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Urinary glutathione S-transferases in the pathogenesis and diagnostic evaluation of acute kidney injury following cardiac surgery: a critical review

Blaithin A. McMahon^a, Jay L. Koyner^b, and Patrick T. Murray^a

^aUniversity College Dublin School of Medicine and Medical Science, Catherine McAuley Centre, Nelson Street, Dublin, Ireland ^bSection of Nephrology, Department of Medicine, University of Chicago, Chicago, Illinois, USA

Abstract

Purpose of review—A focused review of the nature, source, physiological role and rapidly expanding evidence for glutathione S-transferase (GST) subtypes π and α as biomarkers of acute kidney injury (AKI) in patients undergoing cardiac surgery. Expanded insights into the site-specific expression of the GSTs in defined parts of the nephron during renal damage are presented, with particular emphasis on the pathogenesis of cardiac surgery and cardiopulmonary bypass (CPB)-associated AKI and the role of GSTs in oxygen radical disposal.

Recent findings—Recent developments have highlighted a potential role of urinary α -GST and π -GST in the diagnostic evaluation of cardiac surgery-associated AKI. Both urinary α -GST and π -GST are detected in the postoperative period. π -GST performed best at predicting AKI severity at the time of the initial diagnosis of AKI. α -GST was able to predict the future development of both stage 1 and stage 3 AKI.

Summary—The current data from a small number of patients suggest a potential role of urinary GSTs in the clinical diagnostic evaluation of AKI following cardiac surgery. The performance of the GSTs for the early diagnosis of AKI needs to be validated in larger multicentre studies and in other patient populations at increased risk of AKI (e.g. patients with acute transplant rejection, septic patients). Comparison with other emerging AKI biomarkers is required to continue the development of π -GST and α -GST. Finally, additional studies examining the pathophysiological role of the GSTs in minimizing oxygen free radical exposure in the renal tubules during CPB may shed further light into their role as promising biomarkers of cardiac surgery-associated AKI.

Keywords

acute kidney injury; cardiopulmonary bypass; glutathione S-transferases

Introduction

Despite numerous recently published studies and reviews on biomarkers in acute kidney injury (AKI), the glutathione S-transferase (GST) protein family have received relatively little attention in the literature [1,2]. The GST protein family, which is divided into three major subclasses α , π and μ , are ubiquitous enzymes that take part in the detoxification of free radicals. Each isoenzyme is composed of two subunits and is named according to its subunit composition. The GST family of proteins have been purified from a wide variety of human tissues (e.g. kidneys, liver, small intestines, testes, ovaries, adrenal glands) and are extremely well characterized. Human kidney contains the α and π forms in relatively high amounts in renal tubules [3]. The α -form has a molecular weight of 51 kDa and the π -form 47 kDa.

Site-specific localization of glutathione S-transferases in the kidney

Urinary GSTs are well validated, histologically defined renal biomarkers whose cellular origins are the key to their diagnostic interpretation. In the nephron, the GST proteins are site-specific; the α -GST isoform is mostly localized in the proximal tubule (Fig. 1a) and the π -GST in the distal tubule [3] (Fig. 1b). These biomarkers are preformed cytosolic enzymes and form 2% of soluble protein of the renal tubules. In in-vitro studies using rat proximal renal tubular cells, in the absence of renal injury, constitutively expressed α -GST activity is low, but is highly inducible both at the mRNA and protein level in response to cytoprotective agents, such as 3H-1,2-dithiole-3-thione, which can protect against hydrogen peroxide and 4-hydroxynonenal (HNE)-induced cytotoxicity [4]. α -GST and π -GST are exclusively released into the urine during renal injury, which makes them very early indicators of tubular damage [5]. In contrast, elevated serum levels of α -GSTs are likely derived from the liver during hepatotoxicity and do not cross the glomerular filtration barrier because of their high molecular weight. Consequently, the measurement of urinary α -GST and π -GST enable a topological diagnostic approach of renal injury because of the site-specific expression of these proteins in the renal tubules [3,5]. Unlike other putative biomarkers of AKI, the exploitation of this discriminatory power makes the urinary GSTs attractive biomarkers for studying site-specific injury to defined parts of the nephron.

