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EDITORIAL

The artificial kidney induces acute kidney injury: yes

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Considerable numbers of lives have been saved after the invention of the artificial kidney, a revolutionary first organ-replacing extra-corporeal therapy, which participated in the development of intensive care. However, life-threatening events such as thrombosis, infection, hemorrhage and dialytic hypotension may complicate renal replacement therapy (RRT) and may theoretically aggravate renal injury in critically ill patients with acute kidney injury (AKI). More insidiously, the RRT device itself and incomplete biocompatibility of membranes may contribute to renal injury.

By analogy with the ventilator-induced lung injury concept [1], our team recently refreshed the possibility of artificial kidney-induced kidney injury [2].

From bedside …: delayed renal recovery induced by RRT

A classical clinical argument for RRT nephrotoxicity stems from the usually rapid decrease of residual renal function after initiation of chronic dialysis, which is more important with hemodialysis than with peritoneal dialysis [3].

Several trials have evaluated the effects of RRT modality on survival and on renal recovery. For instance, the acute renal failure trial network (ATN) study included more than 1000 patients with severe AKI and showed that intensive RRT strategies (more frequent intermittent hemodialysis or higher dose of continuous hemofiltration) did not improve mortality [4]. A post hoc analysis of this trial [5], concluded that more intensive modalities were associated with a greater reduction in urine output during the first 7 days of therapy. In the subgroup of hemodynamically stable patients [6] who received intermittent RRT, increasing frequency from 3 to 6 days per week was associated with impaired renal recovery at day 28. An individual patient data meta-analysis of 8 RCTs (on both continuous and intermittent RRT) confirmed that higher RRT intensity delayed renal function recovery [7].

Contrarily to widespread opinion, CRRT does not confer a better renal prognosis compared with IHD as shown in a recent meta-analysis that included a vast majority of RCTs [8], whereas meta-analyses including mainly observational studies claimed the superiority of CRRT, a finding that likely reflects allocation bias [9].

Obviously, the least intensive RRT modality is no RRT at all in patients with no life-threatening complication of AKI, as shown in the IDEAL-ICU and AKIKI trials [10, 11]. In these two studies, a delayed RRT strategy averted the need for RRT in 38–49% of patients with severe AKI. Recovery of an adequate urine output and spontaneous creatinine decrease were observed earlier with the delayed than with the immediate RRT strategy in the AKIKI study [11]. Moreover, in the subgroup of patients with septic shock, the delayed strategy was associated with a cumulative urine output during the first 2 days that was significantly higher than with the early strategy (1881 ml vs 994 ml, $p = 0.001$). This persisted after exclusion of patients treated with diuretics [12].

To the pathology lab …: old and recent histological observations

Pathological examination (biopsy or autopsy) of patients receiving RRT for 3–4 weeks for ischemic AKI in Vietnam war casualties revealed focal areas of fresh (dating back 48–72 h only) tubular necrosis; whereas the initial

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injury occurred several weeks ago [13]. Similar observations were recently done on an observational series of immediate post-mortem kidney autopsy in 19 septic shock patients with severe AKI [14]. Patients who had received RRT had more tubular lesions such as tubular brush border loss, necrosis and luminal cytoplasmic debris than those who had not received it (because deemed moribund).

And to bench …: mechanistical hypothesis

The first potential mechanism involved in artificial kidney-induced kidney injury is intra-dialytic hypotension [13]. This occurred more frequently with the intensive strategy than with the less intensive strategy in the ATN study [4] because of the increased number of sessions with the former strategy. Such phenomenon may obviously be responsible for altered renal recovery. Mechanisms involved in this RRT-associated hemodynamic instability have been recently reviewed in this *Journal* [15]. *Inter alia*, lowering of cardiac output favored by ultrafiltration, osmotic and oncotic shifts, myocardial sideration and vascular resistance drop were potential mechanisms for this instability.

Biological incompatibility between patient blood and synthetic dialyzer membranes is also involved. Although the advent of so-called "biocompatible" dialysis membranes (polyacrylonitrile, polymethyl methacrylate, polysulfone) in the 1990s has allowed for less neutrophil and complement activation compared to cellulose or cuprophane membranes, hope regarding their positive effect on renal recovery has been tempered in meta-analysis [16]. Such discordant clinical data could reflect persistence of some biological incompatibility whichever the type of membrane: increased platelet activation was observed with so-called "biocompatible" hydrophobic membranes (polysulfone, polymethyl methacrylate), leading to platelets–neutrophils micro-aggregate formation that produced oxidative stress [17]. So hoping that blood–membranes interactions no longer exist and that RRT is safe on this point of view is probably illusory: a polysulfone is not an endothelium.

