional excretion of urate ( $R^2 = 0.15$ ,  $p = 0.009$ ). Urinary sodium excretion was also higher in patients with sustained augmented renal clearance over the study period ( $318 \pm 106$  vs.  $255 \pm 135$  mmol/day,  $p = 0.034$ ).

**CONCLUSION:** The decreased vascular volume resulting from a negative sodium balance is a major precipitating factor of hyponatremia in brain-damaged patients. Predisposing factors for enhanced urinary sodium excretion were high sodium intake, high fractional excretion of urate and augmented renal clearance over the first seven days after ICU admission.

## INTRODUCTION

Salt wasting syndrome (SWS) is a common cause of hyponatremia in the brain-damaged patients, with a reported incidence varying from 0.8 to 34.6% according to the definition [1]. The most widespread theory explaining the renal loss of sodium purports a neurohumoral response involving a pressure-induced natriuresis, an increased level of natriuretic peptides and a hypoaldosteronism syndrome [2, 3]. Some authors also suggested a defect in proximal tubular sodium reabsorption, as suggested by the increased excretion fraction of solutes exclusively transported in the proximal tubule [4].

Although the pathophysiologic mechanisms responsible for SWS remain mainly unknown, the decreased vascular volume resulting from a renal loss of sodium is thought to be the leading mechanism for an enhanced ADH secretion despite an increasing plasma hypoosmolality [2, 4]. Determining volume status is thus of paramount importance in brain-trauma patients, the assessment of which being universally agreed to be inaccurate by usual clinical criteria [3].

The hypothesis pertaining to this study is that a negative sodium balance could be a precipitating factor of hyponatremia during the acute phase of traumatic brain injury. Our objective was thus to explore the underlying mechanisms leading to the occurrence of hyponatremia and enhanced urinary sodium excretion in brain-damaged patients using sodium balance and urinary biochemical analysis.

## METHODS

### 1. Design, population and settings

This study is a retrospective analysis of our local database (declared to the French Data Protection Authority, number 2166637v0) prospectively collected over an 8-month period (June 2018 to January 2019) in every brain trauma patients (Abbreviated Injury Score [AIS] > 3) consecutively admitted in a 25-bed Surgical and Trauma Intensive Care Unit (ICU). Study participants had to have an ICU length of stay alive  $\geq 5$  days and no evidence of congestive heart failure, cirrhosis or chronic renal failure (measured creatinine clearance [CL<sub>CR</sub>] < 60 ml/min/1.73m<sup>2</sup>). Patients who presented hyponatremia (i.e.  $\leq 135$  mmol/L) at ICU admission were also excluded.

As previously described, all patients were managed by a standardized protocol in accordance with French recommendations [5, 6]. Patients who presented at least one episode of hyponatremia underwent BNP (normal range < 100 pg/ml), aldosterone (normal range 53 – 645 pmol/L), TSH (normal range 0.35 – 4.94 UI/L) and cortisol (normal range 100 – 540 nmol/L) measurements and were treated by administration of hypertonic saline. Fludrocortisone (100 – 400  $\mu$ g/day) was used in refractory cases of SWS [7].

Ethical approval was obtained from the Ethics Committee of the French Society of Anesthesiology and Intensive Care (CERAR 00010254-2018-153). The patients and/or next of kin were informed about the inclusion of their anonymized health data in the database, and none declined participation.

## 2. Study protocol and data collection

Plasma and 24-hr urinary samples were recorded daily and  $CL_{CR}$  was calculated as follows: (24-hr urinary volume x urinary creatinine)/plasma creatinine, converted in ml/min and normalized to a body surface area of  $1.73 \text{ m}^2$  (Dubois formula). Sustained augmented renal clearance was considered in patients who presented a mean  $CL_{CR} > 130 \text{ ml/min/1.73m}^2$  over the study period [6]. Free water clearance ( $CL_{H_2O}$ ) was also calculated as follows: 24-h urine volume x  $(1 - \text{Urinary Osmolality} / \text{Plasma Osmolality})$ , converted in ml/min.

Fractional excretion of sodium ( $FE_{Na}$ , normal range  $< 1\%$ ) and urate ( $FE_{urate}$ , normal ranges  $< 11\%$ ) were both calculated with standard formulas. Fluid balance, sodium balance and averaged hemodynamic data (mean arterial pressure [MAP], norepinephrine [NE] infusion) were collected during the first seven days after admission. Metabolic and hemodynamic parameters were averaged over three consecutive periods: an early (day 1 – day 2), intermediate (day 3 – 4) and a late period (day 5 to day 7). The daily sodium intake conversion table is reported in **Supplementary Data**.



### 3. Statistical analysis

Results are expressed as mean  $\pm$  standard deviation or median (25% to 75% interquartile range) for continuous variables and as numbers (percentages) for categorical variables. The data distribution was analyzed by a Kolmogorov-Smirnov test.

The main outcome investigated in this study was the occurrence of at least one episode of hyponatremia during the first seven days after admission for TBI. Only the first episode of hyponatremia was considered over the first seven days after admission. As the occurrence of hyponatremia justified a prompt increase in sodium intake, sodium balances couldn't be compared over the same period between patients who presented or not an episode of hyponatremia. Hemodynamic and metabolic parameters of patients who presented or not a first episode of hyponatremia during the intermediate and late periods were thus compared during the previous period. The association between sodium balance during one period and the occurrence of hyponatremia the following period was also assessed using a receiving operator curve (ROC) analysis. A sample size of 56 patients was necessary to assess the predictive value of sodium balance with an AUC  $\geq$  0.75 and different from 0.5, assuming a 5% type I error rate, an 80% power and a prevalence of hyponatremia  $\geq$  25% [8]. A threshold analysis was also performed using a grey zone approach [9].

Precipitating factors of hyponatremia were also described by comparison of metabolic and hemodynamic parameters during the 48 hours before the occurrence of hyponatremia. Continuous variables were compared using Wilcoxon test for paired samples and categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. For the secondary outcome of this study, linear regression models were used to assess the effect of sodium intake,  $CL_{CR}$ , MAP and  $FE_{urate}$  on urinary sodium excretion averaged over the study period. A  $p$  value  $<$  0.05 was considered statistically significant.

Statistical analyses were performed using XLSTAT 2017 for Windows (Addinsoft Paris, France).

## RESULTS

### 1. Characteristics of the population

Over the study period, 60 TBI patients without chronic renal dysfunction contributed to the database. Overall, 16 patients (27%) presented at least one episode of hyponatremia, occurring after a median duration of 6 [4 – 7] days after ICU admission. Each episode of hyponatremia was adequately treated by administration of hypertonic saline ± fludrocortisone. The characteristics of the population are resumed **Table 1**.

Averaged metabolic and hemodynamic parameters over the study periods are described **Table 2**. Over the study period, there was a prompt decrease of sodium balance ( $163 \pm 193$  vs.  $-12 \pm 154$  mmol/day,  $p < 0.0001$ ), induced by an enhanced sodium excretion ( $202 \pm 183$  vs.  $316 \pm 154$  mmol/day,  $p = 0.0002$ ) and a decrease in sodium intake ( $375 \pm 110$  vs.  $304 \pm 114$  mmol/day,  $p = 0.0003$ ). Similarly, the decreased fluid balance ( $1.3 \pm 1.0$  vs.  $0.6 \pm 0.9$  L/day,  $p = 0.001$ ) was induced by an enhanced diuresis ( $2.5 \pm 0.8$  vs.  $2.0 \pm 1.1$  L/day,  $p = 0.003$ ) and a decreased fluid intake ( $3.3 \pm 0.8$  vs.  $3.1 \pm 0.9$  L/day,  $p = 0.038$ ). Finally, a decreased plasma osmolality ( $307 \pm 12$  vs.  $303 \pm 12$  mOsm/L,  $p = 0.014$ ) and increased urinary osmolality ( $523 \pm 141$  vs.  $605 \pm 124$  mOsm/L,  $p = 0.003$ ) contributed for a decreased free water clearance over time ( $-0.7 \pm 0.7$  vs.  $-1.8 \pm 2.3$  ml/min,  $p < 0.0001$ ).

## 2. Precipitating factors for hyponatremia in brain-damaged patients

The evolution of metabolic and hemodynamic parameters during the 48 hours before the occurrence of hyponatremia are depicted **Table 3**. The rapid fall in Natremia was associated with an increased natriuresis, a negative sodium balance and a significant hemoconcentration over the two previous days. The day of hyponatremia, each patient presented normal values of BNP (41 [26 – 80] pg/ml), aldosterone (90 [72 – 180] pmol/L), TSH (0.6 [0.5 – 1.4] UI/L) and cortisol (396 [308 – 505] nmol/L).

Patients who presented an episode of hyponatremia during the intermediate and late periods had lower sodium balances during the previous period (**Figure 1**). There was no statistical difference regarding other averaged metabolic or hemodynamic data.

A negative sodium balance during one period was associated with an increased risk of hyponatremia the next period (OR = 9.3 [2.2 – 40.5],  $p = 0.001$ ). A negative sodium balance had a sensibility of 80% [95%CI: 48 – 95%] and a specificity of 69% [95%CI: 59 – 77%] to predict hyponatremia the next period. The area under the ROC curves for sodium balance over one period in predicting the occurrence of hyponatremia during the following period was 0.81 [95% CI: 0.64 – 0.97] (**Figure 2**). The rate of patients who belonged to the grey zone was 38%.

### 3. Predisposing factors for enhanced sodium excretion

The averaged urinary sodium excretion was high, but not statistically different in patients who presented or not one episode of hyponatremia over the study period ( $287 \pm 90$  vs.  $282 \pm 133$  mmol/day,  $p = 0.621$ ). Continuous variables associated with averaged urinary sodium excretion were sodium intake ( $R^2 = 0.26$ ,  $p < 0.0001$ ) and  $FE_{urrate}$  ( $R^2 = 0.15$ ,  $p = 0.009$ ). Urinary sodium excretion was also higher in patients with sustained augmented renal clearance over the study period ( $318 \pm 106$  vs.  $255 \pm 135$  mmol/day,  $p = 0.034$ ). The mean MAP was high, but not statistically associated with renal sodium excretion ( $R^2 = 0.035$ ,  $p = 0.151$ ).

## DISCUSSION

To our knowledge, this is the first study aiming to assess the predisposing and precipitating factors of hyponatremia in brain-damaged patients. Over the first seven days after ICU admission, there was an inverse relationship between the prompt increase in urinary sodium excretion and the decrease in free-water clearance. Predisposing factors for enhanced urinary sodium excretion were higher sodium intake, higher  $FE_{urate}$  values and augmented renal clearance over the first seven days after ICU admission. Patients with negative sodium balance and hemoconcentration were particularly at risk for hyponatremia during this period.

