The cardiac surgery–associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage

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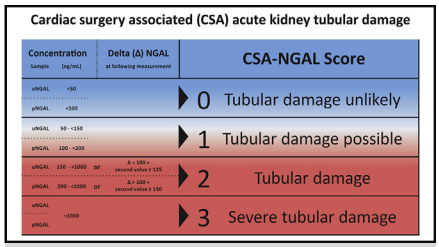
ABSTRACT

Acute kidney injury (AKI), defined as a rise in serum creatinine (functional AKI), is a frequent complication after cardiac surgery. The expression pattern of acute tubular damage biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) has been shown to precede functional AKI and, therefore, may be useful to identify very early tubular damage. The term *subclinical AKI* represents acute tubular damage in the absence of functional AKI (biomarker positivity without a rise in serum creatinine) and affects hard outcome measures. This potentiates an tubular-damage–based identification of renal injury, which may guide clinical management, allowing for very early preventive-protective strategies. The aim of this paper was to review the current available evidence on NGAL applicability in adult cardiac surgery patients and combine this knowledge with the expert consensus of the authors to generate an NGAL based tubular damage score: The cardiac surgery–associated NGAL Score (CSA-NGAL score). The CSA-NGAL score might be the tool needed to improve awareness and enable interventions to possibly modify these detrimental outcomes. In boldly doing so, it is intended to introduce a different approach in study designs, which will undoubtedly expand our knowledge and will hopefully move the AKI biomarker field forward. (J Thorac Cardiovasc Surg 2016;151:1476-81)



CSA-NGAL score.

Central Message

This paper introduces a biomarker based tubular damage score that constitutes a key paradigm shift in cardiac surgery-nephrology.

Perspective

Identification of cardiac surgery–associated tubular damage with the CSA-NGAL score has the potential to aid the early diagnosis of acute kidney injury. This might enable interventions and therapies to reduce the incidence of cardiac surgery–associated acute kidney injury.

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Worldwide, more than 2 million cardiac surgeries are performed each year. Cardiac surgery–associated acute kidney injury (CSA-AKI) is a serious postoperative complication, and is the second most common cause of AKI in the intensive care unit.[1] An incidence of CSA-AKI of up to 39% has been reported, varying depending on patient-related baseline characteristics and the type of surgery.[2] Between 3% and 6.5% of all surgical patients require renal replacement therapy. This worst stage of CSA-AKI is independently associated with a very high mortality rate.[3] Other clinical consequences of CSA-AKI are increased length of hospital stay, increased risk of chronic kidney disease (CKD), and increased risk of death within 5 years after surgery.[4] The success of interventions or new therapeutic strategies aimed at reducing the incidence of CSA-AKI and its related outcomes depends on the optimum time of their application, which is at the very early stages of AKI.

DIAGNOSIS OF FUNCTIONAL AKI

To create uniformity in the diagnosis of AKI, the RIFLE (risk of renal injury/injury to the kidney/failure of kidney function/loss of kidney function/end-stage disease) criteria were proposed in 2004,[5] followed by the Acute Kidney

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Abbreviations and Acronyms

AKI = acute kidney injury
AKIN = Acute Kidney Injury Network
CKD = chronic kidney disease
CSA = cardiac surgery associated
eGFR = estimated glomerular filtration rate
KDIGO = Kidney Disease–Improving Global Outcomes
NGAL = neutrophil gelatinase-associated lipocalin
RIFLE = risk of renal injury/injury to the kidney/failure of kidney function/loss of kidney function/end-stage disease
SCr = serum creatinine

Injury Network (AKIN) criteria in 2007[6] and the Kidney Disease–Improving Global Outcomes (KDIGO) criteria in 2012.[7] These criteria express the deterioration of kidney function as a decline in the estimated glomerular filtration rate (eGFR), which is based on an increasing serum creatinine (SCr) concentration and a declining urine output. However, in health, the kidneys have a significant degree of excess capacity, such that 50% of the functional kidney mass can be damaged without any drop in SCr-based eGFR. Therefore, an increase in SCr occurs relatively late after the initial injurious event (24-48 hours), with hemodilution related to pump priming as an additional contributor to this delay.