Clinical utility of glutathione S-transferases in renal diseases

The clinical utility of GST isoenzymes as biomarkers for kidney injury has been studied in a variety of clinical settings including cyclosporine-induced nephrotoxicity [5], cadmium exposure and administration of nephrotoxic antibiotics, acute transplant rejection [5], assessment of graft function from machine-preserved nonheart-beating donor kidneys [6], proteinuric states with normal glomerular filtration rate (GFR) [7], diabetic patients with varying degrees of albuminuria [8•], patients undergoing vascular surgery [9], critically ill patients in the ICU [10,11], and in particular, in patients undergoing cardiac surgery [12•, 13•] (Table 1).

The pattern of urinary GST release can reflect the nature of the renal insult. In a recent study of 457 patients with diabetes with increasing albuminuria but with normal renal function (as measured by serum creatinine), π -GST but not α -GST correlated with the degree of

albuminuria and appeared to identify renal damage that is related to, but distinct from, urine albumin/creatinine ratios (glomerular injury) [8••]. In sepsis syndrome, elevations in π -GST without a change in α -GST levels suggest that sepsis-associated AKI [defined by the Acute Kidney Injury Network (AKIN) criteria, stage 1–3] is perhaps a distal tubular injury [11]. Urinary α -GST has been used in clinical practice to assess the degree of damage from warm ischaemic time and consequent chance of nonfunction of machine-preserved nonheart-beating donor kidneys [6]. Acute graft rejection after renal transplantation greatly increases the excretion of π enzyme in the urine without affecting the levels of the α protein, correlating with the distal tubular injury seen in the renal biopsies [14]. In contrast, nephrotoxic drug injury caused by calcineurin inhibitors may principally affect proximal tubules and can result in elevations of α -GST with no change in π -GST expression [5]. In this manner, nephron segment-specific biomarkers may allow for the early diagnosis and discrimination between these two common conditions (rejection vs. calcineurin inhibitor-induced nephrotoxic injury) in the renal transplant patient presenting with new onset renal insufficiency in the perioperative period.

Pathophysiological aspects of cardiopulmonary bypass

In cardiovascular surgery, the use of cardiopulmonary bypass (CPB) is associated with AKI [15]. The pathogenesis of CPB-associated AKI involves multiple pathways with haemodynamic, inflammatory, nephrotoxic factors and the release of labile iron contributing to oxidation from reactive oxygen species. Haemolysis is a common consequence of CPB, which is caused by mechanical stress in the perfusion circuit. Haemolysis results in the release of haemoglobin from lysed erythrocytes into the plasma and may be a major contributor to renal injury [16•,17]. Accordingly, CPB-associated AKI may be a form of pigment nephropathy, in which, in an acidic urinary environment, the conversion of haemoglobin to methaemoglobin results in the formation of tubule-obstructing casts [17]. The potential for injury during CPB is accentuated further by aortic cross-clamping, leading to ischaemic insults.

Contact of the patient's blood with the artificial surface of the bypass circuit, ischaemia-reperfusion injury, endotoxemia, operative trauma, and nonpulsatile blood flow are all possible causes of immune activation seen in the systemic inflammatory response to CPB. During CPB, there is widespread activation of neutrophils and the vascular endothelium, with upregulation of adhesion molecules such as CD11b and CD41 [18]. Platelets also undergo activation, degranulation, and adherence to vascular endothelium. These events lead to the elaboration of cytotoxic oxygen-derived free radicals, proteases, cytokines, and chemokines such as interleukin (IL)-6, tumour necrosis factor- α , and IL-8 [15].

