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The Essence of Acute Kidney Injury from Renal Replacement Strategies

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Editorial

Guidelines for patient selection and timing of renal replacement therapy (RRT) [1] were published in the journal Blood Purification in 2016, however, there is still controversy over early versus delayed initiation of renal replacement strategies in critically ill patients with acute kidney injury. A study by the Artificial Kidney Initiation in Kidney Injury Study Group (AKIKI) [2] found no significant difference in mortality between early and delayed initiation of renal replacement therapy. In contrast, the ELAIN randomized clinical trial [3] concluded that early renal replacement therapy in critically ill patients with acute kidney injury is associated with reduced mortality during the first 90 days compared with delayed initiation of renal replacement therapy. The contradictory conclusion of these two randomized controlled trials have created confusion for many physicians [4,5]. How could the results have been so discrepant? After comparing these studies (Table 1), we propose the following possible explanation.

Variables	AKIKI	ELAIN
Study design	Multicenter RCT	Single-center RCT
Inclusion criteria	KIDGO stage 3 with ventilator and/or vasopressor	KIDGO stage 2 and plasma NGAL>150 ng/ml
SOFA score	~10.9	~16
RRT initiation in delayed group	Within 6 h after inclusion; 100% patients were treated by RRT	Within 8 h after inclusion; 100% patients were treated by RRT
RRT initiation in delayed group	Immediate RRT indication or oliguria for more than 72 h; 51% patients were treated by RRT	Immediate RRT indication or within 12 h after progressed to stage 3 AKI; 91% patients were treated by RRT
RRT modalities	CRRT: 30%	CRRT: 100%
Primary outcome	60-day mortality	90-day mortality
Results	60-day mortality did not differ, (early vs delayed 48.5% vs 49.7%)	90-day mortality was significantly lower in the early group (early vs delayed, 39.3% vs. 54.7%)
	Early group was more likely to experience CRBSI and Hypophosphatemia. Diuresis occurred earlier in the delayed-strategy group.	Early group was more likely to have recovered renal function, shorter RRT duration and shorter hospital stay

Table 1: Comparison between AKIKI and ELAIN.

Apart from time, the two major variables in the Kidney Disease Improving Global Outcomes (KDIGO) definition of acute kidney injury are urinary volume per hour and serum creatinine concentration. Appropriate assessment of these two variables alone omits a crucial additional factor from the perspective of renal perfusion pressure. Figure 1 depicts our theory, which is based on the contention that the blood circulatory system of the human body has two interacting and interconnected components; namely, the systemic circulation and the circulation to individual organs. Perfusion of organs is generally considered to be determined by the systemic circulation. In our theory, we regard the perfusion pressure of an organ as the key point, this pressure being determined by the difference between the mean arterial pressure (MAP) and central venous pressure (CVP). Specifically, in the human kidney, the renal perfusion pressure (RPP) is determined by the difference between the renal pre- (MAP) and post-loads (CVP) (Formula: RPP=MAP−CVP). Once the RPP is outside the range that the human body can tolerate, the two consequences of reduction in urinary volume per hour and increase in serum creatinine concentrations are inevitable. Thus, a reduction in urinary volume per hour or an increase in creatinine or both do not necessarily mean that the kidney has sustained substantial injury. Clinically, such changes are associated with two factors; namely, a reduction in renal preload and an increase in renal post load (Figure 1).

If a reduction in urinary volume per hour or increase in creatinine or both are caused by a reduction in MAP, the required interventions are providing volume expansion or administration of inotropic agents or both. In contrast, if a reduction in urinary volume per hour or increase in creatinine or both are caused by an increase in renal post load (a higher CVP), the required intervention is to reduce the CVP. Initiation of renal replacement therapy is therefore indicated only in patients with substantial acute kidney injury associated with normal pre- and post-loads. In the AKIKI study, patients defined as having acute kidney injury may have included some in whom reduction of urinary volume per hour or increased creatinine or both was caused by high renal post load or low preload or both, resulting in inconsistencies in the inclusion criteria.

Although other potential biases were well controlled by the methodology of the design of the AKIKI trial, deficiencies in the KIDGO definition of acute kidney injury resulted in inconsistent inclusion criteria, which in turn resulted in the drawing of invalid conclusions. In contrast, the ELAIN trial partly avoided this problem by using the biomarker neutrophil gelatinase-associated lipocalin (NGAL). Thus, according to our hypothesis, the conclusions of the ELAIN trial are likely more reliable than those of the AKIKI trial.

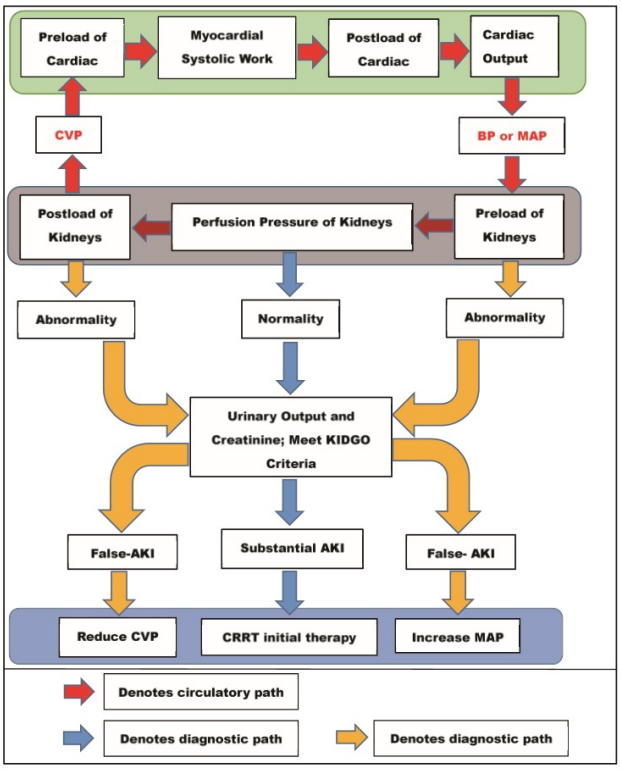

Figure 1: Differentiating those patients with substantial acute kidney injury. Background columns: Green color denotes the big circulation (Systemic circulation); Grey color denotes the small circulation (Organic circulation); Blue color denotes interventional strategies. Abbreviations: AKI: Acute Kidney Injury; CVP: Central Venous Pressure; BP: Blood Pressure; MAP: Mean Raterial Pressure; KIDGO: Kidney Disease Improving Global Outcomes.

Competing Interests

All authors have no relationships with companies that might have an interest in the submitted work over the previous 5 years. Their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and none of the authors have non-financial interests that may be relevant to the submitted work.

Authors' Contributions

Wei Zhang and Miao Chen produced the main idea, Wei Zhang and Xiaoting Feng wrote the first manuscript, Xiaoting Feng and Wei Zhang revised the last manuscript, Wei Zhang is the guarantor of the commentary.

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