Drug-Induced Alterations in Renal Hemodynamics

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Abstract

Renal dysfunction and injury secondary to medications are common. Drug-related kidney injury can present as subtle damage or rapid progressive renal failure and is thought to be one of the major causes of renal failure. Most of the nephrotoxic medications involve directly or indirectly renal tubulointerstitial injury via immune process and lead to specific clinical findings, including microangiopathy, Fanconi syndrome, acute tubular necrosis, acute interstitial nephritis, nephrotic syndrome, obstruction, nephrogenic diabetes insipidus, electrolyte abnormalities, and chronic renal failure. Some drugs perturb renal perfusion and induce loss of filtration capacity. In vivo and in vitro research on drug-related kidney diseases had greatly enhanced our understanding on drug nephrotoxicity in the past decade. Understanding the mechanisms involved and recognizing the clinical presentations of renal dysfunction arising from the use of commonly prescribed medications are important if injury is to be detected and prevented earlier. Knowledge of drug effects on renal hemodynamics can also give us an insight into the nature of progression of renal failure from drug-induced renal injury, which constitutes a major cause of end-stage renal disease. Drug-induced alternations in renal hemodynamics have rarely been a subject of attention. This paper reviews the clinical features and basic processes of renal hemodynamic alteration related to the use of common drugs.

KEY WORDS: drug-related nephrotoxicity, glomerular filtration rate, renal blood flow, renal hemodynamics

Drug-Induced Tubulointerstitial Renal Disease

Tubulointerstitial disease is one of the most underestimated causes of end-stage renal disease (ESRD) (1-3). Drug and infection are the two main causes of chronic or acute renal tubulointerstitial disease (4). The pathogenesis of drug-induced tubulointerstitial disease is not well understood (5). Typically, the development of drug-induced renal tubulointerstitial disease is usually not dose-dependent. Recurrence or exacerbation of the disease can occur with a second exposure to the same or a related drug. Frequently, eosinophils are identified as a component of the interstitial cellular infiltrate (6). The classic clinical presentations of drug-induced tubulointerstitial disease suggest a possible immune mechanism. However, many patients with drug-induced tubulointerstitial disease frequently have no symptoms or signs suggestive of a hypersensitivity syndrome and rarely have dramatic anaphylactic manifestations (7). Moreover, some of these patients progressed to advanced renal failure without involving much the inflammatory process in their kidney and along their clinical course (8, 9). Steady renal hemodynamics is essential to sustaining a well-functioning kidney (10). It is likely that hemodynamic factor might play an important role in the development and progression of drug-induced tubulointerstitial disease. In vivo (11-14) and in vitro (5, 15) studies on drug-related kidney diseases have greatly enhanced our understanding on
the drug nephrotoxicity in recent years. Knowledge of drug effects on renal hemodynamics can also give us an insight into the nature of progression of renal failure from drug-induced renal injury, which constitutes a major cause of end-stage renal disease (1).

Renal Hemodynamics

Physiologically, there is a large renal blood flow (RBF) at rest, equivalent to about one fifth of cardiac output to an organ that weighs less than 1% of body weight. It takes larger blood flow to effectively excrete metabolic wastes and maintain internal homeostasis. On the other hand, adequate blood flow delivers necessary oxygen and nutrition for the heavy-duty kidney. Maintaining renal hemodynamics is essential for normal renal function and internal homeostasis (16). Regulation of renal hemodynamics is primarily achieved via changes in arteriolar resistance, which can affect both RBF and glomerular filtration rate (GFR).

The control of renal arteriolar constriction/dilatation is mainly related to the function of the macula densa and juxtaglomerular apparatus (JGA). The function of the JGA is controlled by a number of physical and humoral factors. These factors can be categorized into four different but interacting afferent messages for maintaining a constant RBF and GFR. These factors exert both intrinsic and extrinsic effects on renal hemodynamics. These multiple factors work in concert to sustain a constant GFR despite wide variations in systemic pressures (17) (Table 1).

Table 1. Factors regulating the renal blood flow

<table>
<thead>
<tr>
<th>Intrinsic Factors</th>
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<td>Autoregulation mechanism</td>
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<td>Nitric oxide</td>
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<td>Atrial natriuretic peptide</td>
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Autoregulation Mechanisms

Pressure-Mediated Myogenic Mechanism

The autoregulation mechanism maintains a consistent GFR despite mean arterial pressure fluctuations from 70 to 210 mmHg. Two mechanisms are involved in the autoregulatory phenomenon: the myogenic and the tubuloglomerular feedback (TGF) mechanisms. Myogenic autoregulation depends on stretch-activated ion channels in vascular smooth muscle in afferent arterioles that, when stretched, allow calcium ions to enter and induce contraction. The afferent arterioles constrict or dilate in response to the alteration of mean arterial pressure, which transmit to the baroreceptors in afferent arterioles. This response prevents direct transmission of the altered arterial pressure to the glomerulus, thus maintaining a normal GFR (16). The efferent arterioles, in comparison, have different characteristics. They do not seem to respond directly to changes in stretch and therefore do not contribute directly to the myogenic response. The reason why this occurs is not clear, but the apparent absence of L-type voltage-gated Ca\(^{2+}\) channels in the efferent arterioles may play a contributory role (15).