Performance of glutathione S-transferases as potential biomarkers of acute kidney injury after cardiac surgery

The GST family proteins are generally viewed as phase II enzymes, primarily involved in the detoxification of electrophilic compounds by catalysing the formation of reduced glutathione (GSH)-electrophile conjugates [19]. Several studies have demonstrated that GSTs play a critical role in protecting cells from oxidant-mediated injury by catalysing the

composition of lipid hydroperoxides generated from oxidative damage of cellular lipid molecules [20,21]. In particular, α -GST can detoxify lipid peroxidation end-products such as 4-HNE via the formation of GSH conjugate, thereby limiting their cytotoxicity [4,21]. Inactivation of these reactive oxygen species by the reduction of glutathione by the GST proteins limits the toxic effects of oxidative intermediates on tubular cells and provides a physiological response to injury by the tubular cells. α -GST and π -GST are preformed cellular proteins, exclusively released into the urine during renal injury and detectable within 1 h of the initiation of CPB [9]. Prolonged length of time on CPB is a well recognized risk factor for the development of AKI. This association may relate to the prolonged generation of oxidative stress, free haemoglobin and toxic iron and the depletion of preformed GST proteins in tubular cells, all providing a platform for the development of AKI.

The current data from a limited number of human studies evaluate the potential role of urinary α -GST and π -GST in the diagnostic evaluation of CPB-associated AKI (summarized in Table 1). In general, these studies are conflicting and many involve only small patient numbers. The study by Eijkenboom *et al.* [23] attempted to assess the diagnostic accuracy of the urinary GSTs for the early detection of AKI (as defined by a 50% or 0.3 mg/dl increase in serum creatinine from baseline) following elective cardiac surgery. Additionally, they sought to determine the site of tubular injury as reflected by the pattern of urinary GST enzyme excretion. However, of the 84 patients enrolled in the study, only one patient had AKI. The authors reported a small but statistically significant increase in both urinary α -GST and π -GST following adult cardiac surgery, but both tended to return to normal levels after 24 h. The authors concluded that this transient increase in GST protein excretion did not correlate with changes in serum creatinine and did not predict clinically relevant changes in renal function. However, the low incidence of clinical AKI in this patient cohort makes it difficult to draw any valid conclusions regarding the diagnostic performance of GSTs to predict AKI following cardiac surgery, including the possibility that transient postoperative urinary GST increases might represent subclinical renal tubular injury (without serum creatinine increase) and/or a tubular response to oxidant stress.

In another study by Yavuz *et al.* [13•], α -GST was measured in 51 patients who were randomized to either on-pump or off-pump bypass surgery. Patients with pre-existing chronic kidney disease and plasma creatinine levels ranging between 1.5 and 2 mg/dl were included in the study. AKI was defined according to the Risk Injury Failure Loss and End-stage (RIFLE) classification; the F-criterion (failure of renal function, at least 300% increase in the plasma creatinine from baseline). α -GST showed reasonable accuracy when discriminating AKI ($n = 16$) from non-AKI ($n = 35$) at 24 h postoperatively [area under the curve (AUC) = 0.84]. α -GST values were significantly lower in the off-pump patients compared with on-pump surgery patients [13•]. α -GST showed moderate correlation with both 24-h creatinine clearance ($r^2 = 0.467$, $P < 0.001$) and fractional excretion of sodium ($r^2 = 0.559$, $P < 0.001$), but a weak correlation with plasma creatinine in the whole study population ($r^2 = 0.337$, $P < 0.001$). Furthermore, in this study, α -GST failed to predict the need for renal replacement therapy (RRT). This study is limited in its total number of AKI events (seven in the off-pump and nine in the on-pump), with only 5 of these patients progressing to require RRT (two in the off-pump and three in the on-pump). Other

limitations of the study include the failure to include a non-chronic kidney disease patient group; inclusion of only severe cases of AKI ('F' of the RIFLE criteria); and failure to measure other AKI biomarkers, such as π -GST. The performance of biomarkers of AKI in patients with preexisting renal disease with tubular damage has recently been studied [12•, 28•]. Many biomarkers perform better in those with no history of chronic kidney disease. In the study by Koyner *et al.* [12•], π -GST and α -GST performed better in those patients with estimated GFRs greater than 60 ml/min, but such patients were not included in the study by Yavuz *et al.* [13•].

