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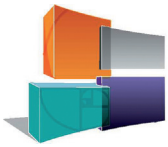

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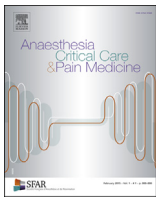

Original Article

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

Cedric Carrie [a,*], Alexandre Lannou [a], Sebastien Rubin [b], Hugues De Courson [a], Laurent Petit [a], Matthieu Biais [a,c]

[a] Anaesthesiology and critical care department, CHU de Bordeaux, 33000 Bordeaux, France
[b] Nephrology department, CHU de Bordeaux, 33000 Bordeaux, France
[c] Université Bordeaux Segalen, 33000 Bordeaux, France

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ABSTRACT

Background: The aim of the present study was to explore the relationship between creatinine clearance (ClCr), 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 ClCr $\geq$ 130 mL/min/1.73m^2. A mixed effect model was constructed to explore covariates associated with ClCr 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 ClCr values and RVI (r = −0.495; P = 0.005) but not between ClCr and CI values (r = 0.023; P = 0.967) at day 1. Using a mixed effect model, only age remained associated with ClCr 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.

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_{Cr}) exceeding 130 mL/min/1.73m^2 [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].

* Corresponding author at: Surgical and Trauma Intensive Care Unit, anaesthesiology and critical care department, hôpital Pellegrin, CHU de Bordeaux, place Amélie-Raba-Léon, 33076 Bordeaux cedex, France.
E-mail addresses: cedric.carrie@chu-bordeaux.fr (C. Carrie), alexandre.lannou@chu-bordeaux.fr (A. Lannou), sebastien.rubin@chu-bordeaux.fr (S. Rubin), hugues.de-courson@chu-bordeaux.fr (H. De Courson), laurent.petit@chu-bordeaux.fr (L. Petit), matthieu.biais@chu-bordeaux.fr (M. Biais).

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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 m^2/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 m^2 (Dubois formula). As previously described, ARC was defined by a measured $Cl_{Cr} \geq$ 130 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 μmol/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 (π/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 (L/min/m^2). Intra-observer variability coefficient, assessed in ten patients before the study, was 5 ± 3% for RVI and 4 ± 3% for VTI.

2.3. Statistical analysis

Results are expressed as mean ± 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^2 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

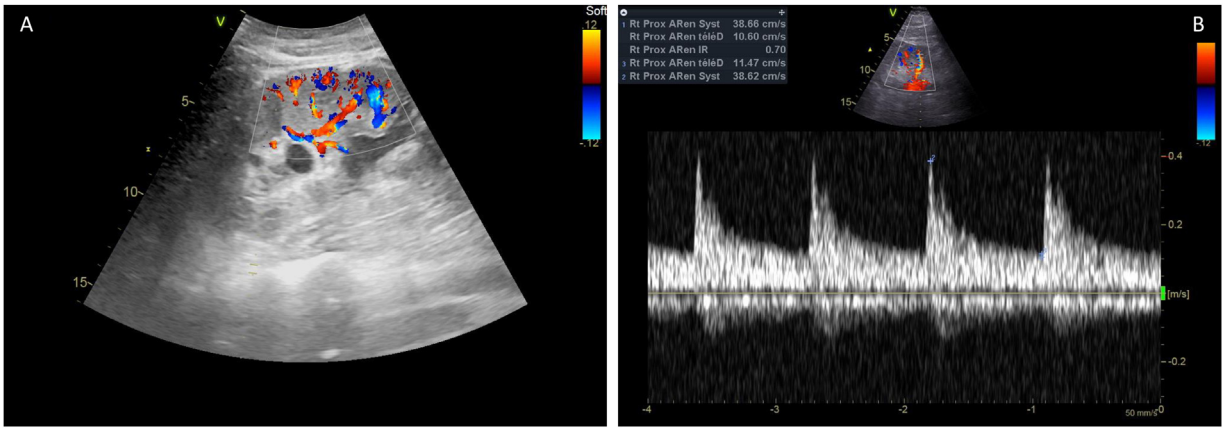

Fig. 1. Principles of measurements of renal Doppler vascular index (RVI). A. Visualization of proximal interlobar arteries in color-Doppler mode. B. Peak systolic velocity (V_{max}) and minimal diastolic velocity (V_{min}) determined by pulsed Doppler from three consecutive similar-appearing waveforms. 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^2)	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_{CL} (mL/min/1.73 m^2)	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^2) on at least one occasion during the first five study days [1]. CI: cardiac index; Cl_{Cr}: 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 Cl_{Cr}, 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 Cl_{Cr} was 128 ± 57 mL/min/1.73m^2 and ARC was found in 61/121 urinary samples (50%). Representation of Cl_{Cr}, RVI and CI over time is shown in Supplementary data. The intra-patient variability coefficients were 15 ± 10% for Cl_{Cr}, 6 ± 4% for RVI and 19 ± 9% for CI without significant difference over the three consecutive days.

