Vascular Heterogeneity in the Kidney

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Summary: Blood vessels and their endothelial lining are uniquely adapted to the needs of the underlying tissue. The structure and function of the vasculature varies both between and within different organs. In the kidney, the vascular architecture is designed to function both in oxygen/nutrient delivery and filtration of blood according to the homeostatic needs of the body. Here, we review spatial and temporal differences in renal vascular phenotypes in both health and disease.

Keywords: Kidney, vasculature, endothelial cells, heterogeneity

The blood vasculature has evolved to meet the diverse needs of body tissues. As a result, the structure and function of blood vessels and their endothelial lining show remarkable heterogeneity both between and within different organs (reviewed by Aird1,2). In most organs, blood vessels are organized in prototypic series: arteries serve as conduits for bulk flow delivery of blood; arterioles regulate resistance and thus blood flow; capillaries are the primary site for the exchange of gases, nutrients, paracrine and endocrine mediators, and secreted molecules; venules mediate trafficking of leukocytes and temporal changes in permeability; and veins serve to drain the preceding capillary bed, transporting deoxygenated blood back to the right side of the heart. However, there are several exceptions to this basic scheme. For example, in the liver, the portal venous system is linked in series to capillaries (hepatic sinusoids) followed by a second venous system (hepatic veins) (reviewed by Aird3). In the lung, the pulmonary artery delivers oxygen-poor, carbon dioxide–rich mixed venous blood to the alveolae, whereas pulmonary veins carry oxygenated blood to the left atrium of the heart. A separate system of bronchial blood vessels meets the metabolic demands of the airways (reviewed by Aird3).

As a final example, the blood vessel architecture in the kidney is configured not only to deliver oxygen and nutrients, but also to process blood for filtration. As a result, renal blood flow is much greater than that which would be necessary to meet the metabolic demands of the organ: the kidneys comprise less than 1% of body weight, but receive 25% of the cardiac output (reviewed by Evans et al3). Renal blood flow is five times that of basal coronary artery blood flow, yet renal oxygen consumption is two times less compared with the heart at rest.3

The goal of the current review, the first in this Seminars in Nephrology treatise on the vascular endothelium, is to highlight site-specific properties of renal blood vessels and their endothelial lining. This review sets the stage for the articles that follow in this issue. An understanding of these vascular bed–specific differences may provide insights into the pathophysiology of kidney disease. We begin with an overview of regional specialization as it pertains to the anatomy of the kidney and vascular segments. Next, we take a virtual tour of the renal circulation from arteries to veins, highlighting examples of heterogeneity. Finally, we apply these considerations to an understanding of renal vascular disease.

There are several important caveats with our approach. First, the classification of the vasculature into distinct segments, although epistemologically valuable, belies the integrative nature of the renal circulation. Second, although vascular heterogeneity clearly is linked to regional specialization, the precise nature of these structure-function relationships, particularly in the postglomerular microcirculation, remains obscure and speculative. A full accounting of these relationships is beyond the scope of the review, let alone beyond our expertise. Third, it also should be emphasized that our knowledge of the renal vasculature is based on studies in diverse species. Although the basic organization and function of the kidney is evolutionarily conserved, interspecies differences do exist. Thus, it is important to use caution in extrapolating results obtained in animals to human beings. Fourth, the list of diseases that we discuss is by no means exhaustive, but rather
includes representative examples. The categorization of these diseases according to the vascular segment is largely artificial in that many, if not most, diseases affect more than one blood vessel type. Finally, each subsection on vascular segments is classified further into some combination of architecture, function, development, endothelial phenotypes, and disease considerations. Not all subsections are treated equally; our choice of categories reflects our current knowledge base and our efforts to prioritize.

REGIONAL SPECIALIZATION

Vascular heterogeneity in the kidney occurs between the cortex and the medulla, and between large vessels and microvessels (Fig. 1).

Figure 1. Overview of renal vasculature. The kidney is supplied by the renal artery, which branches into interlobar followed by arcuate and interlobular arteries. Interlobular arteries give rise to afferent arterioles, which then feed the glomerular capillaries. Blood is filtered in the glomerulus, where the permselectivity is governed by a combination of fenestrated endothelium and its glycocalyx, the basement membrane, and the podocyte foot processes and slit diaphragms. Filtered blood flows through the efferent arteriole and into peritubular capillaries (in the case of cortical glomeruli) or the hybrid capillary-arteriolar descending vasa recta (in the case of juxtamedullary glomeruli). Peritubular capillaries participate in oxygen and nutrient delivery to tubular epithelial cells and modulation of urinary composition. The vasa recta supply oxygen and nutrients to the inner medulla, and are integral to the maintenance of the medullary concentration gradient. The descending vasa recta give rise to a small capillary network followed by the ascending vasa recta. Blood from peritubular capillaries and ascending vasa recta drains into venules, followed by a series of veins that parallels the arterial system. EC, endothelial cell.
Medulla Versus Cortex