Koyner *et al.* [12•] addressed the diagnostic and prognostic accuracy of urinary α -GST and π -GST following adult cardiac surgery in 123 patients. This is one of the largest studies to date examining the diagnostic performance of GSTs in predicting AKI following cardiac surgery. Of the 123 patients, 46 patients (37.4%) developed postoperative AKI, of whom 36 (29.3%) developed only stage 1 AKI (>50% or 0.3 mg/dl absolute increase from baseline creatinine). One patient developed AKIN stage 2 (>100% increase from baseline), whereas nine patients developed AKIN stage 3 (200% increase); eight of these required RRT. Preoperative α -GST was able to predict the development of both stage 1 and 3 AKI, and as a result may be useful in preoperative risk stratification models of adult cardiac surgery. π -GST best predicted the progression to stage 3 AKI at the time of the initial creatinine increase with an AUC of 0.86 ($P = 0.002$). The data were presented adjusted and unadjusted for urine creatinine and performed better when normalized in the presence of clinical AKI.

Glutathione S-transferases as biomarkers of tubular integrity

GST measurements have been performed in several intervention studies in cardiac surgery, including several studies that utilized hydroxyethyl starch (HES) preparations [25–27]. The potential detrimental effect of HES preparations on kidney function has become a source of major concern and debate over recent years [29•,30]. The excretion of π -GST, α -GST, and other tubular enzymes, may potentially be used as markers for subclinical kidney injury during CPB [29•]. In one prospective randomized study [25], 50 patients undergoing cardiac surgery using CPB received either 6% HES 130/0.42 or albumin as control. Urinary concentrations of α -GST and neutrophil gelatinase-associated lipocalin (NGAL) were significantly higher immediately after surgery and 5 h later in the ICU in the albumin group compared with the HES group, potentially indicating subclinical renal tubular injury, with no significant change in serum creatinine levels. Thus, urinary concentrations of α -GST may be more sensitive and reliable to assess the effect of volume replacement strategies on tubular integrity than serum creatinine, a marker of glomerular function. This is also supported by studies demonstrating elevated urinary α -GST levels in patients undergoing on-pump coronary artery bypass surgery when compared with the off-pump surgery patients [13•,24].

Glutathione S-transferases and other patient cohorts

The performance of GSTs for the diagnosis of AKI has similarly been investigated in patient cohorts other than in cardiac surgery. Walshe *et al.* [11] evaluated the performance of GSTs in predicting AKI in a small cohort of critically ill septic patients. Elevations in π -GST

without a change in α -GST levels suggest that AKI in sepsis is a distal tubular injury. In other patient populations, α -GST had excellent discriminatory power in predicting AKI at the time of admission to ICU in critically ill patients (AUC = 0.89) [10], in the early diagnosis of AKI after infrarenal abdominal aortic aneurysm repair [9], and in predicting the need for renal replacement therapy in nonoliguric acute tubular necrosis patients [31].

Conclusion

In conclusion, the current data from a small number of patients suggest a potential role of urinary GSTs in the clinical diagnostic evaluation of AKI postcardiac surgery. In the future, larger multicentre studies will be required to further validate these findings in the cardiac surgery population. Additionally, on the basis of the preexisting literature, further investigations across other cohorts (delayed renal graft function, septic patients) are warranted. Continued comparison with other novel AKI biomarkers is required for the continued development of GSTs for this purpose. Finally, although GSTs have demonstrated some ability to detect AKI in the setting of cardiac surgery and other high-risk AKI clinical settings, these data are limited and warrant further investigation in the evolving field of AKI.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 669).