On the one hand, there is general agreement that the renal loss of sodium is responsible for variable reduction in extracellular volume (ECV), leading to an appropriate ADH secretion that may promote renal free-water retention and hyponatremia despite an increasing plasma hypoosmolality [2, 4]. In this context, Audibert et al. determined blood volume by gold-standard radioisotope dilution methods and demonstrated a significant reduction in ECV after subarachnoid hemorrhage [3]. Authors argued that hyponatremia might be prevented by controlled sodium intake adapted to renal excretion. It should be noticed that the complexity of sodium intake calculation may preclude any clinical application. In this context, our results may suggest that monitoring of hemoconcentration markers (such as BUN or protidemia) should promote a prompt increase in ECV and sodium intake to avoid a sustained plasma hypoosmolality.

On the other hand, the pathophysiology of the enhanced urinary sodium excretion is not completely understood. Some authors previously advocated a decreased sympathetic outflow and an increased level of circulating natriuretic peptides [10, 11]. Moreover, hypoaldosteronism has been considered as a contributing factor for the enhanced sodium excretion [3]. Our results didn't corroborate this neurohumoral theory, with normal BNP and aldosterone values reported in patients experiencing a first episode of hyponatremia. This result was in accordance with Maesaka et al. who first suggested that the contribution of natriuretic factors or renin-aldosterone levels was not straightforward in brain-damaged patients [4].

According to our results, an enhanced tubular fluid output associated with a proximal sodium reabsorption defect should be considered as the leading mechanisms explaining the marked increase in urinary sodium excretion. After the initial resuscitation, the high sodium intake and increased sympathetic stimulation may be responsible for a delayed pressure-induced natriuresis [12]. Our results are not inconsistent with this hypothesis since higher MAP were observed over time despite a progressive norepinephrine withdrawal, probably explained by cessation of anesthetic agents and/or weaning from mechanical ventilation. The hemodynamic compensatory responses allow reaching a new steady state sodium balance at a lower extracellular volume, depending on the extent of renal loss and sodium input [10]. Moreover, perturbations in renal hemodynamics may lead to an enhanced glomerular filtration rate which may be considered as a contributing factor for the enhanced tubular fluid output [13]. Our results are in accordance with a previous report suggesting a significant relationship between  $24\text{-Cl}_{\text{CR}}$  and urinary osmole excretion over the first days after TBI [14]. Finally, the association between high  $\text{FE}_{\text{urate}}$  and enhanced sodium excretion over time may confirm previous studies that hypothesized a defect in sodium transport in the proximal tubule [4]. In this respect, Maesaka et al. first suggested the increased excretion fraction of solutes exclusively transported in the proximal tubule such as lithium, urate and eventually phosphate in patients with SWS [14 – 16]. Moreover, proximal renal tubular dysfunction has recently been described in brain-damaged patients [17]. This study thus reinforces the multifactorial pathophysiology of SWS which deserves further investigations.

Our study was impaired by several limitations. First, we acknowledge a limited number of patients retrospectively included, although contributing for numerous data collected over the first seven days after admission. This period was arbitrarily chosen and thus may under-estimate the incidence of hyponatremia in brain-damaged patients. Moreover, hormonal status could not be compared between patients with or without hyponatremia. Although patients with hyponatremia displayed normal values of BNP and aldosterone, the neurohumoral theory can't be formally refuted. Finally, we didn't aim to differentiate SWS and SIADH as those two entities share several serum and urinary biological criteria. On the other hand, no patient required water restriction to correct hyponatremia, **which is not suggestive for SIADH in this context**. We acknowledge the lack of specific assessment of the extracellular volume, thus further studies are needed to corroborate the hypothesis pertaining to this study.

## CONCLUSION

The decreased vascular volume resulting from a negative sodium balance should be considered as a precipitating factor of hyponatremia in brain-damaged patients. Predisposing factors for enhanced urinary sodium excretion were mean sodium intake, mean  $FE_{urrate}$  values and augmented renal clearance over the first seven days after ICU admission.

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## TABLES AND FIGURES LEGEND

**Table 1:** Characteristics of the population

**Table 2:** Averaged hemodynamic and metabolic parameters during the study period in the overall population

**Table 3:** Evolution of hemodynamic and metabolic parameters in patients who presented a first episode of hyponatremia over the study period (N = 16)

**Figure 1:** Comparison of sodium balances in patients who presented or not a first episode of hyponatremia (A) during the intermediate period [day 3 – 4] or (B) during the late period [day 5 – 7].

**Figure 2:** (A) ROC curve describing the ability of sodium balance during one period to predict the occurrence of hyponatremia the following period. (B) Two-curve graph showing the sensitivity and specificity of the different values of sodium balance to predict the occurrence of hyponatremia the following period.

**Table 1:** Characteristics of the population

	<b>Overall population (N = 60)</b>	<b>Control group (N = 44)</b>	<b>Hyponatremia day 1 – 7 (N = 16)</b>	<b>p</b>
<b>Demographic data</b>				
• Age (years)	48 [32 – 60]	48 [32 – 61]	49 [22 – 59]	0.627
• Male sex	53 (88)	39 (89)	14 (88)	0.903
• Weight (kg)	76 [67 – 88]	78 [69 – 90]	72 [60 – 83]	0.143
<b>Reason for admission</b>				
• Isolated TBI	26 (43)	17 (39)	9 (56)	0.223
• Multiple trauma with TBI	34 (57)	27 (61)	7 (44)	0.223
<b>Prognostic scores</b>				
• Initial GCS	9 [5 – 14]	10 [6 – 14]	7 [4 – 12]	0.213
• SAPS II	45 [36 – 52]	44 [36 – 50]	39 [45 – 53]	0.484
<b>Neurosurgical procedures</b>				
• Intracranial pressure monitoring	35 (58)	27 (57)	10 (63)	0.693
• External CSF derivation	16 (27)	10 (23)	6 (38)	0.253
• Parietal craniotomy	17 (28)	14 (32)	3 (19)	0.321
• Craniectomy	9 (15)	7 (16)	2 (13)	0.744
<b>Intracranial hypertension</b>	24 (40)	14 (33)	9 (56)	0.097
<b>Management in the ICU</b>				
• Use of mechanical ventilation	58 (97)	41 (95)	16 (100)	0.380
• Use of vasopressors	56 (93)	40 (93)	15 (94)	0.921
• Use of osmotherapy	17 (28)	10 (23)	7 (44)	0.122
• Use of hypothermia	17 (28)	10 (23)	6 (38)	0.274
• Use of barbiturates	14 (23)	8 (19)	5 (31)	0.297
• Use of NSAIDs	10 (17)	8 (19)	2 (13)	0.578
• Use of hydrocortisone	6 (10)	6 (14)	0 (0)	0.115
• Use of desmopressine	4 (7)	3 (7)	1 (6)	0.921
<b>Mean fluid and sodium balances</b>				
• Mean fluid balance (L)	0.8 [0.6 – 1.2]	0.9 [0.5 – 1.2]	0.6 [0.6 – 0.9]	0.115
• Mean sodium balance (mmol)	41 [-33 – 104]	41 [-7 – 104]	29 [-41 – 100]	0.621
• Loss of weight	0 [-1 – 2]	0 [-2 – +2]	0 [-1 – 0]	0.843
<b>Outcome</b>				
• Death during the ICU stay	7 (12)	3 (7)	4 (25)	0.052
• Duration under ventilation	9 [5 – 17]	9 [3 – 17]	10 [7 – 15]	0.412
• ICU length of stay	16 [11 – 28]	15 [11 – 26]	18 [13 – 24]	0.616

*Results expressed as number (percentage) or median [interquartile 25 – 75]*

**Table 2:** Averaged hemodynamic and metabolic parameters during the study period in the overall population

	Study period	Day 1 – 2	Day 3 – 4	Day 5 – 7
Natremia (mmol/L)	142 [139 – 144]	142 [140 – 146]	143 [140 – 147]	140 [138 – 143] <sup>*,†</sup>
Hyponatremia (Na ≤ 135 mmol/)	16 (27)	0 (0)	5 (8)	11 (18) *
Fluid intake (L/24h)	3.2 [2.8 – 3.6]	3.3 [2.9 – 3.8]	3.2 [2.7 – 3.7]	3.2 [2.5 – 3.7] *
Diuresis (L/24h)	2.2 [1.9 – 2.8]	1.8 [1.3 – 2.5]	2.2 [1.6 – 2.9]	2.4 [1.8 – 2.9] *
Fluid balance (L/24h)	0.8 [0.6 – 1.2]	1.4 [0.4 – 2.0]	1.0 [0.4 – 1.4]	0.6 [-0.1 – 1.1] *
Sodium intake (mmol/24h)	323 [277 – 378]	363 [299 – 432]	295 [234 – 371]	302 [229 – 365] *
Urinary sodium excretion (mmol/24h)	284 [221 – 362]	132 [91 – 275]	309 [187 – 422]	310 [226 – 409] *
Sodium balance (mmol/24h)	47 [-33 – 104]	215 [84 – 293]	16 [-115 – 106]	22 [-85 – 90] *
24-hr CL <sub>CR</sub> (ml/min/1.73m <sup>2</sup> )	143 [116 – 160]	136 [96 – 154]	143 [110 – 165]	147 [115 – 166] *
Augmented renal clearance	32 (53)	33 (55)	34 (57)	33 (55)
Urinary osmolality (mmol/L)	569 [503 – 653]	498 [423 – 627]	590 [487 – 655]	603 [510 – 700] *
24-hr CL <sub>H<sub>2</sub>O</sub> (ml/min/1.73m <sup>2</sup> )	-1.3 [-1.5 – -1.0]	-0.8 [-1.2 – -0.4]	-1.3 [-1.6 – -0.8]	-1.6 [-2.1 – -1.1] <sup>*,†</sup>
Fractional excretion of sodium (%)	0.94 [0.76 – 1.21]	0.56 [0.33 – 1.15]	0.98 [0.70 – 1.40]	0.94 [0.72 – 1.31] *
Fractional excretion of urate (%)	19 [12 – 22]	13 [11 – 18]	16 [12 – 21]	22 [13 – 28] <sup>*,†</sup>
Mean MAP	92 [87 – 96]	87 [83 – 92]	91 [85 – 97]	93 [88 – 100] *
Use of vasopressor	54 (90)	54 (90)	42 (70)	30 (50) *

Data expressed as median [interquartile 25 – 75] and numbers (percentages).

\* =  $p < 0.05$  between period 1 and period 3; † =  $p < 0.05$  between period 2 and period 3 (continuous variables compared using Wilcoxon test for paired samples).