The cortex is involved primarily in filtration and reabsorption, whereas the chief function of the medulla is to concentrate the urine. In keeping with these distinct functions, the circulatory pathways supplying the renal medulla and cortex are anatomically and functionally separate (reviewed by Evans et al). The afferent arterioles, glomeruli, efferent arterioles, and peritubular capillaries primarily are cortical in location. Blood flow in the cortex is subject to tight autoregulation by virtue of the myogenic response of renal vascular smooth muscle cells and tubuloglomerular feedback at the level of afferent and efferent arterioles. In contrast, the medulla contains the descending vasa recta (DVR) and ascending vasa recta (AVR). Blood flow per unit tissue weight is greater in the cortex compared with the medulla, and is higher in the outer versus the inner medulla (40% and 10%, respectively, of that of the cortex). Because the medulla makes up less than 30% of total kidney volume, it comprises only 10% of total renal blood flow. Low medullary flow is necessary for maintenance of the corticomedullary solute gradient and thus urine concentration. The countercurrent mechanisms that are implicated in removal of free water also affect tissue and vascular content of oxygen. As a trade-off, therefore, oxygen tension in the medulla is low: the partial pressure of oxygen in the cortex is 50 mm Hg, whereas that in the medulla it is only 10 to 20 mm Hg.

Macrovessels Versus Microvessels

The renal artery and its branches function as conduits to distribute and deliver blood to the kidney. Their structure and morphology is geared toward flow efficiency. In contrast, the main function of the afferent and efferent arterioles as well as the peritubular capillaries and vasa recta relates to filtration, reabsorption, and secretion. Thus, their structure is optimized for nephronefficiency. A unique aspect of the renal vasculature is that glomerular capillaries drain into an arteriole (the efferent arteriole) rather than a venule. Moreover, the microvasculature is organized into two capillary beds in sequence: the glomerulus followed by either peritubular capillaries (in the cortex) or vasa recta (in the juxtamedullary and medullary regions). Importantly, the postglomerular microcirculation has no collateral circulation. Thus, a reduction in glomerular blood flow has downstream consequences. Finally, filtered blood in the kidney is drained by the venous system into the inferior vena cava. Interestingly, the partial pressure of oxygen of blood in the renal vein exceeds that of blood in the efferent arteriole, suggesting that arterial-venous oxygen shunting occurs in the cortex. By blunting delivery of oxygen to renal tissue, this arrangement may represent a structural anti-oxidant mechanism (reviewed by Evans et al). Arterial-venous shunting also occurs in the medulla via the countercurrent arrangement of DVR and AVR.

RENAL ARTERIES

Architecture

The renal arteries arise from the abdominal aorta at the level of L2 below the origin of the superior mesenteric artery (reviewed by Urban et al). In 70% of human beings, there is a single renal artery supplying each kidney; 30% have an accessory renal artery. The left renal artery arises below the right, is shorter than the right, and follows a more horizontal course. The renal arteries lie posterior to the renal veins. Each renal artery enters the kidney at the medial aspect of the hilum. The artery branches to form 6 to 10 segmental then interlobar arteries, which ascend within the renal pelvis and renal parenchyma to the corticomedullary junction, where they form the arcuate arteries. The arcuate arteries, in turn give rise to interlobular arteries, which ascend through the cortex toward the renal capsule and at intervals give rise to the afferent arterioles, each of which supplies a glomerulus. The thickness of the arterial wall gradually decreases from arcuate arteries to efferent arterioles, primarily owing to a diminished smooth muscle cell layer. In rats, the arcuate and proximal interlobular arteries have multiple layers of smooth muscle cells, whereas the distal interlobular arteries and afferent and efferent arterioles contain only a single layer of smooth muscle cells, arranged circumferentially around the arteriole.

Vasa Vasorum

The vasa vasorum is a network of small blood vessels that supply the walls of large blood vessels. Previous studies using micro-computed tomography technology in different pig arteries have shown anatomic heterogeneity in the distribution of vasa vasorum. For example, the vasa vasorum density was highest in the coronary arteries, intermediate for renal and carotid arteries, and lowest in the femoral arteries. The diameter of first-order branches of the vasa vasorum diameter was highest in the renal artery, compared with other arteries. Similar findings were shown in human beings. High vasa vasorum density may protect against vessel wall ischemia, while at the same time rendering the vessel more susceptible to atherosclerosis.

Endothelial Phenotypes

The endothelium of renal arteries is folded into small ridges that run longitudinally along the axis of blood flow. These correspond to folds of the underlying internal elastic lamina. The endothelial cells of these arteries and arterioles are spindle-shaped, and are oriented in the same direction as the intimal folds. The cell nuclei bulge into the lumen. The cells also possess microvilli, especially in the nuclear region. In rats, endothelial cells possess actin filaments arranged as peripheral bands in the arcuate and proximal interlobular arteries, and as stress fibers in the distal interlobular arteries (and in afferent and efferent arterioles). In the distal interlob-
ular arteries actin filament bundles are attached to extracellular elastic fibers of the inner elastic meshwork of the vascular wall.7

