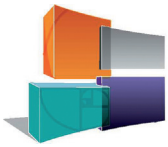
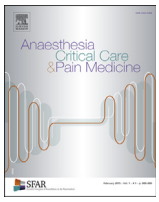
Anaesth Crit Care Pain Med 38 (2019) 335–336



SFAR
Société Française d'Anesthésie et de Réanimation



Editorial

Augmented renal clearance: A real phenomenon with an uncertain cause

ARTICLE INFO

Keywords:
Augmented renal clearance
Kidney
Critical illness
Pharmacokinetics
Drug dosing

Unfortunately, the primary pathophysiology underlying many clinical conditions remains largely unknown. Nevertheless, the lack of such information does not mean treatment should be abandoned, or clinical management not tailored accordingly. On the contrary, critical care medicine is most notable for examples where the absence of a precise diagnosis or mechanism of injury does not preclude intervention. Of course, supportive measures typically only "buy" time, and an accurate understanding of the underlying aetiology is still often required to achieve a definitive solution.

Augmented renal clearance (ARC) has been increasingly reported in adult and paediatric critically ill patients [1,2]. This condition describes the physiological response of the kidney to a variety of stimuli, and is thought to result from use of the 'redundant' capacity of the normal kidney, also known as renal reserve. As a consequence, glomerular filtration is enhanced, and the elimination of circulating solutes subject to glomerular filtration is increased, including drugs such as renally-cleared antibiotics [3–5]. The main consequence is therapeutic under-exposure, which can lead to treatment failure and a greater risk of antibiotic resistance [1]. Of note, the precise sequence of factors leading to ARC is poorly understood and under-studied [1,6–8].

In this issue of Anaesthesia, Critical Care, and Pain Medicine, Carrie et al report the results of a single centre retrospective cohort study in a surgical and trauma intensive care unit (ICU). Thirty critically ill trauma patients were included, providing of 121 days of paired creatinine clearance (CL_{CR}), renal Doppler vascular index (RVI) and cardiac index (CI) data [9]. Doppler ultrasound was employed to measure blood flow velocity, providing information on renal vascular resistance and autoregulation10. A 24-hour CL_{CR} was used to identify ARC (based on a value $\geq$ 130 mL/min/1.73m^2), and CI estimated from echocardiography findings. The major conclusions of the study were as follows:

- ARC was highly prevalent (20 of the 30 patients [67%] manifest ARC on at least one occasion);
- after adjustment for confounding covariates, there was no association between RVI or CI and ARC;
- age remained the only independent variable associated with CL_{CR} over time; and the ARCTIC Score had greater discrimination in identifying ARC, as compared with RVI [11].

The second conclusion is perhaps the most interesting, as arguably this was not expected, given the proposed pathophysiology of ARC. Indeed, RVI has been used for many years in renal vascular disease, hypertension, acute kidney injury and renal transplant. A high RVI ($>$ 0.70) is usually associated with a poor prognosis, limited therapeutic response, or a more rapid decline in renal function in patients with acute or chronic kidney disease. On the other hand, a low RVI ($<$ 0.70) has been associated with an improvement in renal function (following specific therapeutic interventions [12]) or in patients with acute pre-renal conditions [10]. As such, assessing RVI as a means to identify arteriolar vasodilatation (and loss of renal autoregulation) as an important mechanism underlying ARC, appears well justified. In this respect, although Carrie et al found an association between CL_{CR} and RVI on day one, this relationship was modest, with only 25% (r^2 = 0.245) of the variability in CL_{CR} explained by variation in RVI. This reinforces the multifactorial aetiology of ARC and the need for larger sample sizes to more conclusively establish associations between pathophysiological changes and ARC.

A further possible explanation for these results is the inherent variability in physiological parameters over time, resulting in substantial intra-patient heterogeneity in haemodynamics and CL_{CR}. As such, by utilising 24h-CL_{CR} as the reference method, while performing RVI and CI measurements only once a day, the authors were perhaps unlikely to observe a robust correlation between these parameters. Alternatively, the use of shorter intervals for the evaluation of CL_{CR} and serial measurements might have provided greater clarity. In this respect, prior literature suggests a weak correlation between CI and CL_{CR} (r = 0.34, P = 0.003) when using 2h-CL_{CR} and pulse contour arterial waveform analysis [7]. Of interest, this was primarily due to the relationship observed in septic patients, with no correlation observed in the trauma group.

Importantly, the study by Carrie et al consolidates recent data [13–15] concerning ARC, and suggests this phenomenon is highly prevalent in the critical care setting, particularly in trauma patients. In addition, their finding that age was the only

https://doi.org/10.1016/j.accpm.2019.03.002

independent risk factor associated with 24-CL_{CR} fits nicely with the concept of "renal reserve", presumably being greater in younger people due to better glomerular preservation and function [16]. That the ARCTIC score provided better discrimination compared with RVI in this cohort, also reinforces this assertion [11].

