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Alteration of microvascular permeability in acute kidney injury

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Abstract

Functional and structural abnormalities in the renal microvasculature are important processes contributing to the pathophysiology of ischemic acute kidney injury (AKI). Renewed interest in the complex interplay between tubular injury, inflammation and microvascular alterations has emerged in order to gain a better understanding of acute kidney injury syndromes. This review examines alterations of the renal microvasculature as they relate to ischemic and septic AKI with an emphasis on the mechanisms involved in altered microvascular permeability.

Keywords

renal failure; acute; kidney; endothelium

In an average person, approximately one-fifth of the cardiac output is directed toward the kidneys. Blood arrives to the kidney through the arteries in the renal pelvis/inner medulla and subsequently passes through segmental arterial branches toward the renal cortex before it enters the afferent arterioles leading to the glomerular capillaries. The fraction of blood leaving the glomerular capillary system passes through efferent arterioles and then a second capillary system supplying the renal tubules prior to entering the venous circulation. Blood from the efferent arterioles of the juxtamedullary glomeruli not only enters peritubular capillaries but also enters the vasa recta capillary system which forms descending and then ascending vascular bundles between tubules within the renal medulla and serves as an essential component in the formation of countercurrent gradients. In total, the structure and function of the renal vasculature is uniquely suited to support the primary function of the kidney: the regulated production, processing, and excretion of ultrafiltrate in order to maintain internal homeostasis. Accordingly, disruption of renal vascular structure and function plays an important role in diseases of the kidney. The purpose of this review is to highlight insights into the role of renal microvascular alterations in the setting of acute kidney injury with an emphasis on alterations in renal microvascular permeability.

Acute kidney injury (AKI) is a clinical syndrome manifest as a relatively sudden decrease in the production, processing, and excretion of ultrafiltrate by the kidney or more concisely a decrease in glomerular filtration rate (GFR). AKI occurs in approximately 7% of hospitalized patients (Nash et al., 2002) and is associated with an overall mortality of 40–60% in critically ill patients (Liano and Pascual, 1998; Mehta et al., 2004; Uchino et al., 2005). Ischemia, due

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to hypotension or sepsis, is the most common cause of human AKI (Liano and Pascual, 1996; Mehta et al., 2004). The appreciation that altered vascular function contributes to the decrease in GFR during AKI originated over six decades ago (Brun et al., 1955; Sheehan and Davis, 1959). Early investigators observed that renal blood flow is diminished following an inciting insult to the kidney in human AKI (Hollenberg et al., 1968; Reubi and Vorburger, 1976). This observation was also made in animal models of ischemic AKI (Axelsen and Cartwright, 1979; Kashgarian et al., 1976; Steinhausen et al., 1973). A 50–60% reduction in total renal blood flow (RBF) is commonly reported. These findings have been extended to a higher resolution through intravital videomicroscopic studies that demonstrated cessation and even reversal of flow in the renal cortical microcirculation, especially in the peritubular capillaries, during the reperfusion phase in an animal model of ischemic AKI (Yamamoto et al., 2002).

While an overall decrease in RBF has been demonstrated to significantly contribute to the diminished GFR observed in ischemic AKI (Alejandro et al., 1995), the decrease in RBF alone cannot entirely account for the total reduction in GFR during an episode of AKI (Bonventre and Weinberg, 2003; Schrier et al., 2004). Of greater importance are the regional alterations of RBF that occur during AKI. A number of investigators have demonstrated that the decrease in RBF occurs to a greater extent in the outer medullary region of the kidney as compared to the cortex in animal models of AKI (Karlberg et al., 1983; Mason et al., 1984; Olof et al., 1991; Vetterlein et al., 1986). These regional deficits in RBF have more recently been confirmed to occur in humans following ischemic injury to the kidney (Dagher et al., 2003). Of further interest is that these regional blood flow deficits have been demonstrated to be more persistent following injury in disease models predisposed to AKI (Shi et al., 2007). In this study the recovery of regional blood flow was 4–5 times slower in diabetic mice than in background control mice. The persistent deficit in outer medullary blood flow has been posited to be intrinsically linked to the complex interaction of tubular injury, inflammation, and vascular alterations that not only affect GFR (Figure 1) but serve to extend cellular injury beyond the initial insult by promoting continued tissue hypoperfusion (Goligorsky, 2005; Sutton et al., 2002).

