Early Detection and Prediction by Biomarkers of Acute Kidney Injury After Cardiac Surgery

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Increasingly in high-risk patients for renal failure, such as those who are aged or have diabetes mellitus or hypertension, acute kidney injury (AKI) often complicates cardiac surgery. The prevalence of AKI has been reported as up to 30% in the postoperative period¹ and thus associated with an increase in short-term mortality, regardless of the severity of AKI.² AKI is also associated with long-term mortality.³ Therefore, preventing the development of AKI in such patients who undergo cardiac surgery has been a big challenge for us.

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AKI has been diagnosed by consensus-based classification and criteria such as RIFLE (Risk, Injury, Failure, Loss, and End stage) and AKIN (Acute Kidney Injury Network). These use incremental changes in the maximum serum creatinine level from baseline or hourly urine output for the diagnosis. However, an increase in serum creatinine merely reflects “the result” of decreased glomerular filtration rate (GFR) and can take several days to reach the steady state. Once AKI becomes established, we could give only limited treatment. Because the decline in GFR begins before the elevation in serum creatinine, earlier diagnosis of developing AKI has been a critical issue.

The main mechanisms of AKI after cardiac surgery involve hemodynamic, atheroembolic, nephrotoxic, and inflammatory factors. Among them, AKI is largely attributed to acute ischemic tubular necrosis. In the peri-operative period, hemodynamic insults such as hypotension frequently precede the development of AKI. Acute ischemic damage of the tubular cells is followed by their detachment, which causes obstruction of the tubular lumen and subsequent decrease in the GFR. Classical markers of AKI, such as serum creatinine, only detect the last stage of this process. There has been recent development of biomarkers that allow us to detect AKI in the early phase. These biomarkers, which include neutrophil gelatinase-associated lipocalin (N-GAL), kidney injury molecule-1, liver-type free fatty acid-binding protein (L-FABP) and interleukin-18, have shown potential benefit for early detection of AKI.⁴ The biomarkers are classified into 3 types: (1) inflammatory, (2) renal tubular proteins that are excreted in to the tubular lumen after exposure to insult, and (3) surrogate markers of tubular injury.⁵ These biomarkers could uncover the ongoing process of tubular damage that leads to decreased GFR (Figure).

L-FABP is a 14-kDa cytoplasmic protein in the proximal tubules and it plays a physiological role in the cell through

binding free fatty acid and might have a renoprotective action by reducing lipid peroxidation under ischemic conditions.⁶ L-FABP might have potential benefit as a biomarker for early detection of AKI, because it reflects deteriorating renal microcirculation and is elevated in urine by secretion from the proximal tubular cells soon after ischemic insults.⁷

In this issue of the Journal, Matsui et al⁸ report the usefulness of L-FABP in early detection of AKI after cardiac surgery in adults. Similar to the results of their study, L-FABP was been previously shown to be a good marker for detecting developing AKI, even in pediatric patients with cardiac surgery, who usually did not have significant comorbidity such as hypertension or diabetes.⁹ Previous study has also demonstrated that NGAL could be one of the most reliable biomarker for early detection of AKI.¹⁰ The evidence of exposure to ischemic insult might be detected with high sensitivity by NGAL. Matsui et al show the superiority of L-FABP to NGAL in early detection of AKI. They found that L-FABP started to elevate immediately after surgery, earlier than NGAL.⁸ Based on this result, routine measurement of L-FABP could be useful strategy for detect AKI earlier in the perioperative period. One of the most valuable findings from this study is that preoperative measurement of L-FABP could define approximately 80% of the patients at high risk for developing AKI, even though the serum creatinine at baseline was comparable with that of patients who did not developed AKI. These findings suggest that L-FABP could uncover renal micro-circumstances, such as advanced arterio-arteriosclerosis and tubular damage, which might be highly susceptible to ischemic damage (Figure). Most of the previous studies focused on looking for new methods of early detection of AKI immediately after cardiac surgery. However, we cannot stop AKI developing, because of the limited therapeutic options for kidney protection. The scoring system and C-reactive protein level could have potential benefit for the prediction of AKI.^{11,12} In addition, protocolized-measurement of biomarkers such as L-FABP for prediction and early detection of AKI will facilitate timely and effective intervention, if new pharmacological agents for the treatment of AKI become available.¹³ However, we still await such agents. If we can predict before surgery which patients are highly likely to develop AKI, we could prepare for the prevention of AKI. For example, perioperative hemodynamic optimization usefully protects renal function in surgical patients.¹⁴ In terms of maintaining glomerular hemodynamics, decreasing the dose or complete cessation of renin-

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angiotensin inhibitors might be an effective move to prevent a great reduction in glomerular perfusion pressure during cardiac surgery.¹⁵ Moreover, early referral to a nephrology specialist could be associated with improving the outcome of patients who undergo cardiac surgery.¹⁶ Therefore, preoperative consultation with both the nephrologist and anesthesiologist with the information about the preoperative value of L-FABP is critically important. Various precautions from the preoperative to postoperative period, supported by these specialists, would reduce the risk for AKI after cardiac surgery. Further large-scale prospective studies are warranted to determine the efficacy of earlier intervention strategies using biomarkers.

References

1. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol* 2006; **1**: 19–32.
2. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J Am Soc Nephrol* 2004; **15**: 1597–1605.
3. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 2009; **119**: 2444–2453.
4. Thurman JM, Parikh CR. Peeking into the black box: New biomarkers for acute kidney injury. *Kidney Int* 2008; **73**: 379–381.
5. Westenfelder C. Earlier diagnosis of acute kidney injury awaits effective therapy. *Kidney Int* 2011; **79**: 1159–1161.
6. Yamamoto T, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, et al. Renal l-type fatty acid-binding protein in acute ischemic injury. *J Am Soc Nephrol* 2007; **18**: 2894–2902.
7. Negishi K, Noiri E, Doi K, Maeda-Mamiya R, Sugaya T, Portilla D, et al. Monitoring of urinary l-type fatty acid-binding protein predicts histological severity of acute kidney injury. *Am J Pathol* 2009; **174**: 1154–1159.
8. Matsui K, Kamijo-Ikemori A, Sugaya T, Yasuda T, Kimura K. Usefulness of urinary biomarkers in early detection of acute kidney injury after cardiac surgery in adults. *Circ J* 2012; **76**: 213–220.
9. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, et al. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008; **73**: 465–472.
10. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A; NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 2009; **54**: 1012–1024.
11. Candela-Toha A, Elías-Martín E, Abaira V, Tenorio MT, Parise D, de Pablo A, et al. Predicting acute renal failure after cardiac surgery: External validation of two new clinical scores. *Clin J Am Soc Nephrol* 2008; **3**: 1260–1265.
12. Kim DH, Shim JK, Hong SW, Cho KR, Kang SY, Kwak YL. Predictive value of C-reactive protein for major postoperative complications following off-pump coronary artery bypass surgery: Prospective and observational trial. *Circ J* 2009; **73**: 872–877.
13. Jo SK, Rosner MH, Okusa MD. Pharmacologic treatment of acute kidney injury: Why drugs haven't worked and what is on the horizon. *Clin J Am Soc Nephrol* 2007; **2**: 356–365.
14. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; **37**: 2079–2090.
15. Arora P, Rajagopal S, Ranjan R, Kolli H, Singh M, Venuto R, et al. Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008; **3**: 1266–1273.
16. Meier P, Bonfils RM, Vogt B, Burnand B, Burnier M. Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6**: 2215–2225.