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SPECIAL ISSUE INSIGHT

Monitoring of renal perfusion

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Acute kidney injury (AKI) remains associated with short- and long-term mortality and morbidity. Renal hypo-perfusion has long been considered as one of the main predisposing factors for AKI in critically ill patients. With this view, relentless efforts are made to "optimize renal perfusion" to avoid AKI or minimize its severity. However, data have recently challenged this assertion. Indeed, contrary to common beliefs, renal blood flow might actually be increased in sepsis, a clinical entity very commonly associated with AKI. Furthermore, in sepsis, higher renal blood flow might actually be associated with higher AKI severity. These findings underline the major complexity of renal perfusion. For example, medullary perfusion is mainly supported by efferent glomerular arterioles. It depends on delicate adjustments of the vascular tone of afferent and efferent glomerular arteries. In addition, low oxygen concentration in the medullary interstitial fluid is required to allow the generation of Henle's loop concentration gradient. For these reasons and many others, renal macro- and micro-circulation appear, to some degree, disconnected. This, for example, explains the lack of correlation between cardiovascular response to fluid challenge and subsequent diuresis or changes in serum creatinine [1]. Together with uncertainties regarding optimal target for mean arterial pressure during shock, this knowledge prompts the need for real time monitoring of renal perfusion at the bedside. Methods to assess renal perfusion at bedside are limited. Central venous pressure and mean perfusion pressure have been associated with risk of AKI in observational studies but may reflect macrovascular perfusion and congestion rather than intra-renal hemodynamic dysregulation [1, 2]. Para-amino-hippurate assessment of renal plasma flow, used as gold standard in animal studies, usually requires stable renal hemodynamic to be reliable. Although magnetic resonance imaging (MRI) may assess renal perfusion and oxygenation changes, relevancy of this technique at bedside for critically ill patients is debatable [3]. Last, urinary partial pressure of oxygen (PuO2) has been shown to be correlated with renal arterial flow and renal medullary oxygen pressure. This has been however validated with urine samples obtained from renal pelvis and this relationship changes through urinary tract. Therefore, studies validating feasibility and relevancy of continuous bladder urine oxygen monitoring are required [4]. So far, most of the studies performed focused on ultrasound-based tools in assessing renal perfusion at the bedside. Our manuscript will focus more specifically on these later.

Doppler-based renal resistive index (RI) is a rapid and non-invasive tool that was proposed to assess renal perfusion, identify early risk of AKI, or predict renal recovery course. Although feasible even by untrained operators and free from systematic bias when performed by junior operators, this technique is operator-dependent, and confidence interval may be as high as ± 10% [5]. Initially believed to mainly reflect renal vascular resistances, RI is actually influenced by numerous confounders including renal interstitial pressure, intra-abdominal pressure, oxygen or CO_2 arterial concentrations, pulse pressure and vascular compliance. If a relationship with renal vascular resistances has been demonstrated, large, non-physiological, pharmacologically induced changes in renal vascular resistance translated into small RI changes which may be considered within margin of error [6]. Although initial reports in underpowered studies suggested good discrimination in predicting renal prognosis, recent report of a large multicenter study suggested prognostic performance of this technique to be limited [7]. Interestingly, operator expertise had no influence on this finding, and