Initial investigation into the underlying structural and functional microvascular changes that contribute to diminished RBF and GFR also proved insightful. Early morphological studies incriminated endothelial cell injury as playing a key role in the reduction of RBF by contributing to microvascular congestion (Flores et al., 1972; Summers and Jamison, 1971). Later studies demonstrated increased microvascular congestion and the trapping of red blood cells (RBC) in the outer medullary region during AKI (Hellberg et al., 1990a; Mason et al., 1984; Mason et al., 1987). These latter investigators demonstrated that a decreased pre-injury hematocrit reduced microvascular congestion, improved RBF, and prevented the decrease in GFR. On the basis of these studies it was concluded that vascular congestion by RBCs was an important contributor to the reduction of RBF and GFR in AKI. Additional studies by Bayati et al. and Hellberg et al. demonstrated that an increase in microvascular permeability was a primary inciting event that promoted hemoconcentration and subsequent RBC trapping and vascular congestion (Bayati et al., 1990; Hellberg et al., 1990b; Hellberg et al., 1990c). Furthermore, the studies by Hellberg et al. suggested that increased microvascular permeability contributed to an overall decrease in GFR not only by RBC trapping and vascular congestion, but through increased interstitial edema, increased tubular pressure, and increased tubular obstruction. These early studies underscore the importance of altered microvascular permeability in the pathophysiology of AKI.

Enhanced leukocyte-endothelial interactions, loss of the endothelial monolayer, alteration of endothelial cell-cell contacts, and breakdown of the perivascular matrix can all culminate in increased microvascular permeability during AKI (Fig 2). It is unlikely that any one of these

pathways solely contributes to the increased microvascular permeability observed in AKI but rather that all these processes contribute to some extent. Furthermore, it is likely that each of these pathways modulate each other to some degree. However, for the purposes of this review each mechanism will be considered individually in order to examine its role in AKI.

Activation of inflammation is an important component of both the initiation and extension of injury in ischemic and septic AKI (Fig 1). Enhancement of leukocyte-endothelial interactions is a salient feature of this inflammatory process. Numerous studies have demonstrated enhanced endothelial expression of molecules that augment leukocyte adhesion in animal models of ischemic and septic AKI (Friedewald and Rabb, 2004). These molecules include ICAM-1, P- and E-selectin, and B7-1. Strategies to genetically ablate or knock down the expression of these molecules or to pharmacologically block the interaction with leukocytes have been shown to diminish injury and protect kidney function in animal models of septic and ischemic AKI (De Greef et al., 2001; Haller et al., 1996; Jayle et al., 2006; Kelly et al., 1994; Kelly et al., 1996; Nemoto et al., 2001; Rabb et al., 1995; Singbartl et al., 2001; Takada et al., 1997; Wu et al., 2007). Because B7-1 expression is limited to the ascending vasa recta, the study by De Greef et al. is of particular interest because it highlights the importance of alterations in this microvascular bed.

Another aspect with potential impact on endothelial-leukocyte interactions is the presence of the endothelial glycocalyx. The glycocalyx is a sulfated glycosaminoglycan (GAG)-rich layer of up to 0.5 microns that has been suggested to form the first layer of a “double layer” to vascular permeability (Adamson, 1990; Rehm et al., 2004). Shedding of the glycocalyx has been demonstrated following ischemia-reperfusion injury and this shedding occurs in G-protein sensitive fashion (Mulivor and Lipowsky, 2004; Platts et al., 2003; Rehm et al., 2007). The shedding of the glycocalyx has been posited to initiate downstream signaling cascades and increase access of leukocytes to endothelial adhesion molecules. How changes in the glycocalyx modulate endothelial-leukocyte interactions and microvascular permeability in the kidney following injury is unknown and a potentially fruitful area for investigation.

Although it stands to reason that blocking endothelial-leukocyte interactions would moderate the heightened microvascular permeability observed in models of AKI, this remains an open area for study. At least one study has examined the interaction between leukocyte adhesion and increased microvascular permeability (Sutton et al., 2005). This study found no direct spatial correlation between leukocyte adhesion and areas of increased microvascular permeability. However, this study did not directly examine the potential paracrine/organ effects of inflammatory cytokines released by adherent leukocytes in the renal microcirculation on microvascular permeability.

As mentioned above, alterations in endothelial cell morphology have been observed in animal models of AKI. More recent work has demonstrated that disruption of the actin cytoskeleton in renal microvascular endothelial cells occurs in an ischemic model of AKI (Sutton et al., 2002). Disruption of the endothelial actin cytoskeleton has implications for the maintenance of cell structures including cell-cell adhesion complexes and cell-matrix adhesion complexes. Indeed, work by Brodsky et al. has revealed that detachment of cells from the endothelial monolayer occurs in ischemic AKI leaving breaches in the renal microvascular monolayer and providing a structural basis for altered endothelial barrier function and altered microvascular reactivity (Brodsky et al., 2002). Additional studies by Hörbelt et al. (2007) suggest that the loss of endothelial cells is not pervasive and that the endothelial monolayer is primarily intact in areas of increased permeability. While endothelial cell loss may not be the primary mechanism for increased microvascular permeability in this model of AKI, it certainly does not diminish the potential role that endothelial cell detachment may play in the acute alteration of vascular reactivity. In the aforementioned study by Brodsky et al. (2002), infusion of

exogenous endothelial cells not only resulted in the implantation of these cells into the microvasculature but improved microvascular tone and flow in an eNOS dependent fashion.