Diseases
Disorders of the renal arteries include atherosclerosis, fibromuscular dysplasia, renal artery aneurysms, arteriovenous malformations, dissection, thrombosis, neurofibromatosis, vasculitis (eg, Takayasu arteritis and polyarteritis nodosa), and trauma (reviewed by Urban et al9). Many of these conditions lead to stenosis of the renal artery, the most common being atherosclerosis (reviewed by Levin et al11 and Krumme and Donauer12). The atherosclerotic plaque typically is located at the proximal end of the artery and is bilateral in one third of cases. Fibromuscular dysplasia is a noninflammatory disease of truncal or branch kidney arteries that is associated with medial hyperplasia and disruption of the internal elastic lamina. These changes may result not only in renal artery stenosis, but also saccular aneurysms. In contrast to atherosclerosis, fibromuscular dysplasia-associated stenosis typically occurs in the mid-distal renal artery and is bilateral in two thirds of patients. Aneurysms also occur in polyarteritis nodosa. These lesions often are located in more distal branches of the renal artery.

RENAL ARTERIOLES

Architecture
Inflow and outflow of blood in the glomerular capillary bed is regulated by resistance vessels arranged in series (the afferent and efferent arterioles, respectively). Arteriole diameter and glomerular size gradually decrease toward the cortical surface; the largest arterioles and glomeruli are found at the corticomедullary border.4 In mice, the internal diameter of afferent arterioles from superficial glomeruli is greater (≈15 μm) compared with efferent arterioles (≈10 μm) (reviewed by Evans et al4). This helps to preserve glomerular capillary pressure in the face of reduced blood flow. By contrast, afferent and efferent arterioles of juxtamedullary glomeruli have a larger, although comparable, internal diameter (≈20-25 μm).4 Because vascular resistance is inversely proportional to the radius of the vessel to the power of four, similar changes in vessel radius result in less absolute changes in vascular resistance in juxtamedullary, compared with cortical, glomeruli (reviewed by Eppel et al5). Afferent arterioles of juxtamedullary glomeruli arise close to the junction of the arcuate and interlobular arteries. Thus, the vascular path length is relatively short, lessening the impact of changes in the caliber of interlobular arteries on medullary blood flow. The proximal portion of efferent arterioles is covered by a single layer of smooth muscle cells, extending 50 to 100 μm from the glomerulus, whereas pericytes cover the distal parts of the efferent arterioles (and the DVR and peritubular capillaries). At the corticomедullary border, the efferent arterioles are more muscular than those in cortical glomeruli. Efferent arterioles from the cortical glomeruli give rise to peritubular capillaries, which surround the convoluted proximal and distal tubules in the cortex. In the outer cortex, convoluted tubules are associated with capillaries derived from their own efferent arterioles.4 Efferent arterioles of the juxtamedullary glomeruli give rise to the DVR in the outer stripe of the outer medulla.

Function
A primary function of the renal arterioles is to regulate glomerular blood flow and filtration. The afferent and efferent arterioles provide the necessary resistance to maintain sufficient hydrostatic pressure in glomerular capillaries (reviewed by Bell and Welch13). The resistance of afferent and efferent arterioles is differentially regulated. For example, adenosine constricts the afferent arteriole via its A1 receptor, and dilates the efferent arteriole via its A2 receptor.14 As another example, angiotensin II simulates a voltage-activated and nifedipine-sensitive calcium flux in the afferent arteriole, but activates a voltage- and nifedipine-insensitive calcium flux in the efferent arteriole.15 The balance between resistances of afferent and efferent arterioles plays an important role in mediating glomerular filtration rate and renal blood flow. For example, vasoconstriction of the preglomerular afferent arteriole results in reduced glomerular filtration and renal blood flow, whereas increased postglomerular resistance by constriction of the efferent arteriole increases glomerular filtration and reduces renal blood flow. Finally, a concomitant increase in afferent and efferent arteriolar resistance results in reduced renal blood flow without major changes in glomerular filtration.

Endothelial Phenotypes
The proximal (juxtaglomerular) and distal portions of the afferent arteriole are phenotypically distinct (reviewed by Rosivall and Petti-Peterdi16). The proximal portion has fenestrated endothelial cells and its medial layer contains myosin-negative, renin-secreting granular epithelial cells. The fenestrae face the extraglomerular mesangium and renin granular cells (reviewed by Rosivall and Petti-Peterdi16). The pores have diameters that are not uniform in size and lack a diaphragm. It has been proposed that the fenestrae provide a communication pathway between renin granular cells and the lumen of afferent arterioles.16 Endothelium in the distal portion of the afferent arteriole as well as the efferent arteriole is nonfenestrated and contains myosin-positive, renin-negative cells.