Chemistry-Mediated Tubuloglomerular Feedback (TGF) Mechanism

The TGF mechanism is related to the function of the macula densa and JGA. Macula densa is a segment with specified renal tubular epithelial cells at the end of the cortical thick ascending limb of the loop of Henle. These cells sense changes in the delivery and subsequent reabsorption of chloride. The importance of chloride is probably related to the chloride dependence of the Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter in the luminal membrane that promotes the entry of these ions into the cell (18). When luminal and subsequent intracellular sodium chloride increased, the cells mediate vasoconstriction of the afferent arterioles. The cells mediate vasoconstriction of the afferent arterioles, resulting in a return of the GFR toward normal. Conversely, when there is a decrease in glomerular blood flow, there is a decrease in sodium chloride delivered to the macula densa cells. This leads to afferent arteriolar dilatation, increased glomerular blood flow, and return of the GFR toward normal (19). Adenosine and NO have been identified as the
Eicosanoids System

Eicosanoids are vasoactive substances produced locally from the kidney by the glomerular, vascular endothelium, tubular epithelial cells (28), and interstitial cells (29). Eicosanoids include prostaglandins (PGs), thromboxanes, leukotrienes, and monooxygenase products. Some PGs such as PGE1, PGE2, and PGI2 (prostacyclin) are vasodilators. On the other hand, thromboxane, leukotrienes, and some monooxygenase products are vasoconstrictors (29). The physiologic role of the vasoconstrictor substances is unclear, but the vasodilatory PGs play a major role in maintaining RBF in individuals with impaired renal function.

Humoral Regulation

Intrarenal Renin-Angiotensin System (RAS)

The intrarenal RAS is a critical regulator of intrarenal blood flow within the kidney itself. The system is triggered by local and systemic stimuli especially during episodes of hypotension (21). When renal ischemia occurs, the kidney produces renin from the granular cells of the JGA. Renin release is regulated by several intrarenal mechanisms, including the afferent arteriole baroreceptors, macula densa cells, and SNS. Renal baroreceptors located in the afferent arterioles sense the decrease of RBF and mediate the release of renin. On the other hand, the macula densa cells stimulate renin release by sensing a decreased sodium chloride load to the distal nephron because of decreased RBF (22). Activation of SNS also enhances the release of renin (23).

The release of renin leads to production of angiotensin II and aldosterone. Angiotensin II causes vasoconstriction of both afferent and efferent arterioles, but affects the efferent arterioles to a greater degree. Through afferent arteriolar constriction, angiotensin II decreases glomerular blood flow. However, concurrent efferent arteriolar constriction creates a resistance to fluid leaving the glomerular capillaries, which maintains both glomerular hydrostatic pressure and GFR at normal values despite the fall in RBF (24).

In addition to intrarenal afferent and efferent arteriolar vasoconstriction, angiotensin II mediates peripheral vasoconstriction. It also acts on the adrenal cortex inducing release of aldosterone, and stimulates sodium reabsorption in the proximal tubule. Aldosterone increased sodium reabsorption in collecting tubules via the activation of epithelial sodium channels (25, 26). The increased sodium reabsorption leads to the restoration of depleted extracellular fluid and the normalization of RBF (27). These combined effects allow the maintenance of systemic pressure and perfusion of critical body organs with minimal alteration in RBF and GFR.

Antidiuretic Hormone (ADH)

ADH is a hormone for maintaining the homeostasis of water within the body. However, ADH in high plasma concentration also causes renal vasoconstriction and mesangial cell contraction (31). In the presence of ADH, both RBF and GFR decrease. ADH will also trigger the production of PGs that attenuate its own vasoconstrictive effects.

Endothelins

Endothelins are potent vasoconstrictors. Three endothelins have been identified (ET-1, ET-2, ET-3), with ET-1 being the most active in the group. Endothelins are synthesized in the endothelial cells of the kidneys, lungs, cerebellum, and major arteries. They are produced in response to increased vessel wall tension, vasoconstrictive agents (angiotensin II, vasopressin, thrombin), and inflammatory cytokines.
(TNF, interleukin). Endothelin works locally within the organ or vessel in which it is produced. It is thought that there are endothelin receptors in the renal vessels and that endothelin causes increased vascular resistance in both afferent and efferent arterioles leading to decreased RBF and GFR. In contrast to many other vasoactive agents, ET-1 has a longer half-life. As with the other renal vasoconstrictors, the vasoconstrictive effect is balanced by endothelin-induced release of PGs.

**Nitric Oxide (NO)**

NO is a substance released from the vascular endothelium. NO triggers the generation of a vasodilatory messenger that causes the relaxation of vascular smooth muscle. NO is believed to work in conjunction with other vasoactive substances to maintain normal physiologic tone in the glomerular vessels within minutes. NO is released in response to several vasodilators including histamine, bradykinin, serotonin, and acetylcholine. It is speculated that NO may be a mediator of the vasorelaxation produced by these substances. It also seems to be an angiotensin II antagonist at baseline (23). When precursors of NO are blocked, systolic blood pressure increases resulting in decreased RBF and variable changes in the GFR.

