Individualized Goal-Directed Therapy: The Challenge With the Fluids

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GLOSSARY

AKI = acute kidney injury; **CI** = confidence interval; **COX** = cyclooxygenase; **GFR** = glomerular filtration rate; **HFVT** = high-flow volume therapy; **IGDT** = individualized goal-directed therapy; **OR** = odds ratio; **RRT** = renal replacement therapy

The interplay of fluid balance and kidney function has been discussed for decades in the context of critical illness as well as preventive medicine and clinical nephrology. On the one hand, the kidney appears to be very sensitive to hemodynamic comprise because acute kidney injury (AKI) is a very common finding in shock states or sepsis. On the other hand, with a bit of cynicism, it may be argued that the main reason for linking fluid therapy with kidney function is the fact that the kidney excretes urine, which is a fluid. Thus, it is still common in the clinical setting that oliguria is readily interpreted as a sign of dehydration or hypovolemia. In contrast, it is well known that oliguria is an evolutionary mechanism to maintain survival in critical situations, because humans and animals are rather designed for water deprivation than for intravenous fluid therapy.[1] Oliguria in the setting of major surgery, critical illness, or infection may therefore be interpreted as a physiologic finding. Although the improvement of renal arterial blood flow is often seen as the principal goal of hemodynamic therapy, several studies report renal blood flow to be rather increased than reduced, for example, in septic shock, despite a marked reduction in renal function.[2] Such findings suggest that other mechanisms than arterial blood flow are involved in the pathophysiology of AKI.[3] On the other hand, a couple of studies identified venous congestion as a key mediator of AKI in cardiogenic or septic shock.[4,5] Venous congestion is likely to be augmented by generous fluid therapy.

In the complex setting of fluid therapy and renal dysfunction, optimal fluid therapy during kidney transplantation is among the most challenging clinical tasks. Early graft dysfunction occurs in a considerable number of transplant recipients and may be linked to chronic graft dysfunction.[6] Hemodynamic and especially fluid therapy is often seen as the key method to prevent early graft dysfunction. However, evidence-based risk factors include recipient overweight, warm ischemia time, and pretransplant dialysis.[6] Other causes of early graft dysfunction include peracute rejection, early viral infections, urologic complications, large vessel thrombosis, thrombotic microangiopathy, or medical toxicity.[7] Nevertheless, optimal perioperative fluid therapy clearly has a role in the prevention of early graft dysfunction.

The present study of Eriksen et al[8] investigates the effects of high-flow volume therapy (HFVT) versus individualized goal-directed therapy (IGDT) regarding early glomerular filtration rate (GFR) in a porcine model of renal transplantation. It is interesting that the authors found no differences between the study groups regarding early GFR. However, they found evidence that inflammatory response was less pronounced in the IGDT group. Furthermore, the investigators described potential benefits in preservation of glycocalyx as measured by immunofluorescent microscopy in animals receiving IGDT.

There is convincing evidence that positive fluid balance is associated with adverse outcome in critically ill patients[9] and previous trials using liberate fluid resuscitation protocols often failed in proving

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superiority as compared to conservative fluid resuscitation.[10] Especially in patients undergoing organ transplantation, adequate fluid resuscitation management may be of importance regarding outcome. Eriksen et al[8] investigated this part of fluid resuscitation in pigs receiving kidney transplantation by using IGDT versus HFVT regarding delayed renal graft function. The investigators defined the goals for fluid resuscitation as responsiveness to the application of fluid boluses measured by stroke volume in the IGDT group and in changes of mean arterial pressure. The animals of the IGDT group received significantly less fluids as compared to the HFVT group (10.0 ± 1.93 L vs 6.06 ± 1.70 L, mean difference 3.94 L; P = .0002) with consecutive increase in body weight. Perioperative fluid resuscitation in patients undergoing transplantation is a walk on the razor's edge, because hypervolemia is known to impair both organ and patient outcome[11] while hypovolemia is often blamed for reduced organ perfusion pressure and therefore ischemic organ injury. Codes et al[11] described positive fluid balance as an independent risk factor for AKI and renal replacement therapy (RRT) in patients undergoing liver transplantation (odds ratio [OR] = 2.3; 95% confidence interval [CI], 1.37–3.86, P = .02 and OR = 2.89; 95% CI, 1.52–5.49, P = .001 respectively). Interestingly, in the present investigation, the authors found no differences regarding early GFR between the intervention groups, indicating that the resuscitation regime (IGDT versus HFVT) is not the key parameter regarding early graft dysfunction. From the pathophysiologic point of view, pushing the patient to the top of the Frank-Starling-curve will inevitably lead to liberation of natriuretic peptides, which provoke vasodilation, capillary leakage, and (in intention to remove excessive fluids) diuresis. This already happens in healthy subjects.[12] It appears that increased diuresis after fluid therapy is, in most cases, an effect of natriuretic peptides rather than renal perfusion. On the other hand, the described higher inflammatory activity as measured by cyclooxygenase (COX)-2 in animals receiving liberate fluid resuscitation is a strong indicator for the potential harmful effects of aggressive intravenous fluid resuscitation. Similar effects were described by Kulemann et al,[13] who described substantial inflammatory infiltration in intestinal anastomosis as a consequence of intraoperative fluid overload in a rodent model of abdominal surgery. Thus, there is convincing evidence that fluid overload is associated with inflammation in critical organs, a fact that should be considered for clinical perioperative fluid management of patients in the future.