Diseases
Systemic hypertension is associated with increased resistance in the renal vasculature (reviewed by Skov and Bennett17). Animal models suggest that the afferent arteriole represents the primary site of resistance change.
GLOMERULI
Structure and Function
The human kidney contains approximately 1 million glomeruli (in comparison, the rat kidney contains 30,000), 90% of which are located in the cortex. More than 90% of cortical tissue comprises the tubulointerstitial space, with less than 10% of the cortical area occupied by glomeruli. The glomerulus is a highly specialized vascular bed that has been likened to a living ultrafiltration membrane. It functions as a macromolecular sieve, allowing free flow of water and small solutes (eg, sugars, electrolytes, and small proteins), but not plasma proteins, into Bowman’s space (reviewed by Quaggin and Kreidberg). The ratio of albumin in Bowman’s space versus plasma is 1:500 to 1:1,000. In healthy human beings, although this is a controversial area with lively discussion, it has been estimated that 0.4 to 9.0 g of albumin cross the glomerular capillary wall each day. Thus, less than 0.1% of the potential filtered load of albumin crosses the glomerular filtration barrier (reviewed by Salmon et al). Up to 98% of this protein is reabsorbed in the proximal tubule (reviewed by Izzedine et al). Urinary excretion in a normal adult is less than 10 mg/d. Even 20 to 30 mg/d, or high normal, may be biologically abnormal. The cellular components of the mature glomerulus include endothelial cells, glomerular visceral epithelial cells (podocytes), and mesangial cells. Endothelial cells are separated from podocytes by the glomerular basement membrane (GBM), which contains collagen type IV, laminin, nidogen/entactin, and proteoglycans such as agrin and perlecan (reviewed by Satchell and Braet). Mesangial cells, which share certain properties with smooth muscle cells and pericytes, are found adjacent to endothelial cells on the opposite side of the GBM from the podocytes, primarily in the stalk of the tuft (reviewed by Quaggin and Kreidberg). Mesangial cells provide support for the capillary loops (reviewed by Quaggin and Kreidberg).

Development
The glomerular vascular bed develops primarily through vasculogenesis. The earliest endothelial cells, which arise from mesenchyme, migrate into the cleft of the developing glomerulus at the S-shape body stage. They undergo homotypic aggregation into precapillary cords without a recognizable lumen. A single capillary loop grows into the glomerular cleft between the primitive podocytes and the proximal tubule of the S-shaped body (reviewed by Quaggin and Kreidberg). The endothelial cells are initially cuboidal and lack fenestrations (reviewed by Satchell and Braet). As development proceeds, the earliest fenestrations have diaphragms. The capillary loop becomes divided into 6 to 8 loops.

Components of the Glomerular Filtration Barrier
Several components of the glomerulus contribute to the glomerular filtration barrier, including the endothelium and its glycocalyx, the GBM, and the podocyte (reviewed by Haraldsson and Jeansson, Ballermann, Ballermann and Stan, and Navar). The individual contribution of these various elements has long been debated. However, it now is widely accepted that endothelial cells, the GBM, and podocytes act in unison to form a dynamic sieve. Cross-talk between endothelial cells, podocytes, and mesangial cells plays a critical role in mediating barrier function (reviewed by Quaggin and Kreidberg and Vaughan and Quaggin). Selective permeability also is determined by solute properties that affect transglomerular passage including size, radius, shape, deformability, and charge.

Endothelial Phenotypes
Glomerular endothelial cells are unusually flat, with a height of 50 to 150 nm (reviewed by Haraldsson et al). A characteristic feature of these cells is the presence of fenestrae (60 nm in diameter). These plasma membrane-lined circular pores are organized in planar clusters or sieve plates, and constitute 20% to 50% of the entire endothelial surface. Fenestrae permeate continuous endothelium of capillaries involved in high levels of transport, including endocrine glands (eg, pancreatic islets, adrenal cortex), choroid plexus, the gastrointestinal tract, and peritubular capillaries and AVR in the kidney. They also are found in the discontinuous endothelium of the liver, bone marrow, and spleen. The glomerular fenestrae resemble those of other nondiscontinuous fenestrated endothelium, with the exception that they lack a classic diaphragm (reviewed by Satchell and Braet). Consistent with this finding is the observation that the cells do not express plasmalemmal vesicle-associated protein (PV)-1, a type II transmembrane glycoprotein that is associated with bridging diaphragms of endothelial fenestrine and caveolecia. Moreover, caveolin 1–null mice show normal fenestration of glomerular endothelial cells, suggesting that fenestrae do not form from caveolar precursors. As noted earlier, fenestrae are subtended by diaphragms during normal development. Interestingly, in adult rats, Thy-1.1 nephritis was associated with de novo expression of PV-1 in glomeruli and the re-emergence of diaphragm fenestrine, perhaps reflecting a postinjury modeling of the glomerular tuft. Previous studies have shown that the formation and maintenance of fenestrae depend on podocyte-derived vascular growth factor-A (VEGF-A).