**Table 3:** Evolution of hemodynamic and metabolic parameters in patients who presented a first episode of hyponatremia over the study period (N = 16)

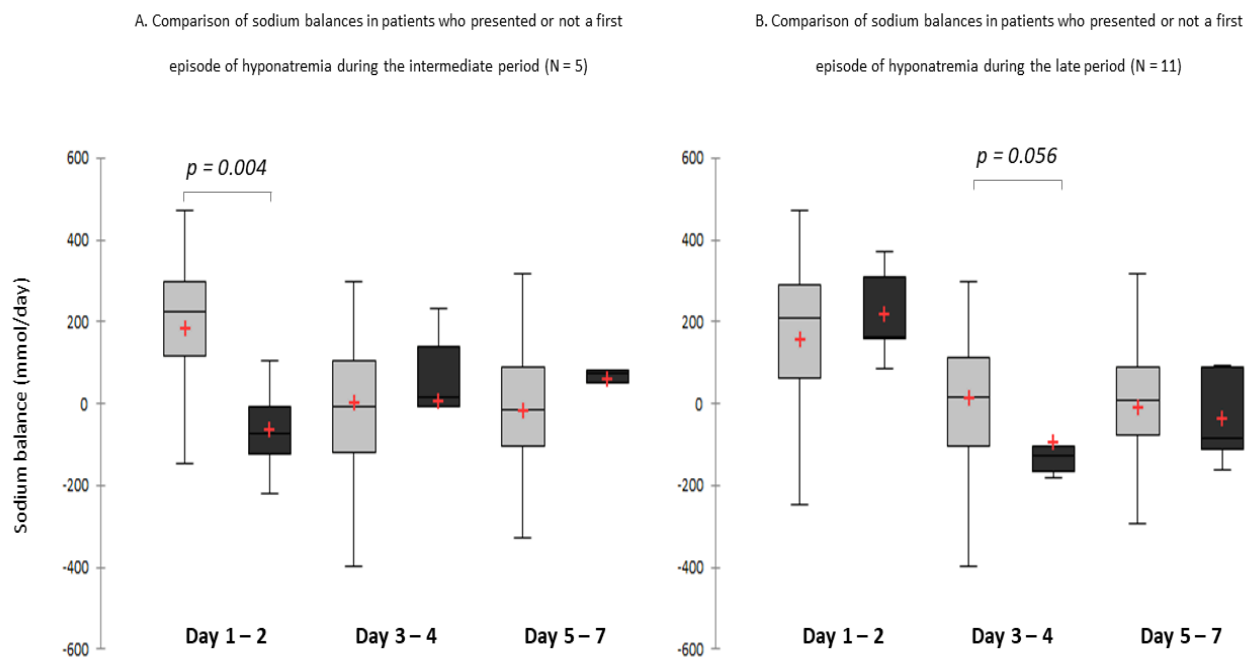
	Day of hyponatremia	Day - 1	Day - 2
Natremia (mmol/L)	135 [134 – 135]	138 [137 – 139]	141 [139 – 144] <sup>*,†</sup>
Fluid intake (L/24h)	3.0 [2.5 – 3.3]	2.5 [2.3 – 3.0]	2.7 [2.6 – 3.0]
Diuresis (L/24h)	2.2 [2.0 – 3.1]	2.3 [1.7 – 3.2]	2.2 [1.9 – 2.6]
Fluid balance (L/24h)	0.6 [-0.1 – 1.0]	0.5 [-0.8 – 0.9]	0.4 [-0.2 – 1.0]
Sodium intake (mmol/24h)	356 [297 – 425]	278 [224 – 363]	288 [252 – 319] *
Urinary sodium excretion (mmol/24h)	316 [178 – 452]	372 [288 – 553]	403 [297 – 466]
Sodium balance (mmol/24h)	87 [-97 – 148]	-98 [-211 – 74]	-130 [-213 – -2]
24-hr CL <sub>CR</sub> (ml/min/1.73m <sup>2</sup> )	145 [127 – 165]	161 [139 – 173]	141 [128 – 163]
Urinary osmolality (mmol/L)	595 [491 – 686]	551 [498 – 712]	636 [483 – 740]
24-hr CL <sub>H<sub>2</sub>O</sub> (ml/min/1.73m <sup>2</sup> )	-1.6 [-1.9 – -1.3]	-1.6 [-1.9 – -1.3]	-1.8 [-2.0 – -1.1]
Fractional excretion of sodium (%)	1.04 [0.52 – 1.80]	0.95 [0.81 – 2.27]	1.15 [0.99 – 1.63]
Fractional excretion of urate (%)	27 [15 – 28]	21 [14 – 27]	23 [16 – 25] *
BUN (mmol/L)	4.9 [3.3 – 6.3]	4.1 [2.5 – 5.2]	3.0 [2.3 – 4.6] *
Protidemia (g/L)	65 [60 – 67]	62 [58 – 68]	58 [53 – 63] <sup>*,†</sup>
Hte (%)	32 [29 – 36]	33 [30 – 35]	31 [30 – 35] †
Mean MAP (mmHg)	92 [86 – 98]	94 [91 – 94]	91 [87 – 94]
Use of vasopressor	5 (31)	8 (50)	8 (50)

Data expressed as median [interquartile 25 – 75] and numbers (percentages).

\* =  $p < 0.05$  between Day -2 and Day 0; † =  $p < 0.05$  between Day -2 and Day -1 (continuous variables compared

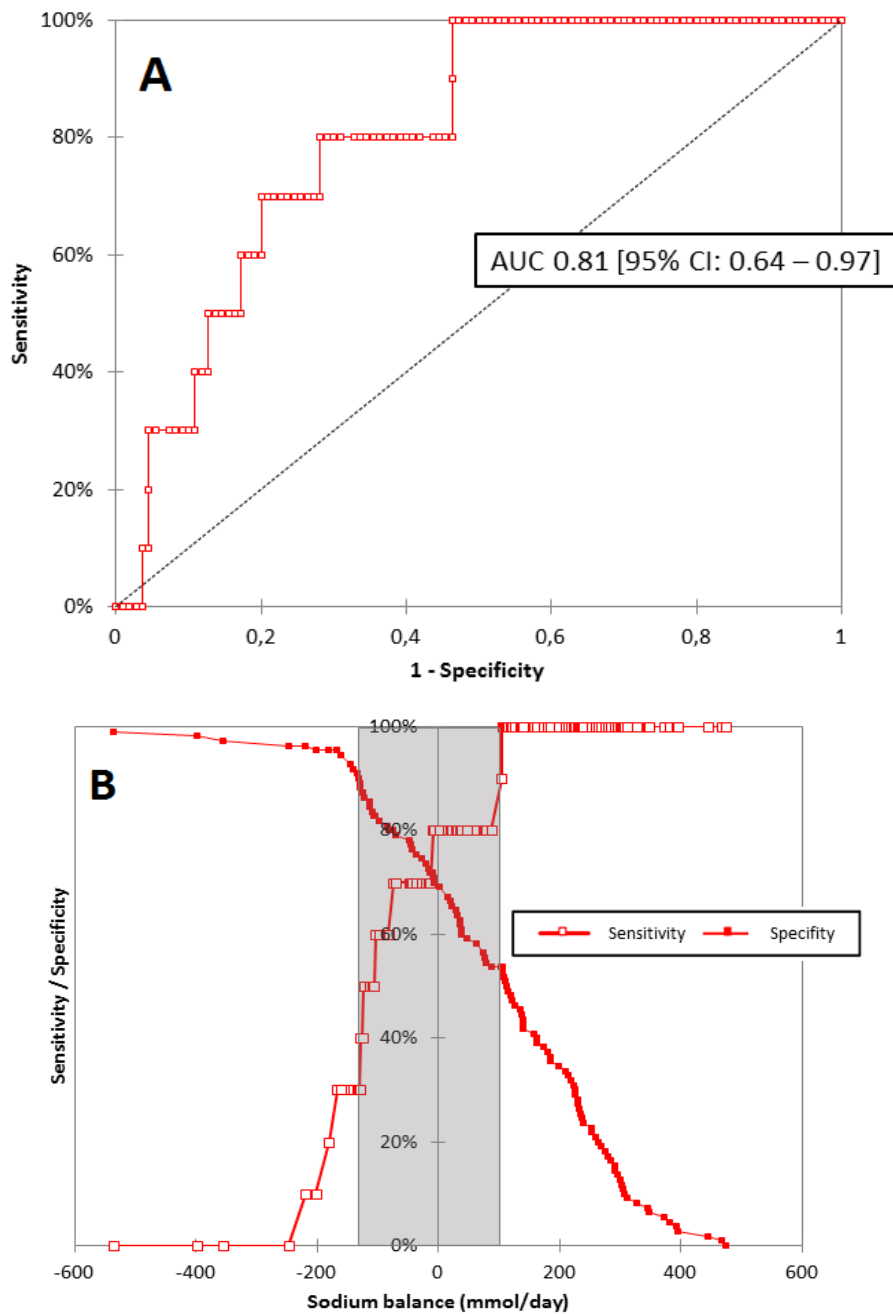
using Wilcoxon test for paired samples).

**Figure 1:** Comparison of sodium balances in patients who presented or not a first episode of hyponatremia (A) during the intermediate period [day 3 – 4] or (B) during the late period [day 5 – 7].



*Dark grey: patients with hyponatremia; light grey: control group*

**Figure 2:** (A) ROC curve describing the ability of sodium balance during one period sodium to predict the occurrence of hyponatremia the following period. (B) Two-curve graph showing the sensitivity and specificity of the different values of sodium balance to predict the occurrence of hyponatremia the following period



The inconclusive grey zone is displayed as a grey rectangle for a sodium balance between -130 and +100 mmol/day

## DISCUSSION

Bien que limités par leur faible effectif, ces travaux ont permis d'élaborer des hypothèses expliquant les mécanismes physiopathologiques des perturbations de la fonction rénale (augmentation de la clairance rénale et syndrome de perte en sel) chez le patient traumatisé crânien en utilisant des marqueurs accessibles en pratique clinique.

### 1. Perturbation de la vasomotricité artériolaire rénale et augmentation de la filtration glomérulaire

Notre première étude suggère que la diminution de la vasomotricité artériolaire rénale serait le principal mécanisme pourvoyeur de l'ACR en traumatologie. Cette hypothèse est suggérée par une association significative entre un index de résistivité rénal bas et une  $CL_{CR}$  accrue ( $r = -0,501$ ;  $p < 0,0001$ ). L'association faible entre le débit cardiaque et la  $CL_{CR}$  ( $r = 0,219$ ;  $p = 0,05$ ) sous-entend que l'augmentation du débit cardiaque n'est pas le mécanisme causal de l'ACR, mais plutôt un facteur aggravant. Dans ce contexte, l'augmentation de la fraction de filtration induite par l'augmentation de la pression capillaire glomérulaire va être responsable d'une augmentation du DFG. La diminution de la vasomotricité artériolaire rénale serait à l'origine d'une perte d'autorégulation, rendant le DSR dépendant de l'hémodynamique systémique.