3.2. Relationship between CrCL, RI and systemic hemodynamic data

There was a significant correlation between Cl_{Cr} values and RVI (r = −0.495; P = 0.005) but not between Cl_{Cr} 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 Cl_{Cr} over time. Gender, mechanical ventilation, CI, mean MAP or norepinephrine doses were not predictive of daily Cl_{Cr}. 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 ARTIC 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).

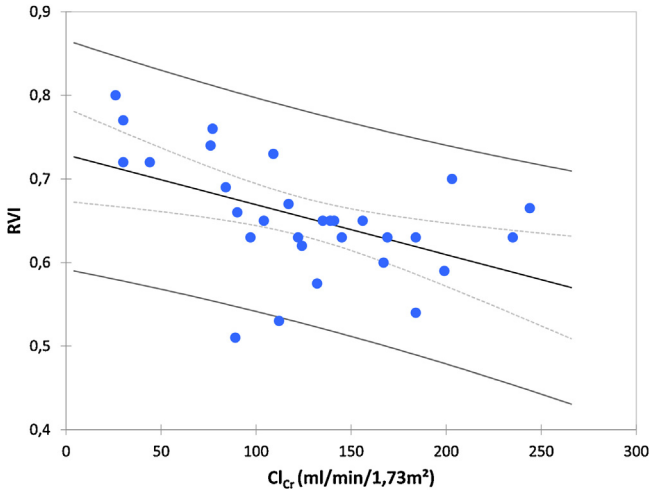

Fig. 2. Relationship between creatinine clearance (Cl_{Cr}) and renal Doppler vascular index (RVI) at day 1 in 30 critically ill trauma patients. Correlations were assessed using Spearman correlation coefficient (R^2 = 0.245, P = 0.005).

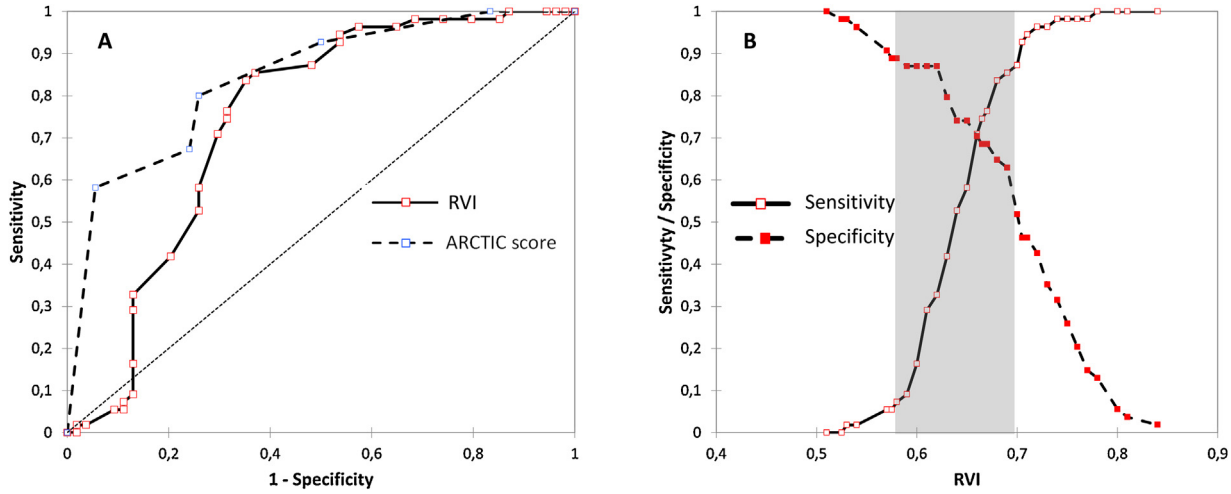

Fig. 3. A. ROC curves of RVI (continuous line, AUC = 0.742 [95% CI: 0.649–0.834]; $P < 0.0001$) and ARTIC score [dotted line, AUC = 0.842 (95% CI: 0.771–0.913; $P < 0.0001$)] for predicting augmented renal clearance ($P = 0.049$). B. The inconclusive grey zone of RVI is displayed as a grey rectangle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