Disruption of endothelial cell-cell contacts (Brodsky et al., 2002) and alteration of cell-cell adhesion complexes (Sutton et al., 2003) have also been observed in a model of ischemic AKI and have been temporally related to an increase in microvascular permeability. Consequently, alteration of endothelial cell-cell contacts is thought to be a prominent mechanism for the enhanced microvascular permeability following ischemic injury. While ischemic and/or septic injury can be associated with depletion of cellular energy stores and breakdown of the actin cytoskeleton leading to alterations in actin based cell-cell structures, there is a growing body of evidence suggesting that cellular signalling mechanisms may be involved in altering endothelial cell-cell contacts in ischemic AKI. Sphingosine-1-phosphate (S1P) is formed by the phosphorylation of the sphingosine and exerts biological activity via a family of S1P G-protein coupled receptors (McVerry and Garcia, 2005). S1P activates endothelial cells and serves to enhance endothelial barrier function. Pharmacologic administration of an S1P₁ receptor agonist in a model of ischemic AKI not only prevented an increase in microvascular permeability but was protective of overall kidney function (Awad et al., 2006). Similarly, administration of hepatocyte growth factor has been demonstrated to prevent an increase in microvascular permeability and be protective of kidney function in a model of ischemic AKI (Mizuno and Nakamura, 2005). Furthermore, activated protein C and simvastatin have both been shown to avert an increase in microvascular permeability and be protective of kidney function in septic models of AKI (Gupta et al., 2007; Yasuda et al., 2006). Suffice it to say, all these compounds have pleiotropic effects including an overall dampening of the inflammatory response which may indirectly protect endothelial barrier function. Little information exists on the role of VEGF signalling on the alteration of non-glomerular vascular permeability in ischemic AKI; however, VEGF antagonism is a model for AKI associated with thrombotic microangiopathies (Kim et al., 2000) and thus effectively precludes inhibiting this pathway as a therapeutic option to limit microvascular permeability in ischemic AKI.

Proteolytic breakdown of the perivascular matrix is associated with increased microvascular permeability especially in models of brain ischemia-reperfusion injury (Armao et al., 1997). Critical constituents of the perivascular matrix, including collagen IV, are known to be substrates of matrix metalloproteinase (MMP)-2 and MMP-9 which are collectively known as gelatinases. Data derived from animal models of stroke and lung ischemia-reperfusion injury have demonstrated that increased gelatinase activation following ischemia to be associated with loss of perivascular matrix and increased microvascular permeability (Aoki et al., 2002; Fukuda et al., 2004; Sehba et al., 2004; Soccacal et al., 2000). Moreover, inhibition of gelatinases by gene knockout or inhibitors was protective in these models (Asahi et al., 2000; Asahi et al., 2001; Romanic et al., 1998; Rosenberg et al., 1998; Soccacal et al., 2004). These findings have recently been extended to AKI. Both MMP-2 and MMP-9 have been shown to be up-regulated in models of ischemic AKI and this up-regulation is temporally correlated with an increase in microvascular permeability (Basile et al., 2004; Sutton et al., 2005). In addition, minocycline, a broad based MMP inhibitor, and the gelatinase specific inhibitor ABT-518 both ameliorated the increase in microvascular permeability in this model (Sutton et al., 2005).

In conclusion, acute alterations of the renal microvasculature, including altered microvascular permeability, are important contributors to the overall pathophysiology of acute kidney injury syndromes. Furthermore, there is growing evidence that these acute microvascular alterations have chronic consequences and ultimately impact the progression of AKI to chronic kidney disease (CKD) (Basile, 2007). However, the overall understanding of non-glomerular endothelial cell biology and how it relates to kidney disease and even normal kidney function is still in a relative early stage as compared to other organs. While significant strides in our

knowledge have been made, there is still considerable progress to be made before this knowledge is translated into meaningful therapeutic advances for AKI and CKD.

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Figure 1. Schematic representation of the interplay between microvascular alterations, inflammation, and tubular injury in ischemic AKI. This interplay serves to initiate and extend injury resulting in diminished GFR and kidney dysfunction.

Microvascular permeability: Alterations in the barrier

Figure 2.
Schematic representation of mechanisms contributing to enhanced microvascular permeability in ischemic and septic AKI.