The described effects of fluid resuscitation on the glycocalyx in the present trial are also interesting, and though the findings of the present trial missed statistical significance, the underlying pathophysiology seems reasonable. Hippensteel et al[14] described a correlation between the administered volume of intravenous fluids and endothelial glycocalyx degradation, indicating that the excessive use of intravenous fluids may induce endothelial injury. Though the evidence for effects of fluid boluses on capillary hydrostatic pressure (P_c) with extravasation and damage of the glycocalyx is still poor,[15] the potential harmful influence of the chosen resuscitation regimen should be kept in focus.

Defining the goal for fluid resuscitation is the major challenge in perioperative fluid therapy. A dichotomic decision to use vasopressors versus fluids for hypotension is too simplistic in most cases. Individual evaluation is always necessary, because both approaches are harmful if not based on a pathophysiologic indication. A complex approach using clinical evaluation, laboratory analysis, and sonographic assessment is often necessary to optimize individual hemodynamic therapy. As the investigators showed in their study, the implementation of cardiac output monitoring might help to guide adequate fluid resuscitation. This kind of monitoring is commonly used in patients undergoing major surgery, yet only occasionally during renal transplant surgery. Future considerations may include a broader use of noninvasive cardiac output monitoring when the technology provides easy and reliable measurements. So actually, the challenge is to identify the patients who would benefit from non- or minimally invasive monitoring and to define individual goals for fluid resuscitation depending on the patient's phenotype. As a rough guide, the overall goal for fluid resuscitation in patients undergoing major surgery according to the current evidence and the present investigation might be "as much as required, as little as possible." Knowing this, it appears evident that optimal fluid therapy in critically ill and perioperative patients will confront the clinician with a real challenge: Just a little bit too less may cause immediate hemodynamic compromise and organ ischemia. And just a little bit too much may impair organ function for days and weeks. This is why we need sufficient education in perioperative fluid and hemodynamic therapy to guarantee optimal bedside management of our patients.

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REFERENCES

1. Thurau K, Boylan JW. Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med*. 1976;61:308–315.
2. Langenberg C, Bellomo R, May C, Wan L, Egi M, Morgera S. Renal blood flow in sepsis. *Crit Care*. 2005;9:R363–R374.
3. Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int*. 2019;96:1083–1099.
4. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589–596.
5. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39:259–265.
6. Hellegering J, Visser J, Kloke HJ, et al. Poor early graft function impairs long-term outcome in living donor kidney transplantation. *World J Urol*. 2013;31:901–906.
7. Goldberg RJ, Weng FL, Kandula P. Acute and chronic allograft dysfunction in kidney transplant recipients. *Med Clin North Am*. 2016;100:487–503.
8. Eriksen JK, Nielsen LH, Moeslund N, et al. Goal-directed fluid therapy does not improve early glomerular filtration rate in a porcine renal transplantation model. *Anesth Analg*. 2020;130:599–609.
9. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA. Both positive and negative fluid balance may be associated with reduced long-term survival in the critically ill. *Crit Care Med*. 2017;45:e749–e757.
10. Schol PB, Terink IM, Lancé MD, Scheepers HC. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. *J Clin Anesth*. 2016;35:26–39.
11. Codes L, de Souza YG, D'Oliveira RAC, Bastos JLA, Bittencourt PL. Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation. *World J Transplant*. 2018;8:44–51.
12. Lobo DN, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. *Crit Care Med*. 2010;38:464–470.
13. Kulemann B, Timme S, Seifert G, et al. Intraoperative crystalloid overload leads to substantial inflammatory infiltration of intestinal anastomoses-a histomorphological analysis. *Surgery*. 2013;154:596–603.
14. Hippensteel JA, Uchimido R, Tyler PD, et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. *Crit Care*. 2019;23:259.
15. Milford EM, Reade MC. Resuscitation fluid choices to preserve the endothelial glycocalyx. *Crit Care*. 2019;23:77.