In view of this limitation of an SCr-based definition of AKI, an additional test indicating that assessment of acute tubular damage might be of value for the clinician. The idea that detection of this so-called "subclinical AKI"[8] (ie, acute tubular damage in absence of an elevated SCr concentration) was recently suggested by the Acute Dialysis Quality Initiative (ADQI)-10 consensus work group.[9] The field of AKI biomarkers is rapidly evolving, and new proteins released by injured tubular cells are constantly being discovered. All of these new biomarkers carry the potential to serve as markers for acute tubular damage in the absence of functional AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is the most well described and studied AKI biomarker in adult patients undergoing cardiac surgery to date, and is our current focus of interest.

NGAL

NGAL is a small siderophoric protein that is intensely up-regulated and excreted in cases of acute tubular damage. It can be detected in both plasma and urine. In the early phases of AKI, NGAL mitigates iron-mediated toxicity by providing a reservoir for excess iron, and in subsequent phases, it promotes regeneration and repair by regulating intracellular iron availability. NGAL is readily filtered in the glomerulus and readily reabsorbed in the proximal tubular segments. Immediately following diverse injurious events, NGAL is up-regulated in the distal parts of the nephron. Consequently, increased levels of plasma and urinary NGAL are detectable, presumably resulting from both apical and basolateral secretion. Impaired proximal tubular reabsorption, due to coexisting or subsequent proximal cellular damage that exceeds the megalin-dependent transport maximum, further potentiates urinary NGAL excretion.[10,11] Although other sources of NGAL exist in various pathological states (ie, inflammation, infection, intoxication, ischemia, and neoplastic formation), a potentiated NGAL response is very discriminative for acute tubular damage, as confirmed by experiments in NGAL-knockout mouse models.[12]

DIAGNOSIS OF ACUTE TUBULAR DAMAGE, OR SUBCLINICAL AKI

Based on the results of a multicenter pooled analysis by Haase et al[8] on the clinical impact of subclinical AKI, defined as NGAL expression in absence of functional AKI, a clear separation in the definition between acute tubular damage and functional AKI seems justified. Acute tubular damage is a pathological process that is separated in time (earlier) from SCr-based dysfunction, which is not always manifested as AKI according to the RIFLE, AKIN, and KDIGO definitions. Nonetheless, the independent presence of acute tubular damage affects patient outcomes and thus should at least be recognized and possibly addressed as a separate clinical entity.[8] We propose the use of NGAL as the biomarker in a new definition of acute tubular damage, the Cardiac Surgery–Associated NGAL (CSA-NGAL) score to further complement the functional diagnosis of AKI.

A PROPOSAL: USE OF THE CSA-NGAL SCORE TO DETECT ACUTE TUBULAR DAMAGE

The CSA-NGAL score (Figure 1) was created by H.R.H.d.G., C.R., M.H., L.J., A.L., and J.-L.V., all experts in the field of critical care and critical care nephrology, after round table discussions. Although the urge to move the field of kidney biomarker research to a different level has been present for awhile, the lack of definite threshold values for biomarkers such as NGAL and a scoring system linked to treatment suggestions has hindered the development of a new scientific approach.

Today, the level of evidence regarding NGAL cutoff values for the detection of acute tubular damage is much higher than that available at the time of the introduction of the RIFLE criteria, which were based on potentially prognostically relevant and memorable SCr cutoff values. Results supporting the prognostic significance of the RIFLE criteria were reported subsequently.[13,14] We propose that the introduction of applicable NGAL cutoff values in the CSA-NGAL score will result in a similar development for the diagnosis of subclinical AKI.