Le facteur causal de la vasodilatation artériolaire rénale reste cependant à explorer. L'hypothèse la plus probable serait un syndrome de réponse inflammatoire systémique via la synthèse de cytokines pro-inflammatoires, de prostaglandines vasodilatatrices ou de monoxyde d'azote (NO) (37-39). Dans ce contexte, des données expérimentales ont suggéré un déplacement vers la droite de la courbe d'autorégulation cérébrale après inhibition de la synthèse du NO (39).

Dans tous les cas, le rôle des facteurs natriurétiques semble peu probable dans ce contexte. Une étude publiée en 2017, par Udy et al ne retrouvait pas de corrélation entre  $CL_{CR}$  et taux d'ANP plasmatique sur une cohorte de 12 patients traumatisés crâniens hyperclairants (19).



## 2. Variations de la balance sodée et syndrome de perte en sel

Notre second travail suggère que l'hyponatrémie chez le cérébrolésé serait la conséquence d'un bilan sodé négatif, induit par une excrétion de sodium accrue ( $202 \pm 183$  vs  $316 \pm 154$  mmol/j ;  $p = 0,0002$ ) et une diminution des apports en sodium au cours de la réanimation initiale ( $375 \pm 110$  vs  $304 \pm 114$  mmol/j ;  $p = 0,0003$ ).

Dans ce contexte, il peut être admis que la perte rénale de sodium est responsable d'une réduction variable du volume extracellulaire (VEC), conduisant à une sécrétion d'ADH appropriée qui peut favoriser la rétention d'eau libre malgré une hypo-osmolalité plasmatique croissante (31) (32). Ces résultats corroborent l'étude d'Audibert et coll. ayant précédemment démontré une réduction significative du VEC chez 53% des patients malgré des bilans sodium et eau positifs et une augmentation du poids moyen sur la période d'étude (34). Les auteurs ne rapportaient aucun cas d'hyponatrémie lorsque l'apport quotidien en NaCl 0,9% était adapté à la natriurèse des 24 heures. Dans ce contexte, le maintien d'un bilan sodé positif pourrait permettre de prévenir la survenue d'une hyponatrémie.

Il convient de noter que la complexité du calcul de l'apport en sodium peut rendre difficile son application clinique. Dans ce contexte, nos résultats peuvent suggérer que la surveillance des marqueurs d'hémoconcentration (tels que l'urée plasmatique ou la protidémie) pourrait témoigner d'une diminution du VEC et inciter à une augmentation des apports en sodium pour éviter une hypo-osmolalité plasmatique soutenue.

### 3. Mécanismes explicatifs de la fuite sodée

D'autre part, les facteurs associés à une natriurèse accrue tendent à suggérer une augmentation du débit tubulaire proximal (natriurèse de pression et augmentation de la clairance rénale) et une diminution de la réabsorption tubulaire proximale (tubulopathie).

Premièrement, plusieurs mécanismes vont concourir à l'augmentation du flux tubulaire proximal :

- Une « natriurèse de pression », réponse physiologique à l'augmentation des apports sodés intraveineux et une augmentation de la pression artérielle systémique (activation du système sympathique ou perfusion de vasopresseurs). Ce rétrocontrôle hémodynamique permet d'atteindre à l'état stable un nouvel équilibre sodique à un volume extracellulaire inférieur (32). L'évolution au cours du temps est marquée par une diminution des apports sodés intraveineux et une diminution de la stimulation sympathique, via l'arrêt des catécholamines et le sevrage de la ventilation mécanique (34). Cette désescalade thérapeutique pourrait favoriser l'hypovolémie et la vasoplégie, et constituer une période à risque d'hyponatrémie [*Résultats non publiés*].
- Les perturbations de l'hémodynamique rénale précédemment décrites peuvent conduire à une augmentation du débit de filtration arrivant au tubule proximal. L'augmentation de la clairance rénale pourrait être un mécanisme explicatif à une excrétion rénale accrue de sodium. Ces résultats confortent l'étude de Udy et coll. qui avaient précédemment démontré une altération de la fonction tubulaire chez les patients en ACR. En outre, une étude ancillaire retrouvait une relation significative entre la clairance de la créatinine et l'excrétion urinaire de sodium au cours des 5 premiers jours après traumatisme crânien. [*Résultats publiés sous forme d'abstract, congrès SFAR 2019*].

Notre deuxième étude fait également évoquer l'existence d'une dysfonction tubulaire proximale chez les patients cérébrólésés, suggérée par une association entre des valeurs de  $FE_{Urate}$  élevées et une excrétion urinaire de sodium accrue. Ces résultats viennent conforter les données de Maesaka et coll. qui retrouvaient une augmentation des fractions excrétées d'urate, de lithium ainsi que de phosphate chez des patients atteints de SPS (40). Par ce biais, les auteurs évoquaient un trouble de la réabsorption proximale chez ces patients, permettant de différencier SPS du SIADH.

Cette hypothèse a récemment été confirmée par Civilletti et coll. qui ont pour la première fois démontré que les patients traumatisés crâniens présentaient à la fois une augmentation de l' $\alpha$ -1  $\mu$ -globuline, du RBP (passant librement la capsule de Bowman et réabsorbées au niveau du tubule proximal) mais aussi de NGAL plasmatique (marqueur d'agression rénale). En outre, l'augmentation de ces marqueurs était corrélée à l'augmentation des médiateurs inflammatoires (IL-6 et MCP-1). D'autre part, dans l'étude réalisée in vitro, le plasma des patients traumatisés crâniens induisait des altérations fonctionnelles et l'apoptose de cellules épithéliales tubulaires humaines : augmentation l'adhésion des neutrophiles, diminution de la résistance électrique trans-épithéliale, effet cytotoxique et pro-apoptotique et diminution de l'expression du récepteur Megalin (44).

Ainsi, nos résultats vont à l'encontre des études ayant précédemment suggéré une augmentation du taux de peptides natriurétiques circulants ou un hypoaldostéronisme chez des patients atteints de SPS. Dans notre étude, les valeurs de BNP (41 [26 – 80] pg/ml) et d'aldostérone (90 [72 – 180] pmol/L) étaient considérées comme normales chez les patients présentant une hyponatrémie inférieure 135 mmol/L. Ce résultat était conforme à Maesaka et al. qui suggérait que la contribution des facteurs natriurétiques ou des taux de rénine-aldostérone ne permettait pas d'expliquer la physiopathologie du SPS (31).

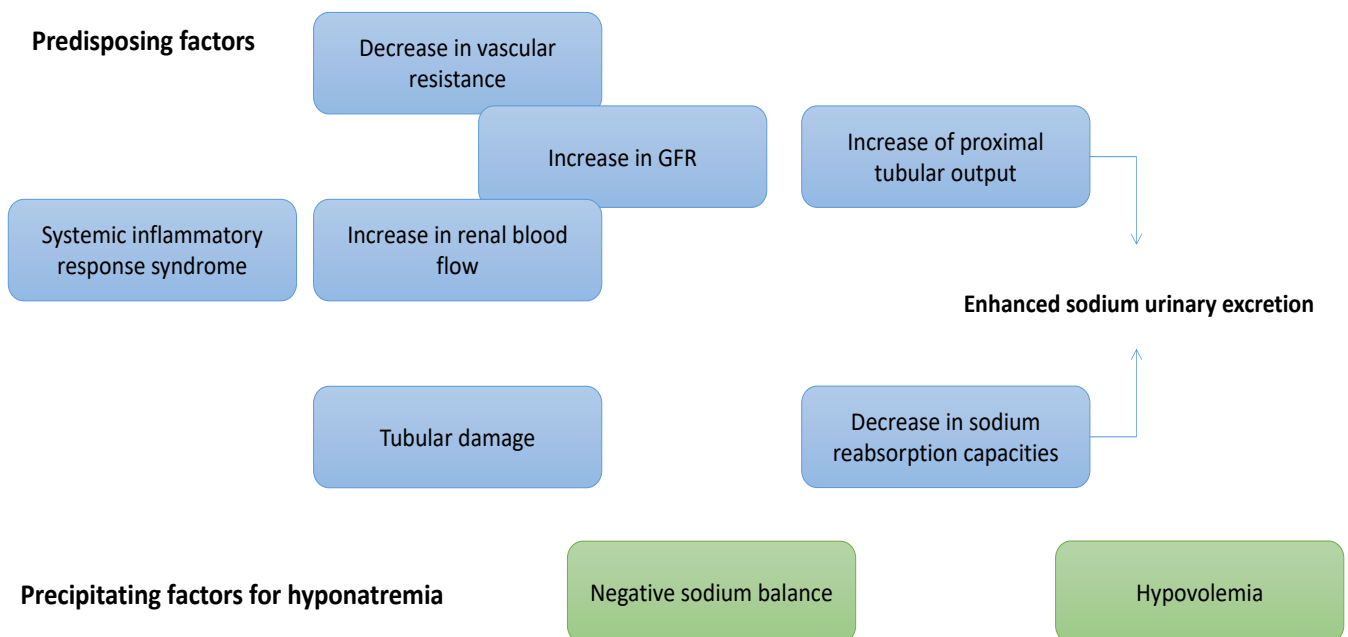
#### **4. Limites des études et perspectives futures**

Ces études sont rétrospectives, monocentriques et concernent un nombre très limité de patient. De plus, l'estimation du débit de filtration glomérulaire par la clairance de la créatinine urinaire n'est pas parfaite. Celle-ci surestime le DFG, mais l'utilisation de marqueurs exogènes ou de l'IRM n'est pas accessible en pratique clinique (16). Enfin, notre deuxième étude est limitée par l'absence d'évaluation de la volémie, ne permettant pas de différencier avec certitude le SPS du SIADH.

Cependant, l'intérêt de ces études préliminaires est de construire un rationnel physiopathologique faisant le lit d'un essai prospectif de plus grande ampleur. Les principaux mécanismes physiopathologiques sont résumés dans la figure ci-dessous.

Selon nos résultats, une augmentation du débit tubulaire associée à un défaut de réabsorption proximale du sodium peut être considérée comme le principal mécanisme expliquant l'augmentation marquée de l'excrétion urinaire de sodium (**figure 4**).

**Figure 4. Facteurs prédisposants et précipitants l'hyponatrémie au cours du SPS**



La constitution d'une dysfonction tubulaire proximale chez les traumatisés crâniens est une perspective intéressante car elle pourrait participer à l'hyperclairance rénale et être à l'origine d'une natriurèse inadaptée. La mise en évidence de cette tubulopathie par l'utilisation de biomarqueurs utilisables en pratique clinique ( $\beta$ 2-microglobuline ou la  $\alpha$ 1-microglobuline) pourrait constituer un nouveau critère diagnostique et permettre la prévention de l'hyponatrémie chez le cérébrolésé.