There are interesting examples of microheterogeneity within the glomerular capillary bed. For example, one study showed that in adults 2% of glomerular endothelial cells have diaphragmed fenestrine and caveolecia. Diaphragmed fenestrine (50-60 nm in diameter) were more uniform in shape and size than nondiaphragmed ones (60-160 nm in largest diameter). In the same report, 1.6% of capillaries stained for PV-1. As another example of microheterogeneity, glomerular endothelial cells at the hilum of the capillary loop, where they are in close
contact with mesangial cells, are thicker and contain few fenestrae.23

Fenestrae allow high permeability to water and small solutes. Indeed, their fractional area (a product of their density and size) is a critical determinant of hydraulic conductivity (the other determinants being the GBM and the slit diaphragms of podocytes). The sieve plates face the podocyte, with cell nuclei facing the center of the glomerulus. Tight spatial control of fenestral position likely is regulated by podocyte-derived factors. In addition to these spatial considerations, fenestrae may be dynamically regulated in time. For example, they may be subject to changes in diameter. In addition, they may regress and reappear, resulting in “rotating” filtration over the glomerular surface.24

The diameter of fenestrae is 15 times the diameter of an albumin molecule. Thus, fenestrae are too large to form a meaningful barrier. However, significant convective flow of large plasma proteins does not normally occur in the healthy kidney (reviewed by Bailerman and Stan27). Indeed, permeability and reflection coefficient for macromolecules across the fenestrated endothelium are similar to those of continuous endothelium. Rather, most evidence points to a primary role of the glycocalyx in determining permselectivity of the glomerular endothelium.

The glycocalyx comprises a thin (10-20 nm) plasma membrane-bound inner layer that coats the luminal side of the glomerular endothelium and a thicker (200-400 nm), more loosely associated outer layer. Collectively, these two layers often are referred to as the endothelial surface layer (ESL), although some investigators reserve the latter term for the loose outer layer (reviewed by Haraldsson et al22). The ESL is challenging to visualize because standard fixation protocols for electron microscopy result in its collapse, and because the integrity of the glycocalyx is dependent on its microenvironment. The ESL is a dynamic, hydrated layer composed of glycoproteins, heparan sulfate proteoglycans, and absorbed plasma proteins. The glycocalyx extends over and covers the fenestrae, forming fenestral plugs that may appear as membrane-associated diaphragms. Interestingly, the glycocalyx differs between fenestral and nonfenestral regions, with that in the fenestrae having a higher ratio of heparan sulfates to sialoproteins.36 Removal of the glycocalyx increases vascular permeability (reviewed by Satchell and Tooke37). Thus, the ESL likely contributes to the high permselectivity of the glomerular wall, retarding passage of macromolecules. Indeed, it has been estimated that the negatively charged surface accounts for retention of 90% to 95% of albumin.26

Endothelial cells from different vascular beds express overlapping but distinct transcriptional programs (reviewed by Aird38). The molecular characterization and transcriptional profiling of glomerular endothelial cells has been hampered by the difficulty in obtaining primary cultures of these cells. Nonetheless, some groups have reported successful isolation of glomerular endothelial cells, and a limited number of studies have shown molecular heterogeneity at the level of glomerular endothelium. For example, the use of serial analysis of gene expression (SAGE) technology and DNA microarrays has uncovered a number of transcripts that are expressed selectively in glomerular endothelial cells, but not aortic endothelial cells39,40 (reviewed by Betsholtz et al41).

Disease

Defects in the GBM may lead to impaired filtration function. For example, Alport syndrome, a disease of collagen IV, is associated with disrupted GBM and mild proteinuria (reviewed by Jarad and Miner30). Pierson syndrome is associated with defects in laminin and results in diffuse mesangial sclerosis. Genetic and acquired defects in podocytes are believed to play an important role in glomerular disease (reviewed by Shankland42). Indeed, all known mutations underlying monogenic nephrotic syndromes are associated with podocyte-specific genes. In addition to GBM and podocyte abnormalities, phenotypic changes in glomerular endothelium have been linked to proteinuria, including endothelial cell swelling (endotheliosis) and endothelial cell detachment from the GBM.

The glomerular compartment is the primary vascular target of diabetes in the kidney. Early structural changes in diabetes include an increase in glomerular size, GBM thickening, mesangial expansion, broadening of podocyte foot processes, and decreased thickness of the glycocalyx (reviewed by Satchell and Tooke37). Previous studies have shown that diabetes is associated with increased VEGF levels. Renal biopsy specimens from patients with type II diabetes showed increased VEGF protein in podocytes, mesangial cells, and glomerular endothelial cells.43 Interestingly, these changes were correlated with increased receptor-bound VEGF, increased phospho-Akt, and increased proliferation of the endothelial cells of glomeruli with mild, but not severe, diabetic injury.43 Increased VEGF–VEGF receptor signaling in the glomeruli may promote survival and contribute to the repair of glomerular endothelial damage. However, it also may lead to increased permeability and unwanted blood vessel growth, especially during the early phases of diabetes development before capillary loss (rarefaction). In addition to VEGF, the angiopoietin family of growth factors (in particular, the ratio of angiopoietin-1 to angiopoietin-2) also has been implicated in the pathophysiology of diabetic nephropathy (reviewed by Nakagawa et al44).