While these data do not provide greater clarity as to the mechanism underlying ARC, they remind the reader of the importance of assessing renal function in the critically ill, as opposed to focusing on the development of kidney injury. Indeed, the implications of ARC primarily relate to the impact on drug-handling, where enhanced renal elimination may result in sub-therapeutic drug exposure. While this has been most frequently reported in reference to antibiotics, a similar paradigm applies to any renally cleared agent (such as some low-molecular-weight heparins or anti-epileptic drugs like levetiracetam). As such, in addition to a deeper understanding of the underlying pathophysiology, pragmatic clinical guidance is also required, particularly given the ubiquitous use of these drugs. We would therefore suggest the following three priorities in tailoring treatment in ARC patients:

- daily measurement of CL_{CR} (as opposed to the use of estimates [17]) so as to accurately identify high-risk patients;
- consideration of higher empirical doses, adapted to augmented renal function and with consideration of the safety window of the drug [18];
- the more frequent use of therapeutic drug monitoring, so as to optimize drug exposure [19].

Although these strategies have a limited evidence base, they offer sensible clinical guidance while further studies investigating the mechanisms responsible and clinical consequences of ARC in the critically ill are forthcoming.

Disclosure of interest

The authors declare that they have no competing interest.
JA Roberts would like to declare unrelated consultancies or grants from Biomerieux, MSD, Astellas, Accelerate Diagnostics and Bayer.

References

[1] Baptista JP. Chapter 7: Augmented Renal Clearance. In: Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill. Adis, Singapore: Springer Nature Singapore Pte.Ltd. ed; 2018.
[2] Dhont E, Van Der Heggen T, De Jaeger A, Vande Walle J, De Paepe P, De Cock PA. Augmented renal clearance in pediatric intensive care: are we undertreating our sickest patients? Pediatr Nephrol Germany 2018.
[3] Huttner A, Von Dach E, Renzoni A, et al. Augmented renal clearance, low beta-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study. Int J Antimicrob Agents 2015.
[4] Baptista JP, Sousa E, Martins PJ, Pimentel JM. Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 2012;39(5):420–3.
[5] Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012;142(1):30–9.
[6] Udy AA, Jarrett P, Stuart J, et al. Determining the mechanisms underlying augmented renal drug clearance in the critically ill: use of exogenous marker compounds. Crit Care 2014;18(6):657.
[7] Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. Crit Care 2013;17(1):R35.
[8] Brown R, Babcock R, Talbert J, Gruenberg J, Czurak C, Campbell M. Renal function in critically ill postoperative patients: sequential assessment of creatinine osmolar and free water clearance. Crit Care Med 1980;8(2):68–72.
[9] Carrie C, Lannou A, Rubin S, DEC H, Petit L, Biais M. Augmented renal clearance in critically ill trauma patients:a pathophysiologic approach using renal vascular index. Anaesth Crit Care Pain Med 2018.
[10] Meola M, Nalesso F, Petrucci I, Samoni S, Ronco C. Ultrasound in Acute Kidney Disease. Contrib Nephrol S Karger AG Basel 2016;188:11–20.
[11] Barletta JF, Mangram AJ, Byrne M, et al. Identifying augmented renal clearance in trauma patients: validation of the augmented renal clearance in trauma intensive care scoring system. J Trauma Acute Care Surg 2017;82(4):665–71.
[12] Viazzi F, Leoncini G, Derchi LE, Pontremoli R. Ultrasound Doppler renal resistive index: a useful tool for the management of the hypertensive patient. J Hypertens 2014;32(1):149–53.
[13] Baptista JP, Martins PJ, Marques M, Pimentel JM. Prevalence and risk factors for augmented renal clearance in a population of critically ill patients. J Intensive Care Med 2018.
[14] De Waele JJ, Dumoulin A, Janssen A, Hoste EA. Epidemiology of augmented renal clearance in mixed ICU patients. Minerva Anestesiol 2015.
[15] Udy AA, Baptista JP, Lim NL, et al. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 2014;42(3):520–7.
[16] Ronco C, Bellomo R, Kellum J. Understanding renal functional reserve. Intensive Care Med 2017;43:917–20.
[17] Baptista JP, Neves M, Rodrigues L, Teixeira L, Pinho J, Pimentel J. Accuracy of the estimation of glomerular filtration rate within a population of critically ill patients. J Nephrol 2014;27(4):403–10.
[18] Roberts JA, Kumar A, Lipman J. Right Dose, Right Now: Customized Drug Dosing in the Critically Ill. Crit Care Med 2017;45:331–6.
[19] Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 2012;73(1):27–36.

João Pedro Baptista[a], Jason A. Roberts[b,c,d,*], Andrew A. Udy[e,f]
[a]*Serviço de Medicina Intensiva, Centro Hospitalar e Universitário de Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal*
[b]*University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia*
[c]*Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, Australia*
[d]*Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia*
[e]*Department of Intensive Care and Hyperbaric Medicine, The Alfred Hospital, Melbourne, Victoria, Australia*
[f]*Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia*

*Corresponding author at: University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia
E-mail address: j.roberts2@uq.edu.au (J.A. Roberts).

Available online 9 March 2019