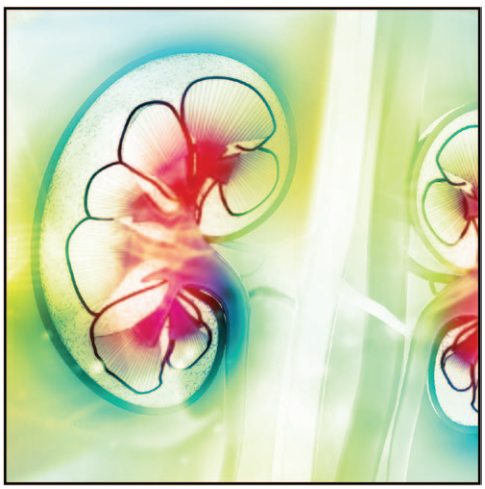
Albumin Supplementation as a Therapeutic Strategy in Cardiac Surgery

Useful Tool or Expensive Hobby?

Yandong Jiang, M.D., Ph.D., Andrew D. Shaw, M.B., F.R.C.A., F.C.C.M., F.F.I.C.M.

ACUTE kidney injury (AKI) is a common complication associated with on-pump coronary artery bypass and off-pump coronary artery bypass (OPCAB) graft surgery.[1,2] The etiology of cardiac surgery–associated AKI is not well understood, and it is almost certainly multifactorial. Apart from intrinsic patient factors (such as comorbidities), the insult from the use of cardiopulmonary bypass (CPB) for on-pump coronary artery bypass graft surgery plays a major role. This is mainly due to (1) blood interfacing with a large extracorporeal surface and triggering a systemic inflammatory response and (2) disabling the filtering effect of the lungs, allowing microemboli to enter the systemic circulation (renal vasculature) directly and cause kidney injury. Therefore, avoiding CPB by the use of OPCAB should theoretically reduce AKI and other complications associated with CPB. However, even though the incidence of AKI seems lower with OPCAB than with on-pump coronary artery bypass surgery,[3] this reduction is very marginal and by no means conclusive.[4] The incidence of severe kidney injury requiring renal replacement therapy associated with these two approaches is actually fairly similar.[5] Therefore, this implies that there are other contributing factors associated with OPCAB. It is critical to identify and modify these factors. One of the potentially modifiable factors for AKI associated with OPCAB is a preexisting low level of albumin.[6]



"[R]estoring the target level of albumin is associated with a reduction in [acute kidney injury] in amplitude greater than that of any known intervention in patients undergoing [off-pump cardiac bypass]."

In this issue of Anesthesiology, Lee *et al.*[7] demonstrate the protective effect of preemptive correction of a low preoperative albumin level by administering human albumin solution, with the goal of preserving renal function in patients undergoing OPCAB. The study is a prospective, randomized, double-blind, placebo-controlled clinical trial that was both well designed and well conducted. The findings of the study include the following: (1) supplementation of exogenous human albumin immediately before surgery predictably achieved the target concentration of albumin and (2) correction of a low albumin concentration is apparently associated with a significant reduction in the incidence of AKI, from 26% in the control group to 13.7% in the albumin group. The observations of Lee *et al.*[7] are important. Scientifically, they validate previous reports[8,9] that a preexisting low albumin level is an independent risk factor for AKI after OPCAB. Clinically, restoring the target level of albumin is associated with a reduction in AKI in amplitude greater than that of any known intervention in patients undergoing OPCAB.

The design of the study was sophisticated. The power analysis was conducted using data from their previous study, where the difference in incidence of AKI between the groups of patients with a serum albumin concentration of less than 4.0 and greater than or equal to 4.0 g/dl was 17%,[6] and assumed that restoring albumin to the target level would

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result in a reduction in incidence of AKI of comparable size (17%). This allowed the authors to complete the study without using an extremely large sample size. Reassuringly, the incidence of AKI after OPCAB in the control group is comparable to what they found in their previous study.[6] Such careful design and execution of the study and its resulting reproducible incidence of postoperative AKI in the control group increase confidence in the results.