Independent of diabetes, microalbuminuria occurs in 25% patients with essential hypertension, especially those with vascular disease.45 Glomeruli normally are exposed to high intracapillary and transcapillary pressures. Further increases, which occur in diabetes or hypertension or as a result of progressive nephron loss, cause hypertrophy of mesangial cells and podocytes, with
eventual loss of podocytes. Podocyte drop-out leads to reduced VEGF levels, secondary endothelial apoptosis, and rarefaction of glomerular capillary loops (reviewed by Schlondorff46).

The therapeutic inhibition of VEGF signaling (eg, with bevacizumab) in patients with cancer may affect the glomerular compartment of the kidney. The incidence of mild, asymptomatic proteinuria ranges from 21% to 63%, whereas heavy proteinuria has been reported in up to 6.5% of renal cell carcinoma patients treated with bev-acizumab (reviewed by Izzedine et al21). Interestingly, inhibition of the VEGF signaling axis has been associated with the inhibition of nephrin,47 which is important for the maintenance of the glomerular slit diaphragm and permselectivity. Renal biopsies of patients receiving anti-VEGF therapy have revealed a spectrum of pathologic changes that resembles thrombotic microangiopathy, including endotheliosis, widening of the subendothelial space of glomerular capillaries, duplication of the glomerular basement membrane, mesangiolysis, and effacement of podocyte foot processes.34 Patients with pre- eclampsia present with reduced glomerular filtration rate and their glomerular endothelium reveals endothelial thickening and reduced size/density of fenestrations. These changes have been ascribed to the VEGF inhibitory effects of soluble VEGF receptor-1 (reviewed by Mutter and Karumanchi48). Endotheliosis, in turn, is associated with proteinuria.

In diarrhea-associated hemolytic uremia syndrome, verotoxin produced by enterohemorrhagic Escherichia coli results in endothelial cell toxicity. Hemolytic uremia syndrome is associated with acute renal failure. Pathology reveals thrombus formation in the glomerular capillaries and afferent arterioles (reviewed by Ballermann26). Verotoxins bind the receptor, globotriaosylceramide Galα1-4GalB1-4 glucosyl ceramide, which is enriched in glomerular endothelial cells and tubular epithelial cells of the kidney. In one study, verotoxin was shown to bind to the detergent-resistant domains (enriched in cholesterol, glycosphingolipids, and sphingomyelin) of glomerular endothelium, resulting in cytotoxicity.49 In contrast, verotoxin bound to detergent-sensitive domains of the tubules, leading to internalization and lysosomal-mediated degradation of the toxin.49 In keeping with the increased incidence of hemolytic uremia syndrome in children, verotoxin binds more avidly to pediatric compared with adult glomeruli.50

Many immune-mediated glomerular diseases result in activation and injury of glomerular endothelial cells.26 This may occur with complement activation at the apical surface of the endothelium (eg, in antineutrophil cytoplasmic autoantibody [ANCA]-mediated vasculitis), and in cases in which complement activation occurs in the subendothelial cell space (eg, diffuse and focal proliferative lupus nephritis and post-streptococcal glomerulonephritis). ANCA are directed against enzymes stored in granules of neutrophils and lysosomes of monocytes, including myeloperoxidase and proteinase-3.51 These ANCA have been implicated in pauci-immune necrotizing crescentic glomerulonephritis, an inflammatory disease that targets the glomerular vasculature (reviewed by van der Veen et al52). A causal role for the autoantibodies in necrotizing crescentic glomerulonephritis is suggested by in vitro studies that show that ANCA can activate tumor necrosis factor-α–primed neutrophils and monocytes, resulting in the generation of oxygen radicals, degranulation of proteases, and cytokine production. Furthermore, co-incubation of ANCA-activated neutrophils with endothelial cells results in endothelial cell lysis. Most importantly, injection of antitymveloperoxidase antibodies in rodents results in enhanced leukocyte-endothelial interactions and the development of necrotizing crescentic glomerulonephritis (reviewed by Van Timmeren et al53).

As an example of molecular heterogeneity in endothelial response to a pathophysiological stimulus, hemorrhagic shock in mice resulted in a rapid (90 min) induction of E-selectin selectively in glomerular endothelial cells. Interestingly, shock was associated with increased vascular cell adhesion molecule-1 protein in nonglomerular vascular compartments, including peritubular capillaries and postcapillary venules. A similar pattern was observed in mice receiving an acute proinflammatory challenge with intravenous tumor necrosis factor-α (Grietje Molema, unpublished observations). The underlying mechanism(s) of segmentally restricted reactivity remains to be elucidated.

