Preemptive renal replacement therapy in post-cardiotomy cardiogenic shock patients: a new concept?

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Post-cardiotomy cardiogenic shock (PCCS) is a much-feared complication of cardiopulmonary bypass (CPB). It can lead to low cardiac output (1) and/or low systemic vascular resistance syndromes (2) requiring inotropic and vasopressor drugs to restore adequate hemodynamic status. In addition to the known risk factors for PCCS established in the literature (3,4), other factors may also come into play during surgery. For example, exposure of blood to non-physiologic surfaces, organ ischemia–reperfusion and/or endotoxin release during surgery with CPB can induce an intense systemic inflammatory response syndrome (5,6). In summary, PCCS has been identified as a major morbid event, associated with multiple organ failure, including prolonged respiratory failure and acute kidney injury (AKI), and 20–50% mortality (7-9).

In their recent paper (10), Tu *et al.* investigated among PCCS and AKI patients the hypothesis that preemptive RRT at early stages of PCCS could potentially limit the worsening of non-renal organ dysfunction that may be exacerbated by AKI, to the benefit of patient outcomes. This was a historically controlled study in a cohort of patients who underwent cardiac surgery in Zhongshan Hospital, Shanghai, one of the largest cardiovascular surgery centres in mainland China. The authors showed that preemptive RRT (tested in Period B), compared with conventional initiation of RRT (as

performed in Period A) reduced in-hospital mortality (38% *vs.* 59.2%, P<0.01), and also led to faster and more frequent recovery of renal function (4.1% *vs.* 19.4%). The reasons proposed by the authors to explain these findings included a trend towards increasing mean arterial pressure (MAP) and decreasing central venous pressure (CVP) in Period B, with doses of norepinephrine and epinephrine that were very significantly reduced after RRT initiation in Period B, but not in Period A. One can only be surprised by these results, which raise several important issues, in addition to the usual bias that is typically inherent to this type of methodology, with retrospective data and a small sample size.

The first remark is that the patients included in the study by Tu *et al.* (10) in Period A had a more severe profile of organ failure at the time of RRT initiation, be it in terms of renal function (with a significant difference in KDIGO 3, 69.7% in Period A *vs.* 39.2% in Period B) or in terms of circulatory failure, with a significant difference also observed between periods in lactates (higher in Period A), MAP (lower in Period A) and the doses of norepinephrine and epinephrine used (higher in Period A). It would have been useful to compare clinical severity between periods, for example in terms of SAPS II score at admission to the intensive care unit (ICU) (11), or the SOFA score (12) at the time of RRT initiation. These variables could have been used for adjustment in multivariate analysis to confirm

whether or not the period of treatment had a significant independent effect on the outcomes.

A second comment relates to the fact that in their study, during Period A, Tu *et al.* waited until severity criteria were met before initiating RRT. These criteria were hyperkaliemia > 6 mmol/L, metabolic acidosis (pH <7.2) or evidence of fluid overload with pulmonary edema, on top of other, classical features such as diuresis or blood urea levels. This could explain why the time from surgery to RRT initiation was significantly shorter in Period B than in Period A (23 *vs.* 47 h, P<0.01), due to initiation criteria for RRT that excluded these emergency criteria. Cumulative fluid overload and percent fluid overload were significantly lower in Period B. This could likely explain the difference in in-hospital mortality observed between the two periods, as was already suggested in the ELAIN study (13). Indeed, the ELAIN study was performed in 231 postsurgical patients (mainly cardiac surgery) in a single center and reported an advantage of the early strategy in terms of mortality. Finally, almost 75% of patients had refractory fluid overload criteria (including worsening pulmonary edema) at baseline but were randomized to immediate or delayed RRT initiation nonetheless. The median delay in RRT between groups was only 21 (interquartiles 18–24) hours. Surprisingly, despite the small magnitude of difference, there was nonetheless a significant reduction in 90-day mortality with the early strategy [49/112 (39%) *vs.* 65/119 deaths (55%); P=0.03]. Furthermore, early initiation of RRT was associated with substantial decreases in the median duration of both RRT (–2 weeks) and hospital stay (–4 weeks), an astounding difference in a randomized trial in the ICU. These intriguing features were underlined in a recent editorial by Liu and Palevsky (14). The difference in mortality was not observed at 60 days, but rather at 90 days only, a finding that is difficult to explain in the ICU setting. The low frailty index (of three patients only) may attest to the fact that single-center studies often overestimate the effect of the experimental arm (15). Two recently-published, large, multicenter RCTs [AKIKI (16) and IDEAL-ICU (17), which involved 620 and 488 patients, respectively] compared early and delayed strategies of RRT in septic shock patients. Mortality was 48% (AKIKI) and 58% (IDEAL-ICU) with the early strategy, and 50% and 54% in the delayed group respectively, with P values of 0.79 and 0.38, for the comparison of early *vs.* late in AKIKI and IDEAL-ICU respectively. Also, many patients escaped RRT (49% and 38% in AKIKI and IDEAL-ICU, respectively).

The results of both these trials (16,17) confirm that the indication for RRT should be based not on the severity of AKI (i.e., KDIGO stage), but rather on complications of AKI (18). Of note, in the study by Tu *et al.* (10), there was no difference in the duration of mechanical ventilation between periods, which is often linked in this population of surgical patients to the intensity and duration of the cardiac failure, and is in turn responsible for pulmonary fluid overload. There was also no indication of a difference in the length of stay, either in the ICU or in hospital. This is probably because of the major complications post-surgery (other than cardiogenic shock), which led to extremely long stays for some patients.

A third and final issue is the potential perspectives that are opened up by Tu's paper. Indeed, this investigation deserves to be pursued to identify patients most likely to benefit from RRT during AKI in the context of PCCS, outside of the usual emergency criteria. This is in line with current thinking on the topic of "personalized" medicine, notably taking account of each patient's individual characteristics (e.g., genetic profile), response to inflammation and response to therapy (19). From a pathophysiological perspective, there is also a pressing need to refine the criteria for initiation of RRT, particularly with regard to the KDIGO stage (20). We probably need to "forget", or at least focus less on the rationale whereby mediators of inflammation should be eliminated at all costs, or endotoxins should be adsorbed at all costs. After all, there have been some publications reporting negative results on these endpoints in recent years (21-23). Other studies are currently ongoing to test new dialysis membranes (24).

In conclusion, the encouraging results observed in the study by Tu *et al.* (10) deserve to be interpreted with caution, in view of the biases and limitations mentioned. Nevertheless, further investigation is warranted in this area in view of the very high mortality in patients who develop PCCS. There is undoubtedly a need for more personalized approaches that do not focus solely on the strategy for initiation of RRT in AKI, as the limitations of this approach have also been clearly shown.

Footnote

Conflicts of Interest: All authors have completed the ICMJE

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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