Catheter-related complications (hemorrhage, infections) may also participate in the scenario [18]. Of note,

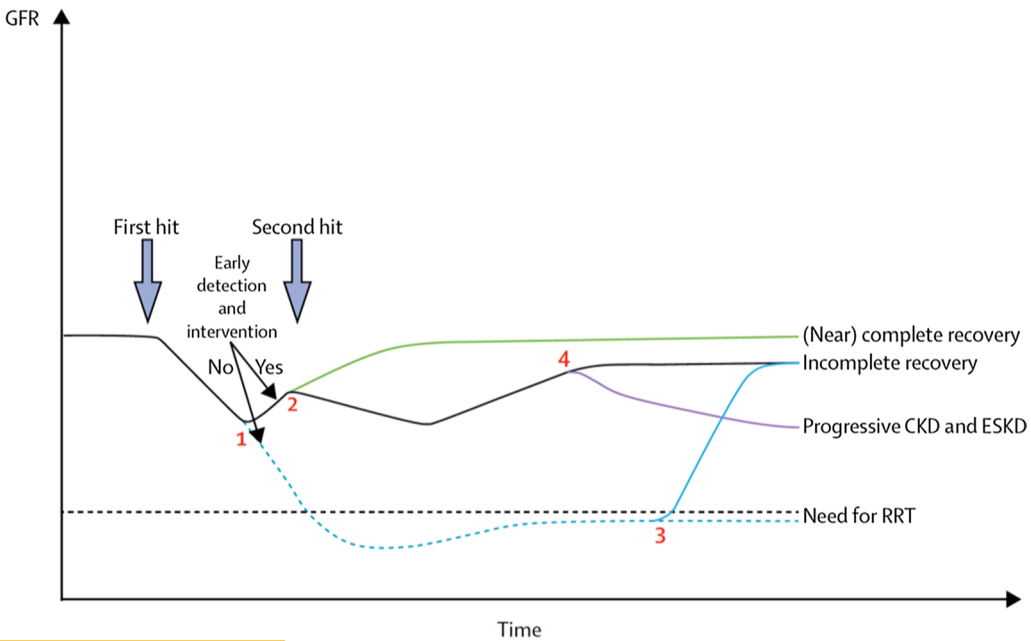

Fig. 1 Course of acute kidney injury over time. (1) Preventive action can be taken when acute kidney injury (AKI) is discovered at an early stage, and progression to the need for renal replacement therapy (RRT; dotted blue line) can potentially be avoided (full black line). (2) During recovery from AKI, the kidneys are more susceptible to further injury, which can result in new deterioration of renal function (full black line) rather than recovery (green line). (3) Patients can recover their kidney function after starting RRT (full blue line). This recovery is often incomplete, which can result in progressive chronic kidney disease (CKD) and eventually end-stage kidney disease (ESKD; full lilac line). (4) Patients who have had a second AKI hit rarely recover their kidney function completely (full blue line), and have an increased risk of progressive CKD and evolution to ESKD over time (full lilac line). The concept of artificial kidney-induced kidney injury would imply that RRT might constitute this second hit. *GFR* glomerular filtration rate
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such infections were more frequent with an early RRT initiation strategy [11].

Another hypothetical mechanism was recently raised: AKI is responsible for Nicotinamide adenine dinucleotide (NAD+) depletion which impedes tubular regeneration [19]. This is all the more important, since RRT may remove circulating niacin, a precursor of NAD+with a molecular weight close to creatinine [2] further compromising renal recovery.

The importance of a "second hit" (infection, shock, toxic drugs) on a repairing kidney was recently emphasized [20] (see Fig. 1). Whichever the exact underlying mechanisms involved, RRT might constitute such "second AKI hit" that applied on an injured tubular epithelium sensitized to a harmful environment may lead to maladaptive repair.

In conclusion, the artificial kidney-induced kidney injury hypothesis is supported by mounting evidence. It might result in a real paradigm shift, as had been the emergence of the concept of ventilator-induced lung injury [1] for ARDS management 20 years ago.

After decades of "interventions race", the old adage "Primum non nocere" would ensure current direction of intensive care in several areas: less ventilation, less sedation, less transfusion, less antibiotics, and now less RRT unless really needed.

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Compliance with ethical standards

Conflicts of interest
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