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Mechanisms of *triple whammy* acute kidney injury

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ABSTRACT

Pre-renal acute kidney injury (AKI) results from glomerular haemodynamic alterations leading to reduced glomerular filtration rate (GFR) with no parenchymal compromise. Renin-angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists (ARAs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, are highly prescribed drugs that are frequently administered together. Double and triple associations have been correlated with increased pre-renal AKI incidence, termed "double whammy" and "triple whammy", respectively. This article presents an integrative analysis of the complex interplay among the effects of NSAIDs, ACEIs/ARAs and diuretics, acting alone and together in double and triple therapies. In addition, we explore how these drug combinations alter the equilibrium of regulatory mechanisms controlling blood pressure (renal perfusion pressure) and GFR to increase the odds of inducing AKI through the concomitant reduction of blood pressure and distortion of renal autoregulation. Using this knowledge, we propose a more general model of pre-renal AKI based on a multi whammy model, whereby several factors are necessary to effectively reduce net filtration. The triple whammy was the only model associated with pre-renal AKI accompanied by a course of other risk factors, among numerous potential combinations of clinical circumstances causing hypoperfusion in which renal autoregulation is not operative or is deregulated. These factors would uncouple the normal BP-GFR relationship, where lower GFR values are obtained at every BP value.

1. Acute kidney injury and the triple whammy syndrome

The term acute kidney injury (AKI) encompasses a number of aetiopathologically heterogeneous conditions leading to an abrupt decline in renal excretory function causing azotaemia, alterations in urinary flow (typically oliguria), or both. According to the international definition and scoring AKI scales, namely RIFLE, AKIN and KDIGO (Sutherland et al., 2015; Thomas et al., 2015), no AKI exists until azotaemia (exemplified by plasma creatinine, Cr_{pl}) increases, reflecting a reduction in the glomerular filtration rate (GFR). AKI is a serious condition from both sanitary and economic points of view. AKI incidence is also high, leading to 1–2% of hospital admissions and occurring in 2–7% of hospitalized patients. In determined settings, AKI incidence can be as high as 30%, with mortality as high as 50–80% of cases, i.e., critically ill patients. AKI costs derived from extended hospital stays, closer monitoring and dialysis represent 5% of the hospital budget (Chertow et al., 2005; Vandijck et al., 2007) and 1% of the overall health expenditure (Kerr et al., 2014).

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ADH, Antidiuretic hormone; AKI, Acute kidney injury; AKIN, Acute kidney injury network; ANP, Atrial natriuretic peptide; ARA, Angiotensin receptor antagonist; AT1, Angiotensin type 1 receptor; AT2, Angiotensin type 2 receptor; ATP, Adenosine triphosphate; BP, Blood pressure; BR, Baroreceptor; cTALH, thick ascending limb of Henle; COX, Cyclooxygenase; Cr, Creatinine; Cr_{pl}, Plasma creatinine concentration; EPI, Epinephrin; GFR, Glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; K_f, Ultrafiltration coefficient; MR, Mechanoreceptor; NSAID, Non-steroidal anti-inflammatory drug; PG, Prostaglandin; PGR, Prostaglandin receptor; PGE_2, Prostaglandin E_2; PGH_2, Prostaglandin H_2; PGI_2, Prostaglandin I_2; RAAS, Renin-angiotensin-aldosterone system; SR, Stretch receptor; RBF, Renal blood flow; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SNS, Sympathetic nervous system; TGF, Tubulo-glomerular feedback; V, Vasopressin.