**PERITUBULAR CAPILLARIES**

**Architecture**

A dense peritubular capillary plexus arises from efferent arterioles and surrounds the proximal and distal convoluted tubules. The efferent arteriole emerging from a given glomerulus does not necessarily perfuse the tubule emerging from the same glomerulus (reviewed by Beeuwkes54). Peritubular capillaries are essential for providing oxygen and nutrients to the tubules and interstitial cells. The endothelium of these thin-walled capillaries is functionally coupled to the tubular epithelium. The capillaries take up solutes and water reabsorbed from the proximal tubular lumen, returning them to general circulation. In the other direction, substances move from vessel to tubule for secretion. Cross-talk between the peritubular capillaries and tubules has been modeled in vitro.55 Peritubular endothelial cells have fenestrae. These resemble the fenestrae in endocrine glands and digestive tract mucosa. Their diameter is between 62 and 68 nm, the pores have an octagonal shape, and they are arranged within sieve plates in ordered parallel linear arrays (reviewed by Ballermann and Stan27). Moreover, unlike their glomerular counterparts, the fenestrae possess thin (5-7 nm) diaphragms. Peritubular capillaries have high permeability to water and small solutes. Although con-
troversial, some studies have shown that bone marrow–derived circulating cells incorporate into peritubular capillaries. Studies in dogs suggest that peritubular capillaries arise from immature sinusoidal capillaries with thick walls and few fenestrae. Previous studies have shown that proximal and distal tubular epithelial cells express VEGF whereas peritubular capillary endothelial cells express VEGF receptors. In a rat model of crescentic glomerulonephritis, VEGF blockade resulted in decreased numbers of peritubular capillaries, which in turn is linked to the development of chronic allograft injury. Chronic allograft nephropathy is associated with circumferential multilayering and splitting of the basement membrane of peritubular capillaries and loss of endothelial fenestrae.60,61

Because peritubular capillaries are sequentially arranged downstream of the glomerular capillaries, any acute or chronic glomerular injury with reduced glomerular blood flow will influence downstream blood flow in the peritubular capillaries (reviewed by Schlundorff46). Moreover, inflammatory mediators released into glomerular capillaries may “spill over” and activate the endothelium of downstream peritubular capillaries. Together, these changes may lead to tubulointerstitial injury with loss of peritubular capillaries and interstitial fibrosis. Hypotension and/or sepsis are common causes of ischemia-related acute kidney injury. Acute renal failure is associated with impaired integrity of peritubular capillary endothelium.

Previous studies have shown that proximal and distal tubular epithelial cells express VEGF whereas peritubular capillary endothelial cells express VEGF receptors. In a rat model of crescentic glomerulonephritis, VEGF blockade resulted in decreased numbers of peritubular capillary endothelial cells.7 Such a loss may in turn contribute to the development and/or progression of interstitial fibrosis.

In various renal diseases including crescentic glomerulonephritis, T lymphocytes preferentially infiltrate the tubulointerstitial compartment, whereas monocytes transmigrate into both the tubulointerstitial and glomerular compartments. Compartmentalized leukocyte recruitment and secondary local endothelial injury have been modeled in vivo by perfusing the renal artery of rodents with antiendothelial antibodies. In the latter study, differential expression of interferon gamma-induced protein 10 (IP10)/chemokine CXC motif ligand 10 (CXCL10) and monocyte chemoattractant protein 1 (MCP-1)/cholecystokinin 2 (CCK2) in peritubular and glomerular endothelial cells, respectively, was implicated in the compartmentalized recruitment process.

### VASA RECTA

#### Architecture

The vasa recta serve the specific needs of the medulla. DVR arise largely from juxtamedullary nephrons. Each efferent arteriole gives rise to many DVR (reviewed by Pallone et al64). DVR are larger than peritubular capillaries. Moreover, unlike other capillaries they are surrounded by pericytes/smooth muscle cells that contract and dilate in response to vasomotor mediators (reviewed by Pallone et al64). It appears that the proximal end of DVR (in the outer medulla) is more responsive to vasoactive factors compared with the distal end (in the inner medulla) (reviewed by Evans et al63). Indeed, DVR have a dual role as vasoactive microvessels and transporting microvessels.64 The outer medulla is organized into vascular bundles, whereas the outer zone of the inner medulla is dominated by clusters of collecting ducts (CD clusters). DVR that arise within the central region of vascular bundles are destined to the inner medulla, descending primarily as unbranched vessels from the inner medulla into the deep papilla.65 DVR at the periphery of the bundle give rise to a capillary plexus that perfuses the interbundle region, which contains thick ascending limbs.66 In the outer zone of the inner medulla, the DVR are arranged predominantly outside CD clusters (the intercluster zone). The DVR eventually breaks up into at least 2 capillary branches (often a more complex capillary network) before connecting with AVR. In the outer zone of the inner medulla, some AVR ascend within the CD clusters, where three to five AVR surround each collecting duct in a symmetric fashion. This architecture may permit AVR to remove excess water from collecting ducts out of the medulla. On the side facing the CD, the vasa recta frequently have concave, scalloped margins. Other AVR are located alongside the DVR in the intercluster zone where they participate in countercurrent exchange, in which solutes are recycled to the inner medulla and water is returned to the general circulation. Once they reach the outer medulla, most AVR ascend alongside DVR within vascular bundles, while others lie in the interbundle region.