## CONCLUSION

- La diminution de la vasomotricité artériolaire rénale, suggérée par un index de résistivité rénal bas, serait le principal mécanisme pourvoyeur de l'augmentation de la clairance rénale en traumatologie. L'augmentation du débit cardiaque n'est pas le principal mécanisme de l'ARC, mais seulement un facteur aggravant.
- L'augmentation de la clairance rénale est un des facteurs prédisposants à une excrétion urinaire accrue de sodium. Les autres facteurs associés à une excrétion urinaire accrue en sodium sont un apport sodé important et une  $FE_{Urate}$  augmentée. Une  $FE_{Urate}$  augmentée pourrait suggérer une dysfonction tubulaire proximale chez le patient cérébrolésé.
- L'inadéquation entre les apports sodés et la natriurèse accrue serait le facteur précipitant de l'hyponatrémie chez le cérébrolésé. Nos résultats permettent d'écarter les théories hormonales telles qu'un taux de peptide natriurétique accru ou un hypoaldostéronisme secondaire.

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## SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité. Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs. Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément. Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés. J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré et méprisé si j'y manque.



## Original Article

# Augmented renal clearance in critically ill trauma patients: A pathophysiologic approach using renal vascular index

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## ABSTRACT

**Background:** The aim of the present study was to explore the relationship between creatinine clearance (Cl<sub>Cr</sub>), cardiac index (CI) and renal vascular index (RVI) in order to assess the potential mechanisms driving ARC in critically ill trauma patient. The secondary objective was to assess the performance of RVI for prediction of ARC.

**Methods:** Every trauma patient who underwent cardiac and renal ultrasound measurements during their initial ICU management was retrospectively reviewed over a 3-month period. ARC was defined by a 24-hr measured Cl<sub>Cr</sub>  $\geq$  130 mL/min/1.73m<sup>2</sup>. A mixed effect model was constructed to explore covariates associated with Cl<sub>Cr</sub> over time. The performance of RVI for prediction of ARC was assessed by receiver operating characteristic (ROC) curve and compared to the ARCTIC (ARC in trauma intensive care) predictive scoring model.

**Results:** Thirty patients, contributing for 121 coupled physiologic data, were retrospectively analysed. There was a significant correlation between Cl<sub>Cr</sub> values and RVI ( $r = -0.495$ ;  $P = 0.005$ ) but not between Cl<sub>Cr</sub> and CI values ( $r = 0.023$ ;  $P = 0.967$ ) at day 1. Using a mixed effect model, only age remained associated with Cl<sub>Cr</sub> variations over time. The area under the ROC curve of RVI for predicting ARC was 0.742 (95% CI: 0.649–0.834;  $P < 0.0001$ ), with statistical difference when compared to the ROC curve of ARCTIC [0.842 (0.771–0.913);  $P < 0.0001$ ].

**Conclusion:** Ultrasonic evaluation of CI and RVI did not allow approaching the haemodynamic mechanisms responsible for ARC in patients. RVI was inaccurate and not better than clinical score for predicting ARC.

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## 1. Background

For several years, augmented renal clearance (ARC) has been increasingly investigated in critical care practice, currently defined by an increased urinary creatinine clearance (Cl<sub>Cr</sub>) exceeding 130 mL/min/1.73m<sup>2</sup> [1]. This is a major concern as ARC has been recognised as one of the leading causes of subtherapeutic antibiotic

exposure, potentially responsible for poor clinical outcome in septic patients [2–4]. Although a prompt recognition of ARC should be crucial for optimising empirical antibiotic dosing, few screening tools available at the bedside have shown adequate predictive abilities for identifying patients with ARC [5,6].

Moreover, the pathophysiologic mechanisms responsible for ARC in critically ill patients remain mainly unknown, although alterations in both glomerular filtration and renal tubular function have been observed [7]. The most widespread theory involves an increase in cardiac index (CI), resulting in an enhanced renal blood flow (RBF) and therefore an increased glomerular filtration rate (GFR) [8]. On the other hand, some authors suggested that changes in vasomotor tone and intra-glomerular filtration pressure were potentially the main mechanism underlying ARC in critically ill patients [9].

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Renal Doppler vascular index (RVI) has been used to reflect regulation of renal vascular tone in the critical care settings [10]. A recent meta-analysis suggested that abnormally high RVI was associated with further renal impairment in septic critically ill patients [11]. In addition, RVI seems to be of interest in evaluating changes in renal perfusion as a consequence of therapeutic interventions [12–14]. The ability of RVI to predict ARC remains questionable and still needs to be demonstrated.

The main objective of this study was thus to investigate the relationship between  $Cl_{Cr}$ , RVI and CI in critically ill trauma patients with or without ARC. The secondary objective was to assess the performance of RVI for the early prediction of ARC.

## 2. Methods

### 2.1. Design, population and settings

This study is a retrospective analysis of our local database (declared to the French Data Protection Authority: declaration number 2166637v0) prospectively collected in a 25-bed Surgical and Trauma Intensive Care Unit (ICU). Ethical approval for this analysis was obtained from the Ethics Committee of the French Society of Anaesthesia and Intensive Care Medicine (IRB number: CERAR 00010254-2018-089). The patients and/or next of kin were informed about the inclusion of their anonymised health data in the database, and none declined participation.

During the study period, every trauma patient who underwent cardiac and renal ultrasound during the initial ICU management was included. The ultrasound measurements were performed by one of our attending physician as part of a standard care over a 3-month period. Non-inclusion criteria were pregnancy, age < 18 years, end-stage renal failure or indication for renal replacement therapy, known renal artery stenosis, cirrhosis, congestive heart failure, atrial fibrillation or arrhythmia.

### 2.2. Data collection and ultrasound measurements

Our local database included daily metabolic, haemodynamic and ultrasound measurements prospectively collected as part of a standard care in every trauma patient. Data collection started within 48 hours of ICU admission and was discontinued at 1) ICU discharge, 2) development of severe renal impairment ( $Cl_{Cr} < 30 \text{ mL/min/1.73 m}^2$ ) or institution of renal replacement therapy, 3) removal of invasive monitoring or 4) day 5, whichever came first. Plasma and urinary samples were recorded during the first five days after admission and measured  $Cl_{Cr}$  was calculated as follows: converted in mL/min and normalised to a body surface

area of  $1.73 \text{ m}^2$  (Dubois formula). As previously described, ARC was defined by a measured  $Cl_{Cr} \geq 130 \text{ mL/min/1.73 m}^2$  [1]. A predictive scoring model called ARCTIC (ARC in trauma intensive care) was also calculated each day as originally described [15]:  $SCr < 62 \mu\text{mol/L}$  (3 points), male sex (2 points), Age < 56 years (4 points) or 56–75 years (3 points).

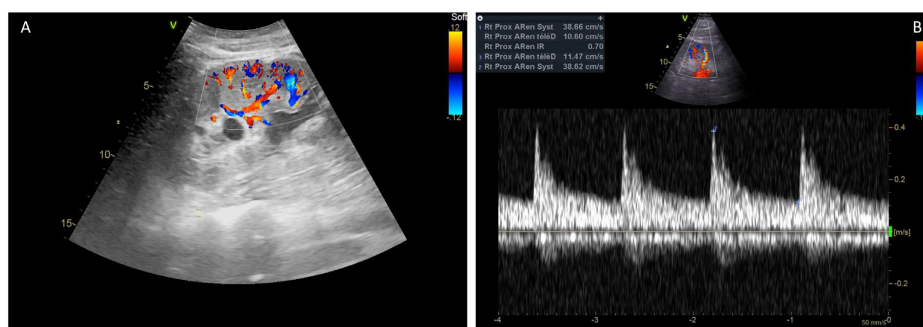
All cardiac and renal ultrasound measurements were performed using a General Electric Vivid S6 machine (GE Healthcare, Wauwatosa, WI, USA) by an experienced physician unaware of the measured  $Cl_{Cr}$ . As previously described, RVI was obtained from the most representative proximal interlobar arteries [10]. The peak systolic velocity ( $V_{max}$ ) and the minimal diastolic velocity ( $V_{min}$ ) were determined by pulse wave Doppler, and RVI was calculated as  $(V_{max}-V_{min})/V_{max}$ . The results from three consecutive similar-appearing waveforms were averaged for each kidney (Fig. 1). Using echocardiography, stroke volume (SV) was calculated as the product of the aortic valve area ( $\pi/\text{diameter}^2/4$ ) by the area under the envelope of the pulsed-wave Doppler measured at the aortic annulus and averaged over three consecutive measurements. Cardiac output was calculated as the product of heart rate (HR) and stroke volume, indexed to the body surface area ( $\text{L/min/m}^2$ ). Intra-observer variability coefficient, assessed in ten patients before the study, was  $5 \pm 3\%$  for RVI and  $4 \pm 3\%$  for VTI.

### 2.3. Statistical analysis

Results are expressed as mean  $\pm$  standard deviation or median (25% to 75% interquartile range) for continuous variables and as numbers (percentages) for categorical variables. The data distribution was analysed by a Kolmogorov-Smirnov test. Non-paired analysis of continuous variables was performed using the Student *t*-test or the Mann-Whitney test as appropriate. Categorical variables were compared using the Chi<sup>2</sup> test or Fisher's exact test as appropriate.

The first paired data were compared using Spearman's correlation coefficient. To model changes of  $Cl_{Cr}$  over time, a random components mixed-effects model was constructed [1]. Relevant covariates were added as a forward stepwise procedure to obtain the smallest Akaike information criterion (AIC). The addition of covariates was stopped when no further decrease of AIC was obtained.

For the secondary outcome of the study, the accuracy of RVI to predict ARC was assessed using a receiving operator curve (ROC) analysis. The best threshold values were chosen to maximize Youden index. A threshold analysis was also performed using a grey zone approach [16]. Furthermore, recent data have been suggesting that an ARCTIC score of 6 or higher was an appropriate cutoff to screen for ARC, although external validation is lacking. We



**Fig. 1.** Principles of measurements of renal Doppler vascular index (RVI). A. Visualization of proximal interlobar arteries in color-Doppler mode. B. Peak systolic velocity ( $V_{max}$ ) and minimal diastolic velocity ( $V_{min}$ ) determined by pulsed Doppler from three consecutive similar-appearing waveforms. RVI calculated as  $(V_{max}-V_{min})/V_{max}$  [10].