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Figure 1. Distinct distributions of glutathione S-transferases along the nephron
(a) Immunohistochemical localization of alpha-glutathione S-transferase in the human kidney (proximal tubules). Reproduced with permission from [3]. (b) Immunohistochemical localization of pi-glutathione S-transferase in the human kidney (distal tubules). Reproduced with permission from [3].

Table 1

The potential role of urinary alpha-glutathione S-transferase and pi-glutathione S-transferase in the diagnostic evaluation of cardiopulmonary bypass-associated acute kidney injury

Reference	Year	Patients/methods	Outcome	Key results
Koyner <i>et al.</i> [12•]	2010	123 patients undergoing cardiac surgery with and without CPB	AKI (serum creatinine-AKIN criteria)	Preoperative α -GST was able to predict the future development of both stage 1 and stage 3 AKI. π -GST best predicted the progression to stage 3 AKI at the time of creatinine increase (AUC = 0.86, $P = 0.002$).
Yavuz <i>et al.</i> [13•]	2009	51 patients with preoperative renal dysfunction randomized to on-pump or off-pump CABG	Worsening AKI (serum creatinine-'F' of RIFLE criteria)	Urinary α -GST levels were significantly lower in off-pump surgery patients compared with on-pump surgery patients at 24 h postoperatively. Urinary α -GST measurements were poor predictors of AKI development. No significant correlation between urinary α -GST and plasma creatinine.
Lema <i>et al.</i> [22]	2006	Nine children undergoing cardiac surgery with CPB	AKI (GFR measured by insulin clearance + serum creatinine)	Urinary α -GST levels were moderately increased 1 h after surgery, however, without statistical significance. No change in serum creatinine or GFR 1 h after surgery.
Eijkenboom <i>et al.</i> [23]	2005	84 patients undergoing CABG using CPB	AKI (50% rise in serum creatinine)	Cardiac surgery with CPB results in increased urinary α -GST and π -GST as compared with healthy controls; however, this increase in GSTs did not predict clinically significant AKI.
da Silva Magro and de Fatima Fernandes Vattimo [24]	2004	41 patients with normal renal function randomized to on-pump or off-pump CABG	AKI (reduction in creatinine clearance <75 ml/min)	Urinary α -GST levels were significantly lower in off-pump surgery patients compared with on-pump surgery patients at 24 h postoperatively. Urinary α -GST measurements were poor predictors of AKI development.
Boldt <i>et al.</i> [25]	2009	50 patients with normal renal function undergoing CPB randomized to receive either a high dose of a balanced HES or an albumin-based priming strategy	AKI (Changes in serum creatinine)	Urinary α -GST levels were significantly higher immediately after CPB and 5 h later in the ICU in the albumin group compared with the HES group. No change in serum creatinine perioperatively after 60 days after hospital discharge in both groups.
Boldt <i>et al.</i> [26]	2008	50 elderly patients undergoing CPB randomized to receive either a balanced 6% HES or human-balanced HES volume replacement regimen	AKI (changes in creatinine clearance 24 h postsurgery)	Urinary α -GST levels were higher 5 h after CPB and increased until the first and second POD in both groups with the significantly higher increase in the unbalanced group. Mean serum creatinine was elevated beyond normal without showing significant differences between the two groups.
Boldt <i>et al.</i> [27]	2007	50 patients with nonoliguric kidney injury undergoing CABG using CPB were randomized to receive either a HES with a low molecular weight and a low molar substitution or a 5% albumin-based volume replacement priming strategy and given until the second postoperative day	Worsening AKI (changes in serum creatinine and eGFR)	Urinary α -GST levels were significantly higher than normal in both groups at baseline and significantly increased until the second POD in both groups without showing significant group differences. Urinary NGAL levels increased more in the albumin-treated than the HES-treated group. No further deterioration in kidney dysfunction between the two treatment groups.

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AUC, area under the curve; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; GST, glutathione S-transferase; HES, hydroxyethyl starch; POD, postoperative day; RIFLE, Risk Injury Failure Loss End-stage.

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