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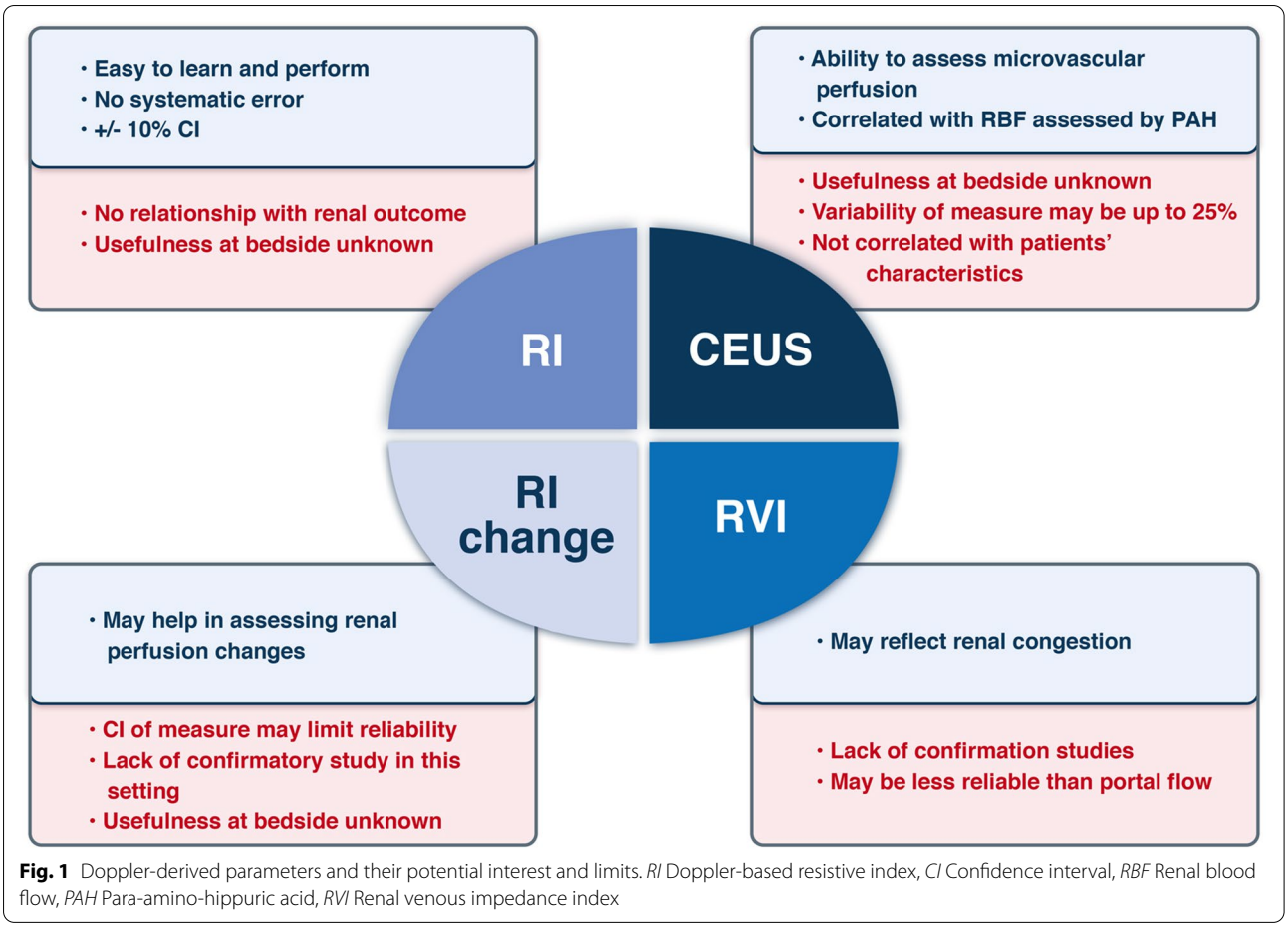

Fig. 1 Doppler-derived parameters and their potential interest and limits. *RI* Doppler-based resistive index, *CI* Confidence interval, *RBF* Renal blood flow, *PAH* Para-amino-hippuric acid, *RVI* Renal venous impedance index

technique was poorly efficient both for expert operator as inexperienced ones [8].

Although Doppler-based RI failed as a tool to assess renal outcome, several areas of uncertainty remains. First, some studies suggested that Doppler-based RI could allow the assessment of renal perfusion changes following therapeutic intervention such as administration of a vasopressor or a fluid challenge [9]. Even though, this point may deserve further evaluation, the fact that RI is imperfectly related to renal blood flow and renal vascular resistances, may limit its application. In this line, RI failed to be associated with sublingual micro-circulation in patients with shock [10]. Furthermore, confidence interval of measures when performed by different operators may strongly impair ability of this technique to detect slight changes in RI accurately [5]. More recently, venous Doppler and more specifically renal venous impedance index were used to assess renal congestion [11] and suggested as a tool to individualize fluid resuscitation in critically ill patients. These studies are however, preliminary and confirmation studies are required before recommending routine use of these techniques at bedside.

Contrast-enhanced ultrasonography (CEUS) may be more suited to accurately assess changes in renal perfusion [12]. Briefly, microbubble-based contrast agent is used in association with conventional low intensity ultrasonography. CEUS enables real time visualization of renal micro-circulation and identification of perfusion defects. In addition, intravascular distribution of microbubbles and their sensitivity to high-power acoustic pulses (destruction-refilling sequences) enable to approximate renal blood volume and to derive parameters proportional to blood flow [12]. A proof-of-concept study performed in healthy volunteers confirmed the ability of this technique to detect renal perfusion changes following angiotensin II or angiotensin-converting enzyme inhibitors administration [13]. However, subsequent studies assessing changes in CEUS-derived parameters in patients following terlipressin or norepinephrine administration, reported heterogeneous and unpredictable changes in hemodynamic parameters, without relationship with patients' characteristics [14]. Nevertheless, preliminary studies suggest CEUS may be discriminant in identifying patients who will develop severe AKI [15].

These studies need to be confirmed and reliability of CEUS in assessing renal perfusion at bedside in critically ill patients remains to be validated.

Altogether, to date, none of the available ultrasound-based tools have proved to be really useful in assessing renal perfusion at the bedside. Doppler-based resistive index and renal impedance index may enable to individualize resuscitation strategy, but further studies are needed to confirm preliminary reports. Doppler-based RI seems to be devoid of any performance in predicting short-term renal outcome. Last, CEUS, although grounded in strong rational, failed so far to demonstrate its usefulness although additional studies are needed. These studies along with refinements of machine setting, homogenization of infusion modalities of contrast media and of technical analysis or use of 3D probes might allow assessing performance of the technique (Fig. 1).

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Declarations

Conflicts of interest
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