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The most frequent form of AKI is "pre-renal AKI", which reflects altered renal haemodynamics leading to reduced glomerular filtration pressure or reduced renal blood flow (or both), resulting in a decrease in the GFR. Pre-renal AKI accounts for 60–70% of all AKI cases (Kaufman et al., 1991). Pre-renal AKI with no damage to the renal tissues but with azotaemia and uraemia is typically resolved through hydration. Pre-renal AKI commonly results from severe hypotension (e.g., from surgical or traumatic blood loss, burns and mild sepsis), dehydration (from vomiting, diarrhoea, bleeding or hypovolaemia), heart failure, liver failure, narrowing of renal arteries, renal microangiopathy, exposure to vasoactive drugs and toxins, etc. (Kaufman et al., 1991; Uchino, 2010). "Renal AKI" develops when the primary cause of AKI is parenchymal injury, caused by drugs, toxins, and ischaemia. Moreover, "post-renal AKI" reflects the obstruction of the urinary system, particularly the ureters.

Angiotensin receptor antagonists (ARAs), angiotensin-converting enzyme inhibitors (ACEIs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics represent nephrotoxic or potentially nephrotoxic drugs (Hricik & Dunn, 1990; Whelton & Hamilton, 1991; Delmas, 1995; Jolobe, 2001; Schoolwerth et al., 2001; Gambaro & Perazella, 2003; Patzer, 2008; Coca et al., 2013) frequently used in multidrug therapies. These drug families have been associated with nephrotoxicity upon chronic exposure and AKI (Musu et al., 2011). Although beneficial in many circumstances, diuretics also aggravate AKI under certain conditions (Karajala et al., 2009; Ejaz & Mohandas, 2014; Wu et al., 2014). The Centre for Clinical Epidemiology of Canada determined that the joint administration of these three types of drugs might increase the risk of AKI by 30%, whereas single and double treatments are associated with lower AKI rates (Adhiyaman et al., 2001; Loboz & Shenfield, 2005; Fournier et al., 2012; Lapi et al., 2013). AKI resulting from combined therapy with NSAIDs, ARAs/ACEIs and diuretics is referred to as "triple whammy" (Thomas, 2000; Loboz & Shenfield, 2005; Lapi et al., 2013; Onuigbo, 2013). This article analyses the combined mechanisms of action and determinants leading to pre-renal, triple whammy AKI.

2. Systemic and renal glomerular haemodynamic regulation

Due to renal autoregulation and the synchronized interplay of afferent and efferent contraction and dilation, both renal blood flow (RBF) and GFR remain constant within a mean blood pressure (BP) range from approximately 80 to 180 mm Hg (Carlström et al., 2015, Fig. 1). Renal autoregulation responds to changes in BP and GFR independently from BP fluctuations. Renal autoregulation protects renal structures and maintains GFR mostly upon increments in BP (Loutzenhiser et al., 2006; Carlström et al., 2015), as most humans and animals live within the lower limits of the renal autoregulatory range (Fig. 1A). The GFR-BP relationship is shifted to the right in hypertension; thus, hypertensive individuals also live within the same range under basal conditions, i.e., near the lower limit of autoregulation (Palmer, 2002; Bidani & Griffin, 2004). Accordingly, the inhibition or alteration of autoregulation does not reduce the GFR (Loutzenhiser et al., 2006), per se, but rather leads to an increment in the GFR. Thus, a decline in the GFR reflects a reduction in BP below the lower limit of the autoregulatory range.