**Table 1**  
Characteristics of the population.

	Overall (n = 30)	Non ARC patients (n = 10)	ARC patients (n = 20)	P
Demographic data				
Age	48 [32–67]	69 [66–84]	37 [29–54]	0.002
Male sex	27 (90)	10 (100)	17 (85)	0.197
Body mass index (kg/m <sup>2</sup> )	26 [22–29]	27 [23–30]	26 [21–28]	0.416
Reason for admission				
Multiple trauma with brain trauma	13 (43)	4 (40)	9 (45)	0.794
Isolated brain trauma	9 (30)	4 (40)	5 (25)	0.398
Multiple trauma without brain trauma	8 (27)	2 (20)	6 (30)	0.559
SAPS II at ICU admission	42 [22–49]	50 [46–54]	31 [19–42]	0.0003
ISS	34 [29–50]	46 [29–57]	32 [28–42]	0.184
Mechanical ventilation at ICU admission	22 (73)	7 (70)	15 (75)	0.770
Norepinephrine at ICU admission	14 (47)	6 (60)	8 (40)	0.301
Median duration for norepinephrine infusion	1 [0–2]	1 [0–1]	1 [0–2]	0.697
Median values from day 1 to 5				
Serum creatinine (μmol/L)	58 [50–79]	84 [56–106]	55 [46–65]	0.019
24-hr urinary Cr <sub>CL</sub> (mL/min/1.73 m <sup>2</sup> )	127 [84–170]	64 [46–94]	157 [131–192]	< 0.0001
RVI	0.65 [0.61–0.70]	0.72 [0.67–0.75]	0.63 [0.60–0.67]	0.008
CI (L/min)	2.59 [2.16–3.26]	2.48 [1.95–2.81]	2.63 [2.26–3.37]	0.344
MAP (mmHg)	87 [80–97]	91 [81–103]	86 [75–94]	0.06
ARCTIC Score	7 [5–9]	5 [5–6]	8 [6–9]	< 0.0001
Length of stay in ICU	12 [8–17]	14 [8–17]	12 [9–15]	0.203
Death in ICU	3 (10)	2 (20)	1 (5)	0.197

Results expressed in numbers (percentages) or median [25% to 75% interquartile range]. ARC patients: patients who manifested ARC ( $Cr_{CL} > 130$  mL/min/1.73 m<sup>2</sup>) on at least one occasion during the first five study days [1]. CI: cardiac index; Cr<sub>CL</sub>: creatinine clearance; ICU: intensive care unit; ISS: injury severity score; MAP: mean arterial pressure; RVI: renal vascular index; SAPS: simplified acute physiologic score.

thus aimed to compare areas under ROC curves between RVI and ARCTIC score using the DeLong test [17].

A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2017 for Windows (Addinsoft Paris, France).

### 3. Results

#### 3.1. Population

The final dataset consisted of 121 coupled individual data of Cr<sub>CL</sub>, RVI and CI collected from 30 trauma patients. Overall, 67% (20/30) of the patients manifested ARC on at least one occasion during the first five study days. The characteristics of the population are resumed Table 1.

Mean value for Cr<sub>CL</sub> was  $128 \pm 57$  mL/min/1.73m<sup>2</sup> and ARC was found in 61/121 urinary samples (50%). Representation of Cr<sub>CL</sub>, RVI and CI over time is shown in Supplementary data. The intra-patient variability coefficients were  $15 \pm 10\%$  for Cr<sub>CL</sub>,  $6 \pm 4\%$  for RVI and  $19 \pm 9\%$  for CI without significant difference over the three consecutive days.

#### 3.2. Relationship between Cr<sub>CL</sub>, RI and systemic hemodynamic data

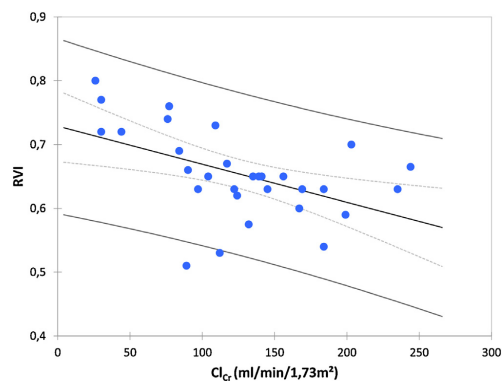
There was a significant correlation between Cr<sub>CL</sub> values and RVI ( $r = -0.495$ ;  $P = 0.005$ ) but not between Cr<sub>CL</sub> and CI values ( $r = 0.023$ ;  $P = 0.967$ ) at day 1 (Fig. 2). There was a significant correlation between RVI values and age ( $r = 0.676$ ;  $P < 0.0001$ ). There was no correlation between RVI and MAP ( $P = 0.679$ ), whether in patients with or without ARC. For a given MAP, lower RVI values were observed in ARC patients (Supplementary data).

Using a mixed effect model, only age (AIC 1069.8;  $p < 0.001$ ) and RVI (AIC = 1083;  $P < 0.047$ ) remained associated with Cr<sub>CL</sub> over time. Gender, mechanical ventilation, CI, mean MAP or norepinephrine doses were not predictive of daily Cr<sub>CL</sub>. A model parameterized with the two covariates (i.e. age and RVI, model  $n + 1$ ) had an AIC of 1071 and was no statistically different from the model  $n$  (i.e. age) by the likelihood ratio test ( $P = 0.34$ ). The random component variance (RVI or CI) did not have a significant effect on the global model.

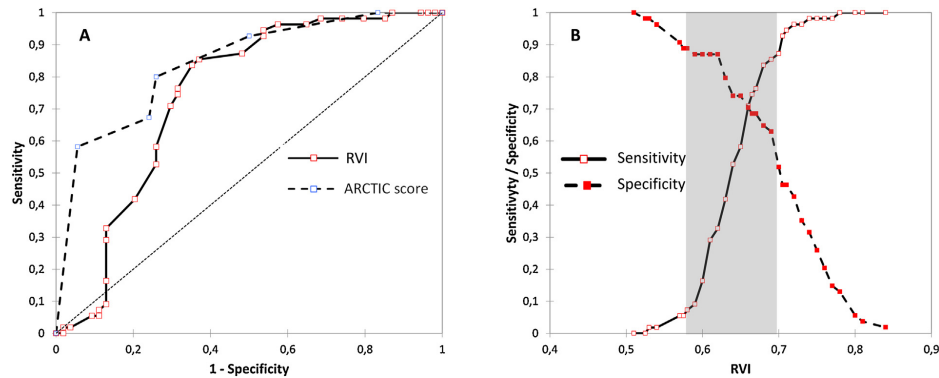
#### 3.3. Performance of RVI in predicting the occurrence of ARC

The area under the ROC curve of RVI for predicting ARC was 0.742 (95% CI: 0.649–0.834;  $P < 0.0001$ ) (Fig. 3). A threshold of RVI < 0.68 had a sensitivity and specificity of 0.84 (95% CI: 0.71–0.91) and 0.65 (95% CI: 0.51–0.76) respectively. The grey zone approach was comprised between 0.57 and 0.70, with 64% of RVI measurements falling in the inconclusive grey zone.

On the other hand, an ARCTIC Score > 6 had a sensitivity and specificity of 0.82 (95% CI: 0.70–0.90) and 0.73 (95% CI: 0.61–0.83) respectively. The area under the ROC curve of ARCTIC for predicting ARC was 0.842 (95% CI: 0.771–0.913;  $P < 0.0001$ ) with statistical difference when compared to RVI ( $P = 0.049$ ).



**Fig. 2.** Relationship between creatinine clearance (Cr<sub>CL</sub>) and renal Doppler vascular index (RVI) at day 1 in 30 critically ill trauma patients. Correlations were assessed using Spearman correlation coefficient ( $R^2 = 0.245$ ,  $P = 0.005$ ).



**Fig. 3.** A. ROC curves of RVI (continuous line, AUC = 0.742 [95% CI: 0.649–0.834];  $P < 0.0001$ ) and ARCTIC score [dotted line, AUC = 0.842 (95% CI: 0.771–0.913;  $P < 0.0001$ )] for predicting augmented renal clearance ( $P = 0.049$ ). B. The inconclusive grey zone of RVI is displayed as a grey rectangle for an RVI between 0.57 and 0.70 (64% of RVI measurements).

#### 4. Discussion

To our knowledge, this is the first study assessing the potential hemodynamic mechanisms underlying ARC using RVI in critically ill trauma patients. The hypothesis pertaining to this study was that:

- lower RVI for a given MAP should reflect the inhibition of arteriolar tone responsible for ARC in critically ill patients;
- the sustained vasodilatation may contribute to kidney autoregulation impairment;
- RBF and GFR becoming dependent of changes in systemic haemodynamics.

Despite an inverse correlation between RVI and  $Cl_{Cr}$ , neither RVI nor CI remained associated with ARC after adjustment for confounding covariates. Age remained the only independent variable associated with  $Cl_{Cr}$  over time.

The demographic characteristics of ARC patients should reflect the higher renal functional reserve in younger patients [18]. Renal functional reserve is defined by the ability of the kidney to respond to an increased physiological demand through a combination of nephron recruitment, increase in renal blood flow and/or glomerular hyperfiltration. This hypothesis was also suggested by Udy et al. who demonstrated an elevation of glomerular filtration and high renal plasma flow using exogenous markers in 20 critically ill patients with ARC [9]. For a given renal plasma flow, authors observed considerable variations in filtration fraction. These data indicate that changes in intra-glomerular filtration pressure (due to variable afferent and efferent arteriolar tone) are potentially a key mechanism underlying ARC in critically ill patients [9]. In agreement with these data, some authors thus assumed that the combination of an inhibition of arteriolar vascular tone coupled with an increased renal blood flow in patients with a greater physiological reserve should be accepted as the leading mechanism for ARC [7].

However, our study failed to estimate arteriolar vascular tone using RVI in a specific population at risk for ARC. Several factors should explain our negative results. First, determinants of RVI are multiple, including renal vascular resistances (RVR) and compliance, renal interstitial pressure, ureteral pressure or systemic arterial pressure [19]. Former data demonstrated that the relationship between vascular resistance and RVI was linear only when vascular compliance was normal [20,21]. In this context,

age-related arterial stiffening may greatly influence RVI values [22]. Moreover, most of patients with ARC displayed physiological range of RVI reported in healthy subjects ( $0.60 \pm 0.01$ ) [23]. Physiological RVI values cannot be interpreted as a decreased vascular tone explaining supraphysiological  $Cl_{Cr}$  values. The correlation between RVI and  $Cl_{Cr}$  may thus be explained by the interdependence between age and these two covariates. Finally, we did not observe any statistical association between RVI and MAP, although ARC patients displayed lower RVI values for a given MAP. Although RVI is not a valuable reflect of RBF, Lerolle et al. previously demonstrated a negative relationship between MAP and RVI which could be consistent with the physiological increase in RVR in hypoperfusion situations [24]. This assessment was challenged by Dewitte et al. in which such a relationship was only observed in patients without persistent AKI, suggesting that RVI could only reflect renal autoregulation before the occurrence of renal vascular or tubular damage [25]. The ability of RVI to reflect renal autoregulation thus remains questionable and still need to be demonstrated.