#### Function

The renal medullary circulation is arranged as a countercurrent exchanger to maintain the corticomедullary gradients of NaCl and urea. Countercurrent exchange traps NaCl and urea deposited in the interstitium by the CD and loops of Henle, which in turn allows for urinary concentration. As a consequence of the countercurrent mechanism, oxygen that enters the DVR diffuses into the interstitium. It can diffuse to the surrounding tubules where it is consumed for active transport processes or it can be reabsorbed into the AVR and carried back to the cortex. Thus, nutrient delivery and oxygen tension in the medulla are low (the PO2 in the medulla is 10-25 mm Hg; it may be as low as 4 mm Hg in the papillary tip).
Endothelial Phenotypes

The endothelium of DVR is of the continuous type and expresses specific transporters for urea (urea transporter-B) and water (the water channel, aquaporin-1). Knockout of urea transporter-B results in impaired renal water conservation with higher than normal urine output and lower urine osmolality (reviewed by Fenton and Knepper). Studies of these mice reveal a “urea selective” urinary concentrating defect characterized by an impaired ability to concentrate urea. This defect has been ascribed to altered countercurrent exchange of urea between AVR and DVR. Aquaporin-1 promotes transcellular osmotic water permeability, with water efflux occurring along NaCl and urea osmotic gradients in the outer medulla. Aquaporin 1-null mice also show a significant urinary concentrating defect (reviewed by Verkman). A previous study has shown that the DVR endothelium functions as an electrical syncytium, a property that is attributed to gap junctions.

In contrast to the DVR, AVR endothelial cells are fenestrated (with diaphragm) and express PV-1. In rats, these fenestrae are 50 to 80 µm in diameter. The fractional area of fenestrated endothelium area is greater in the inner compared with outer medulla. In the terminal portion of DVR, there is overlap of PV-1 and urea transporter-B expression, suggesting that fenestrations begin before the end of DVR. Indeed, in the papilla, a distinction between AVR and DVR can be determined only by direction of blood flow. Up to 15% of DVR may have terminal fenestrated segments that carry blood in a descending direction. Microvilli in AVR endothelial cells make contact with the collecting ducts, anchoring the AVR to the tubule.

RENAL VENULES AND VEINS

Architecture

The intrarenal veins are larger than the arteries but their distribution is similar. Small interlobular vessels drain the renal cortex and join medullary veins to form the arcuate veins, which run along the corticomedullary junction. Vascular parallelism may play a role in thermoregulation and/or countercurrent exchange. Some veins in the cortex (so-called intralobular veins) are not accompanied by arteries. Instead, they are surrounded by tubules, and probably arise from confluence of peritubular capillaries. The arcuate veins communicate with each other and drain into the interlobar vessels, which in turn form three to four lobar veins. In contrast to renal arteries, there are multiple communications between segmental and arcuate veins. These unite anterior to the renal pelvis to form the main renal vein. The renal vein usually lies anterior to the renal artery at the hilum. The left renal vein is 3 times longer than the right renal vein (reviewed by Urban et al). The left renal vein is always single and has two tributaries: the suprarenal (adrenal) and gonadal veins. In contrast, radiographic studies show two or three right renal veins in up to 40% of individuals.

Endothelial Phenotypes

Renal veins have remarkably thin walls, consisting of attenuated endothelium and a delicate basal lamina, and occasional collagen fibers. The endothelial cells of veins are polygonal in shape. Interestingly, the endothelium of interlobular, arcuate, and interlobar veins is fenestrated (diameter, ~71 nm). The fenestrae contain a diaphragm. Large portions of the walls of intrarenal veins are closely apposed to the tubules, with the interlobular veins showing the greatest degree of apposition. In some cases, the basal laminae of venous endothelium and tubular epithelium are fused. Moreover, tubules bulge into the lumen of these vessels, creating a “tubule relief” on the venous wall. Compared with arcuate and intralobular veins, the endothelium of interlobular veins is thinner and contains more fenestrae. Indeed, their structure is more characteristic of capillaries (eg, peritubular capillaries) than of veins. Thus, they appear adapted for passive fluid transport from the interstitium. Endothelial cell–cell junctions also vary between segments, with larger veins showing more interdigitating cell contacts. Previous studies in pigs have shown the presence of endothelin-1–positive mast cells in the intima of renal veins, between the internal elastic membrane and basal membrane of the endothelium.

Diseases

Renal vein thrombosis occurs in patients with hypercoagulable states, including those with the nephrotic syndrome (reviewed by Beckmann and Abrams). Extrinsic compression of the renal vein from an extravascular mass, such as a tumor, may lead to stasis of blood flow and secondary thrombus formation. Renal vein thrombosis also may occur as an early vascular complication after renal transplantation. Left renal vein enlargement from spontaneous splenorenal shunts has been reported in patients with portal hypertension. As a final example, patients with renal allografts may develop inflammation of the arcuate and interlobular veins.

CONCLUSIONS

In summary, the vasculature of the kidney is not only different from that of other organs, but also displays striking intra-organ heterogeneity. These latter differences reflect a functional compartmentalization of the kidney. An important corollary of vascular and endothelial heterogeneity in the kidney is the unique vulnerability of each vascular segment to pathophysiological processes. Important goals for the future are to understand causal links between site-specific endothelial cell phenotypes and physiology and to determine how these links may be leveraged for therapeutic gain in patients with focal renal vasculopathic disease.
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REFERENCES