However, a significant decline in BP must occur to induce a sufficient reduction in GFR and subsequently lead to AKI. Due to the renal functional reserve, for Cr_{pl} to increase, more than 60–70% of the overall renal mass must be functionally void (Pfaller & Gstraunthaler, 1998; Nan-Ya et al., 2015). Indeed, the overall GFR declines only when the number of remaining functional nephrons decreases under a certain threshold (approximately 70%). However, Cr_{pl} does not increase in parallel, as the tubular secretion of Cr increases and compensates for reduced filtration. Only after secretion becomes saturated does Cr_{pl} increase (Fig. 1B). Notably, the severe decline in BP required for AKI might not be compatible with life. However, there are other conditions that might lead to AKI upon milder decreases in BP. Specifically, a concomitant alteration of the autoregulatory capacity (e.g., through drug-mediated inhibition) might amplify the effect of slight reductions in BP on GFR, leading to AKI. This effect might occur within the autoregulatory range but also below the autoregulatory range (pressure drops not sufficiently large enough alone to lead to AKI). Under these conditions (i.e., for 50–60 > BP < 80 mm Hg), autoregulatory mechanisms attempt to maintain the GFR, although these mechanisms become progressively less effective as BP gradually declines and GFR concomitantly decreases. Inhibiting the mechanisms elicited under these circumstances to maintain GFR consequently amplifies the reduction in GFR (Fig. 1C,D). This scenario likely underlies many cases of pre-renal AKI. Typically, to elicit pre-renal AKI, both BP (i.e., renal perfusion pressure) decreases below the lower limit of autoregulation (<80 mm Hg) and the inhibition, distortion, alteration or uncoupling of autoregulation must occur.

Sections 2.1 thru 2.4 analyse the feedback mechanisms activated through changes in BP, volaemia and GFR to subsequently characterize the effects of NSAIDs, ARAs/ACEIs and diuretics.

2.1. Role of the macula densa in Glomerular Filtration Rate regulation

In the tubuloglomerular feedback (TGF) mechanism, when BP increases, the afferent arteriole contracts, and the efferent arteriole dilates to stabilize RBF and GFR (Vallon, 2003). The opposite effect occurs when BP decreases. Independently from BP, when GFR increases, more Na^+ and Cl^- reach the *macula densa* (Barajas, 1979; Fig. 2A), while the opposite occurs when GFR decreases. When stimulated through low Na^+ and Cl^- concentrations (upon reduced GFR), the *macula densa* signals to dilate the afferent arteriole. *Macula densa* cells produce a number of mediators, including vasodilator prostaglandins (derived from the cyclooxygenase-2 [COX-2] pathway) (Harris et al., 1994), NO, vasoconstrictor ATP and adenosine, with a net vasodilator effect on the afferent arteriole when GFR decreases. COX-2-derived prostaglandins produced from *macula densa* cells reach juxtaglomerular or granular cells in the afferent arteriole and prime these cells to secrete renin to its immediate entourage and into the circulation (Harris & Breyer, 2001; Schnermann, 2001; Harris, 2003; Harris et al., 2004; Green et al., 2012; Harris, 2013). Renin activates the systemic and local renin-angiotensin-aldosterone system (RAAS), which increases BP and GFR through an increase in peripheral vascular resistance, thereby reducing natriuresis and diuresis, resulting in the contraction of the efferent arteriole (Hall et al., 1990; Hall, 1991; Fig. 2B).

In contrast, when elevated sodium chloride reaches the *macula densa* as a result of increased BP, GFR, or both, ATP is released from cells through pannexin channels (Carlström et al., 2010; Praetorius & Leipziger, 2010; Arulkumaran et al., 2013). Extracellular ATP is converted to adenosine, which binds to adenosine A1 receptors on extraglomerular mesangial cells, triggering an increase in intracellular calcium levels (Olivera et al., 1992a, 1992b) and inducing mesangial cell contractions (Olivera et al., 1989), thereby reducing GFR (López-Novoa et al., 1987). This calcium signal is subsequently propagated via gap junctions to adjacent cells, including granular cells of the juxtaglomerular apparatus and vascular smooth muscle cells of the afferent arteriole, resulting in afferent arteriole vasoconstriction and decreased renin release (Macías-Nuñez et al., 1985; Vallon, 2003).

2.2. Mechanisms of the Blood Pressure-mediated regulation of Glomerular Filtration Rate

In addition to activating the TGF, a reduction in BP induces other effects that modulate GFR. Some of these effects are directly induced through BP effects on renal structures, while other effects are mediated through regulatory responses elicited to restore BP (summarized in Fig. 3):

a) The afferent arteriole acts as a mechanoreceptor that swiftly responds with appropriate vasomotor myogenic contraction or