In this context, RVI was inaccurate and not better than the ARCTIC score for predicting ARC in critically ill trauma patients. The considerable overlap in RVI values between patients with and without ARC precludes the use of RVI as a screening marker for ARC. The ARCTIC score is a practical and pragmatic system that can help the clinician to consider dosing adjustments. Our results corroborate the predictive value of a score greater than or equal to 6 as an appropriate threshold for ARC screening [15]. On the other hand, a prompt recognition of ARC is crucial in critically ill patients to optimise empirical antibiotic dosing. Commonly used formulas underestimate measured  $Cr_{Cl}$  and frequently misclassify ARC [5,6]. Measured  $Cl_{Cr}$  remains the reference and should be monitored daily in at-risk patients [1].

The current study has some limitations. First, the design was monocentric with a retrospective analysis over a relatively short period, with potential selection bias that limits the generalizability of the results. Moreover, we acknowledge a limited number of patients, although contributing for numerous ultrasound measurements, prospectively collected and blinded for  $Cl_{Cr}$  values. Second, RVI and CO levels were measured once per day whereas  $Cl_{Cr}$  was recorded from the 24-hr urinary samples. As those parameters may vary widely over 24 h in ICU patients, it is uncertain that  $Cl_{Cr}$  data correspond to the actual  $Cl_{Cr}$  at the time of other physiologic parameters measurements. This limitation could explain the poor correlation between CI and 24-hr  $Cl_{Cr}$  when compared to other studies assessing continuous CI

measurements [8]. Finally, 24-hr measured  $Cl_{Cr}$  is known to overestimate glomerular filtration rate and RVI is far from being the most valuable marker of renal vascular resistance or plasma renal flow [26]. On the other hand, the clinical evaluation of renal autoregulation is restricted because of the lack of non-invasive RBF assessment at the bedside [18]. Standardised and valuable measurements of GFR and RBF by exogenous markers, contrast-enhanced ultrasound and/or magnetic resonance imaging might be necessary to corroborate the hypothesis pertaining to this study.

## 5. Conclusion

Ultrasonic evaluation of CI and RVI does not allow approaching the haemodynamic mechanisms responsible for ARC in patients. RVI was inaccurate and not better than the ARCTIC Score for predicting ARC in critically ill trauma patients. Further studies are thus needed to explore haemodynamic determinates in this specific population at risk for ARC.

## Ethics approval and consent to participate

Ethical approval for this single-center, non-interventional study was obtained from the Ethics Committee of the French Society of Anesthesiology and Intensive Care (IRB number: CERAR 00010254-2018-089) which waived the need for written consent. According to the French law, the database was declared to the French Data Protection Authority (declaration number: 2166637v0). The patients and/or next of kin were informed about the inclusion of their anonymized health data in the database, and none declined participation.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Funding

Only departmental funds were used for this study. No external funds were obtained.

## Authors' contributions

CC helped to conceive the study and design the trial, helped to analyse the data and to draft the manuscript. AL performed all ultrasound measurements and supervised data collection. SR and LP helped to analyse the data and to draft the manuscript. HDC and MB helped to provide statistical advice and to draft the manuscript. All authors read and approved the final manuscript.

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgments

Not applicable

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, <https://doi.org/10.1016/j.accpm.2018.12.004>.

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Letter to the Editor

**Renal response after traumatic brain injury:  
A pathophysiological relationship between  
augmented renal clearance and salt wasting syndrome?**

Dear Editor,

Traumatic brain injury (TBI) is frequently associated with perturbations of renal function including augmented renal clearance (ARC) or salt wasting syndrome (SWS) [1]. In this context, we hypothesised that the enhanced osmole excretion could be (at least partially) induced by the increased glomerular filtration rate and proximal tubular fluid output. The main objective of this pilot study was thus to explore the relationship between creatinine clearance ( $CL_{CR}$ ), urinary osmole excretion ( $Osm_U$ ) and free water clearance ( $CL_{H2O}$ ).

For this purpose, we performed a retrospective analysis of a local database prospectively collected over an 8-month period (June 2018 to January 2019) in every trauma patient consecutively admitted in a 25-bed Surgical and Trauma Intensive Care Unit (ICU). Patients were excluded if they received mannitol, desmopressin, radiographic contrast agent, diuretics, angiotensin-converting enzyme inhibitors or mineralocorticoids during the first week of ICU management. Ethical approval was obtained from the Ethics Committee of the French Society of Anaesthesia and Intensive Care Medicine (CERAR 00010254-2018-153). Our local database included metabolic and haemodynamic parameters prospectively collected as part of a standard care in every trauma patient [2]. Plasma and urinary samples <https://mail.chu-bordeaux.fr/owa/UrlBlockedError.aspx> were recorded daily and measured  $CL_{CR}$  was calculated as follows:

$$\frac{24\text{-h urinary volume (ml/day)} \times \text{urinary creatinine (mmol/L)}}{\text{plasma creatinine } (\mu\text{mol/L})}$$
, converted in ml/min and normalised to a body surface area of  $1.73\text{ m}^2$ . ARC was defined by a 24-hour urinary  $CL_{CR} \geq 150\text{ ml/min/1.73m}^2$  for women and  $160\text{ ml/min/1.73 m}^2$  for men [3]. Free water clearance ( $CL_{H2O}$ ) was also calculated as follows:

$$24\text{-h urine volume} \times \left(1 - \frac{\text{Urinary osmolality (mmol/kg)}}{\text{Plasma Osmolality (mmol/kg)}}\right)$$
, converted in ml/min/1.73m<sup>2</sup>. The first paired data were compared using Spearman's correlation coefficient. A mixed effect model was generated to assess the variations of  $CL_{CR}$ ,  $Osm_U$  and  $CL_{H2O}$  over time. Data between day 7 and day 1 were compared using paired samples Wilcoxon test. Finally, multiple linear regression models were used to assess the adjusted effect of time-averaged  $CL_{CR}$ ,  $Osm_U$  and  $CL_{H2O}$ . Adjustment was considered for mean values of fluid intake, sodium intake and doses of norepinephrine.

The final dataset consisted of 199 coupled individual data of  $CL_{CR}$ ,  $CL_{H2O}$  and  $Osm_U$  collected from 30 brain trauma patients (11 missing urinary samples). Patients were mainly young (33 [47–57] years), admitted for a severe TBI (initial Glasgow score of 9 [6–13]) with a median SAPS2 of 39 [28–46]. Only 10 patients (33%) underwent a neurosurgical procedure and 3 (10%) were treated for

a refractory intracranial hypertension (craniectomy, barbiturates and/or hypothermia). Overall, 77% (23/30) of the patients manifested ARC on at least one occasion during the first seven study days. The evolution of haemodynamic and metabolic parameters over time is shown in Table 1. At day 1, there was a significant correlation between  $CL_{CR}$ ,  $Osm_U$  and  $CL_{H2O}$  values ( $R^2 = 0.249$ ,  $P = 0.007$  and  $R^2 = 0.146$ ,  $P = 0.041$ , respectively). As shown in Fig. 1, the evolution of the  $CL_{CR}$ ,  $Osm_U$  and  $CL_{H2O}$  over time was parallel until day 4 (adjusted effect  $3.88 \pm 1.53$ ,  $P = 0.02$  and  $-0.005 \pm 0.002$ ,  $P = 0.01$ , respectively). Beyond this period,  $Osm_U$  and  $CL_{H2O}$  reached a plateau despite a decrease in  $CL_{CR}$  values (adjusted effect  $0.36 \pm 1.24$ ,  $P = 0.772$  and  $-0.001 \pm 0.001$ ,  $P = 0.40$  respectively). Finally, there was no significant correlation between  $CL_{CR}$  and natriuresis or urine osmolality, similar values being observed in patients who manifested or not ARC during the first seven study days ( $128 \pm 34$  vs  $127 \pm 45$  mmol/L,  $P = 0.769$  and  $615 \pm 110$  vs  $555 \pm 111$  mOsm/L,  $P = 0.220$ , respectively).

In this highly selected population, our results confirmed a significant association between  $CL_{CR}$  and enhanced  $Osm_U$  over the first study days, independently of fluid and salt intake or norepinephrine doses. The hypothesis underlying these results was that:

- the marked increase in GFR should be associated with an increased tubular fluid output, responsible for an enhanced diuresis and osmole excretion;
- the decreased vascular volume resulting from negative sodium balance should be the trigger for increased renal free-water reabsorption after antidiuretic hormone (ADH) secretion [1].

However, the relationship between both parameters was only modest, with only 25% ( $r^2 = 0.249$ ) of the variability in  $Osm_U$  explained by variation in  $CL_{CR}$ . Moreover, there was no significant correlation between  $CL_{CR}$  and natriuresis. In this respect, ARC should not be considered as a leading mechanism of SWS, high median values of natriuresis or urine osmolality being found in patients without ARC. This result reinforces the multifactorial pathophysiology of SWS in brain-damaged patients, which deserves further investigations.

Moreover, the association between  $CL_{CR}$  and  $Osm_U$  was not straightforward after day 5, where  $Osm_U$  reached a plateau despite a decrease in  $CL_{CR}$  values. Several hypotheses may explain this "escape phenomenon". First, decreased vascular volume resulting from negative sodium balance may lead to the physiological increase of pre-glomerular arteriolar resistance, which counterbalances the theoretical mechanism for ARC. Second, the GFR may be reduced by the tubuloglomerular feedback in response to the enhanced distal tubular fluid flow rate. Third, some authors hypothesised a defect in sodium transport in the proximal tubule, as suggested by the increased excretion fraction of solutes exclusively transported in the proximal tubule such as lithium, 100

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**Table 1**  
Evolution of haemodynamic and metabolic parameters over time.