There are a few aspects of the study that could affect the interpretation of their findings. First, Lee *et al.* chose 0.9% NaCl in the control group in order to match the equal volume replacement in the albumin group. However, this same group has reported data suggesting that NaCl is an important factor causing AKI in patients undergoing coronary artery bypass surgery.[10] Even though the total amount of NaCl infused in the control group was small, it is at least theoretically possible that giving NaCl created a bias potentially exaggerating the AKI incidence in the control group. Second, it is possible that the actual benefits were intravascular volume supplementation and a subsequent increase in cardiac output rather than albumin level correction, as mixed venous oxygen saturation in the albumin group was 2% (75% for the albumin group and 73% for the control group) higher than that in the control group 10 min after completion of the infusion.[7] Such an increase in mixed venous blood oxygen saturation is estimated to be equivalent to an increase in cardiac output by 8%, assuming that the hemoglobin concentration and oxygen consumption of the patients were constant. Furthermore, the total albumin concentrations at 24 h after operation, including preemptive replacement, were not different. The median volumes of albumin given were 0 *versus* 100 ml intraoperatively and 170 *versus* 85 ml postoperatively for control and albumin groups, respectively. It is understandable that restriction of postoperative administration of albumin might not be practical due to ethical concerns and the culture of local practice. However, not restricting albumin replacement postoperatively could have resulted in bias. In other words, the protective effect of preemptively correcting albumin levels in the albumin group may be underestimated if postoperative correction of low albumin level in the control group was also effective. The protective effect of preemptively correcting low albumin level may be greater than what Lee *et al.* claimed, thus making their finding more valuable.[7] Of course, a study restricting postoperative supplementation of albumin would clarify this notion. Third, the presurgery renal function of the patient population in the study by Lee *et al.* was normal. Therefore, their finding should not be extrapolated to those who have preexisting renal insufficiency. Finally, the protective effect is detectable only by a change in creatinine level but not in terms of incidence of requiring renal replacement therapy, reducing mortality rates, or decreasing length of hospital and intensive care unit stay. Accordingly, further study is required to clarify whether the chemically detectable effect of albumin replacement on renal function is clinically valuable. If it is, what is the cost-effectiveness of albumin replacement?

The study by Lee *et al.*[7] was not intended to explore the mechanism of how the replacement of albumin protects renal function in patients undergoing OPCAB. Rather, the study's intention was to assess whether or not there is a detectable effect. These protective effects may be multifactorial. One of the important observations by Lee *et al.* is the significant increase in intraoperative urine output (49%, or 370 ml for the control group *vs.* 550 ml for the albumin group) even though there was no difference in the total amount of IV fluid, any drugs given, and intraoperative hemodynamics between the two groups. It seems plausible, therefore, that the protective effect of replacing albumin is *via* improvement of renal perfusion. Whether this is due to (temporary) intravascular volume expansion (albumin as fluid) or a pharmacological effect (albumin as drug) is unclear, and it is an interesting question for future studies.

The study by Lee *et al.*[7] raises several interesting questions. They did not explain why they chose to replace albumin immediately before the beginning of the surgery. Since the half-life of albumin is approximately 18 to 21 days,[11,12] the replacement could be completed much earlier, which allows time for equilibration. Whether timing for the correction of low albumin level is clinically valuable needs further investigation. Another interesting observation is the dramatic reduction in albumin level at the end of the surgery in both the control and the albumin groups even though the actual level in the albumin group is still higher than that in the control group. Because the albumin level was only presented 10 min after completion of replacement and at the end of the surgery, but not in between, it is unknown how long the intraoperative hypoalbuminemia lasted. If the intraoperative hypoalbuminemia is detrimental and restoring and maintaining albumin greater than or equal to 4.0 g/dl provides a fully protective effect, then perhaps a more rigid regimen should be applied. Either additional volumes of albumin should be given intraoperatively if the level is less than 4.0 g/dl or hypoalbuminemia should be overcorrected preoperatively in order to ensure extra reserves to eliminate intraoperative hypoalbuminemia. The observations from this study generate several interesting areas that deserve further investigation.

The findings by Lee *et al.* further emphasize that a low albumin level is a modifiable factor for AKI associated with OPCAB.[7] Whether this is also true for on-pump surgery remains to be demonstrated. Preemptive correction of a low albumin level is apparently a safe and effective therapy for mitigating AKI for OPCAB patients. Their findings further support the notion that our research efforts should focus on identifying modifiable contributing factor(s) and developing therapeutic regimens to modify the modifiable factors and improve our patient care. We congratulate Lee *et al.* on completion of this important study. We hope their study inspires more investigators to research not only the contributing but

also the modifiable factors and develop therapeutic regimens accordingly to optimize the care of patients undergoing OPCAB.

Competing Interests

Dr. Shaw has worked as a consultant for Grifols, Los Angeles, California, a manufacturer of albumin. Dr. Jiang is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Jiang: yandong.jiang@vanderbilt.edu

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