	Day 1 N=29	Day 2 N=29	Day 3 N=29	Day 4 N=30	Day 5 N=30	Day 6 N=27	Day 7 N=25
Fluid intake (ml/24h)	2776 [2477–3494]	3052 [2694–3628]	2727 [2368–3578]	2886 [2509–3578]	2906 [1999–3554]	2716 [2156–3388]	2598 [1959–3248]
Fluid balance (ml/24h)	1331 [683–1777]	1153 [611–2130]	1055 [247–1860]	999 [357–1728]	772 [–110–1661]	660 [–335–1106]	174 [–426–721] <sup>a</sup>
Sodium intake (mmol/24h)	336 [309–409]	326 [277–408]	293 [255–405]	300 [229–352]	298 [253–338]	263 [198–400]	263 [216–330] <sup>a</sup>
Sodium balance (mmol/24h)	230 [148–293]	140 [48–267]	105 [–72–191]	–49 [–130–78]	–13 [–168–185]	–19 [–115–149]	23 [–107–87] <sup>a</sup>
Mean MAP (mmHg)	85 [81–92]	89 [83–93]	89 [83–96]	92 [86–96]	94 [86–97]	95 [91–100]	91 [89–102]
Use of mechanical ventilation	27 (93)	25 (83)	21 (70)	21 (70)	18 (60)	13 (48)	12 (44) <sup>a</sup>
Use of vasopressor	21 (72)	15 (50)	12 (40)	12 (40)	7 (23)	2 (7)	3 (12) <sup>a</sup>
Diuresis (ml/24h)	1600 [1000–2000]	1600 [1263–2363]	1550 [1313–1975]	2100 [1700–2500]	2000 [1525–2488]	2000 [1600–3075]	2200 [1800–3200] <sup>a</sup>
Serum creatinine (μmol/L)	67 [58–79]	59 [52–70]	55 [50–63]	58 [46–65]	55 [45–62]	53 [44–67]	52 [47–64] <sup>a</sup>
Urinary creatinine excretion (mmol/24h)	14 [12–17]	15 [12–17]	14 [11–16]	15 [11–17]	13 [10–17]	13 [10–15]	12 [10–14]
24-hr Cl <sub>CR</sub> (ml/min/1.73m <sup>2</sup> )	146 [110–162]	153 [105–176]	156 [129–179]	162 [131–186]	162 [122–178]	146 [126–166]	139 [122–157]
Plasma Osmolality (mOsm/kg)	295 [296–303]	299 [296–302]	300 [294–304]	303 [297–310]	300 [296–306]	300 [295–304]	299 [295–305]
Urinary Osmole excretion (mOsm/24h)	827 [629–993]	948 [684–1152]	995 [821–1201]	1317 [1031–1621]	1387 [1021–1589]	1393 [1126–1592]	1222 [988–1604] <sup>a</sup>
24-hr Cl <sub>H<sub>2</sub>O</sub> (ml/min/1.73m <sup>2</sup> )	–0.70 [–1.06–0.52]	–0.83 [–1.26–0.60]	–1.09 [–1.29–0.67]	–1.36 [–1.81–0.96]	–1.43 [–1.73–1.15]	–1.51 [–1.83–1.25]	–1.28 [–1.79–1.09] <sup>a</sup>
Natremia (mmol/L)	140 [138–141]	141 [139–143]	141 [139–143]	141 [139–145]	141 [139–143]	140 [137–142]	140 [137–141]
Urinary sodium excretion (mmol/24h)	118 [86–190]	166 [126–275]	208 [109–347]	321 [231–451]	299 [215–395]	276 [188–433]	248 [160–414] <sup>a</sup>
Fractional excretion of sodium (%)	0.51 [0.26–0.70]	0.53 [0.35–0.87]	0.74 [0.27–1.01]	0.96 [0.62–1.40]	0.86 [0.52–1.32]	0.83 [0.47–1.31]	0.82 [0.56–1.33] <sup>a</sup>
Serum urea (mmol/l)	4.6 [3.5–5.8]	3.7 [3.0–5.9]	3.5 [2.6–5.1]	4.0 [2.9–6.4]	5.5 [3.7–6.0]	5.8 [4.5–7.0]	5.7 [5.1–8.0] <sup>a</sup>
Urinary excretion (mmol/24h)	378 [223–419]	348 [246–448]	319 [247–477]	215 [155–282]	549 [344–630]	551 [466–677]	536 [415–693] <sup>a</sup>
Fractional excretion of urea (%)	35 [30–39]	37 [31–45]	38 [33–48]	42 [37–53]	46 [37–48]	45 [33–53]	45 [41–55] <sup>a</sup>
Serum Urate (μmol/L) <sup>b</sup>	193 [140–221]	139 [105–175]	123 [94–150]	115 [89–143]	113 [84–142]	123 [97–134]	117 [98–138] <sup>a</sup>
Urinary urate excretion (mmol/24h) <sup>b</sup>	4.1 [3.3–4.8]	3.6 [2.7–5.0]	4.1 [3.6–4.7]	4.5 [3.7–5.4]	4.3 [3.3–5.0]	5.1 [3.8–5.4]	4.1 [3.5–5.9]
Fractional excretion of urate (%) <sup>b</sup>	12 [8–17]	14 [10–16]	15 [11–18]	15 [11–19]	16 [12–18]	16 [13–20]	17 [14–19] <sup>a</sup>
BNP values (pg/ml) <sup>c</sup>	30 [21–65]	71 [20–187]	55 [28–173]	97 [44–302]	113 [80–209]	44 [34–60]	69 [23–151]

Data expressed as median [interquartile 25–75] and numbers (percentages).

<sup>a</sup> P < 0.05 between day 1 and day 7.

<sup>b</sup> At least one value available in 26 patients.

<sup>c</sup> At least one value available in 23 patients.

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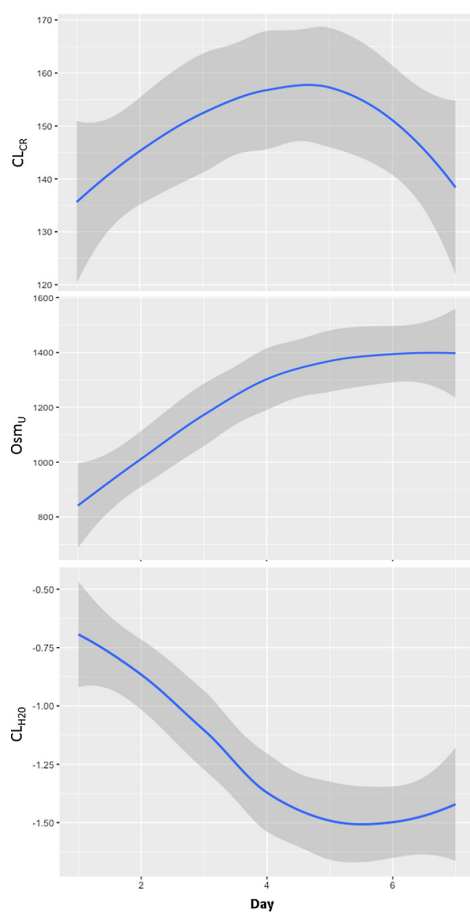


Fig. 1. Mixed-effect model describing creatinine clearance (CLCR), urinary osmole excretion (OsmU) and free water clearance (CL<sub>H2O</sub>) variations over time.

urate and eventually phosphate [4]. Our results might comfort this hypothesis, high  $FE_{urate}$  values being reported with a significant increase over time. Moreover, proximal renal tubular dysfunction has also been advocated in brain-damaged patients [5]. Whether the defect in proximal tubular function is a consequence of ARC remains to be investigated.

In conclusion, augmented renal clearance is highly prevalent in TBI patients, associated with enhanced urinary osmole excretion over the first study days. ARC should be considered as a risk factor for hypovolaemia and may be the trigger for increased renal free-water reabsorption. Further studies are needed to explain the consequences of TBI in proximal tubular function.

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**Disclosure of interest**

The authors declare that they have no competing interest.

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**Augmented renal clearance in critically ill trauma patients:  
a pathophysiologic approach using renal vascular index.**

**BACKGROUND:** In critically ill trauma patients, augmented renal clearance (ARC) is common and may result in subtherapeutic antibiotic exposure. The aim of the present study was to explore the relationship between creatinine clearance ( $Cr_{CL}$ ), cardiac output (CO) and renal Doppler vascular index (RVI) in order to assess the potential mechanisms driving ARC in this population.

**METHODS:** This study involves a retrospective review of a prospectively collected database of every trauma patients consecutively admitted to a 25-bed Surgical and Trauma Intensive Care Unit (ICU) over a 3-month period. Were included every trauma patients who underwent cardiac and renal ultrasound measurements over three consecutive days during their initial ICU management. ARC was defined by a 24-hr urinary measured  $Cr_{CL} > 130$  ml/min

**RESULTS:** Thirty patients, contributing for 86 coupled physiologic data, were retrospectively analyzed. There was an inverse correlation between  $Cr_{CL}$  and RVI values ( $\rho = -0.501$ ;  $p < 0.0001$ ). The best threshold value for RVI to predict ARC was 0.65 (sensitivity 76% [62 – 86]; specificity 72% [56 - 84]). There was only a slight correlation between  $Cr_{CL}$  and CO values ( $\rho = 0.219$ ;  $p = 0.05$ ). There was no statistical correlation between RVI and MAP ( $\rho = -0.09$ ;  $p = 0.41$ ), whether in patients with or without ARC.

**CONCLUSION:** The combination of an inhibition of arteriolar vascular tone coupled with an increased cardiac output in patients with a greater physiological reserve should be accepted as the leading mechanism for ARC.

**Salt wasting syndrome in the brain-damaged patients:  
a pathophysiologic approach using sodium balance and urinary biochemical analysis**

**PURPOSE:** To explore the underlying mechanisms leading to the occurrence of hyponatremia and enhanced urinary sodium excretion in brain-damaged patients using sodium balance and urinary biochemical analysis.

**METHODS:** We conducted a retrospective analysis of a local database prospectively collected in 60 brain trauma patients without chronic renal dysfunction. Metabolic and hemodynamic parameters were averaged over three consecutive periods over the first seven days after admission. The main outcome investigated in this study was the occurrence of at least one episode of hyponatremia.

**RESULTS:** Over the study period, there was a prompt decrease in sodium balance ( $163 \pm 193$  vs.  $-12 \pm 154$  mmol/day,  $p < 0.0001$ ) and free water clearance ( $-0.7 \pm 0.7$  vs.  $-1.8 \pm 2.3$  ml/min,  $p < 0.0001$ ). The area under the ROC curves for sodium balance in predicting the occurrence of hyponatremia during the next period was 0.81 [95% CI: 0.64 – 0.97]. Variables associated with averaged urinary sodium excretion were sodium intake ( $R^2 = 0.26$ ,  $p < 0.0001$ ) and fractional excretion of urate ( $R^2 = 0.15$ ,  $p = 0.009$ ). Urinary sodium excretion was also higher in patients with sustained augmented renal clearance over the study period ( $318 \pm 106$  vs.  $255 \pm 135$  mmol/day,  $p = 0.034$ ).

**CONCLUSION:** The decreased vascular volume resulting from a negative sodium balance is a major precipitating factor of hyponatremia in brain-damaged patients. Predisposing factors for enhanced urinary sodium excretion were high sodium intake, high fractional excretion of urate and augmented renal clearance over the first seven days after ICU admission.

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**Thèse de doctorat en médecine**

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**Mots clés :** Traumatisme crânien, Augmentation de la clairance rénale, Syndrome de perte en sel, Hyponatrémie, Fonction rénale.

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