**Atrial Natriuretic Peptide (ANP)**

ANP is a hormone secreted by specialized granular cardiac cells primarily in the right atrium in response to right atrial distention and increased right atrial pressure. ANP induces vasodilation of the afferent arterioles and vasoconstriction of the efferent arterioles, resulting in an increased GFR. Natriuresis and diuresis are enhanced. ANP blocks directly ADH release and interferes with aldosterone release directly at the adrenal gland, thus increasing sodium and water loss from the kidney. The cumulative effects are reduced peripheral and renal vasoconstriction and decreased circulating volume. The effect is important in conditions of volume overload to reduce the circulating volume and induce vascular relaxation.

**Dopamine**

Dopamine receptors within the renal vasculature respond to low-dose dopamine by increasing both renal plasma flow and GFR through vasodilation. However, the role of dopamine in normal renal hemodynamics is not clear.

**Sympathetic Nervous System (SNS)**

The sympathetic nerves enter the kidney at the hilum and parallel the arterial system. The nerve endings terminate in the smooth muscle cells of both afferent and efferent arterioles. The SNS detects systemic volume changes via cardiac and arterial baroreceptors and can increase or decrease secretion of renin and catecholamines. Catecholamines, especially norepinephrine, act on the adrenergic receptor on the arterioles causing vasoconstriction. In hypovolemic states, the SNS mediates arterial vasoconstriction including vasoconstriction of the renal vasculature, which plays a major role in defending hypovolemia (32).

**Renal Hemodynamic in Volume Depletion**

In generalized low volume states, there is increased SNS activity and catecholamine production as a result of decreased stretch detected by the cardiac and arterial baroreceptors. The effect results in generalized vasoconstriction including the renal arterial system. Subsequently, the autoregulation mechanism is turned on, particularly the myogenic component, to maintain the GFR by dilating the afferent arterioles. The activated SNS also initiates the renin-angiotensin cascade. Angiotensin II causes further systemic and intrarenal vasoconstriction. These efforts are directed towards maintaining the mean arterial pressure (MAP) at the expense of non-priority organs, including the kidney. Although the RBF falls in response to angiotensin II, the fall in GFR is not of equal magnitude because angiotensin II maintains pressure within the glomerular capillary by causing greater vasoconstriction of the efferent than of the afferent arterioles.

To protect the sacrificed renal hemodynamics, angiotensin II simultaneously stimulates the release of vasodilatory PGs, which will attenuate to some degree the intrarenal vasoconstriction induced by RAS and SNS. NO and bradykinin may also limit the vasoconstrictive effects of angiotensin II. ADH is produced in hypovolemic status primarily for the retention of water. On the other hand, ADH also stimulates release of PGs in an effort to diminish its concurrent intrarenal vasoconstrictive effects.

The cumulative result of all these forces, in an individual with normal renal function, would increase vascular resistance with a fall in RBF and GFR. The decrease in GFR will not be as great as it would be without the protective effects of efferent arteriolar vasoconstriction, PGs, NO, and bradykinin. These mechanisms allow for the maintenance of a reasonable MAP and protection of the kidney from severe ischemia simultaneously. However, the ability to
maintain renal hemodynamics becomes impaired at MAP below 70 mmHg. In this setting, both GFR and RBF fall in proportion to the drop in blood pressure and the GFR ceases when the systemic pressure reaches 40 to 50 mmHg. If the hypovolemic status is not controlled, eventually these protective mechanisms will be exhausted, the GFR will decline, and renal failure will develop.

**Renal Hemodynamics in Volume Expansion**

In contrast to these hormonal changes with volume depletion, volume expansion tends to be associated with increased renal perfusion and perhaps a mild rise in GFR. Reduced secretion of angiotensin II and norepinephrine and enhanced release of dopamine and ANP may all contribute to this response. Dopamine dilates both afferent and efferent arterioles, thereby raising RBF while producing a smaller increment or no change in GFR. ANP, on the other hand, appears to produce the unusual combination of afferent dilation and efferent constriction, both of which will raise the GFR with a smaller alteration in RBF since total renal vascular resistance is relatively unchanged. These hormonal alterations also facilitate excretion of excess sodium and water. With all these taken together, the volume returns to normal via increase of GFR, sodium and water diuresis.

**Medullary Microcirculation**

Constant and adequate perfusion of the renal medulla plays an important role in maintaining fluid and electrolyte balance. The hemodynamics in medullary microcirculation is strictly regulated to maintain interior homeostasis (33). The pericytes surrounding the descending vasa recta (DVR), which are derived from the efferent arterioles of juxtamedullary glomeruli, are the major target of regulation. Pericytes are smooth muscle-like cells that have contractile function for the DVR, the arteriolar segments that supply the medulla with blood flow. Angiotensin II induces DVR contraction and decreases medullary blood flow (34). To a less extent, ET-1 also induces DVR contraction. In the volume depletion status, DVR plasma equilibrates with the interstitium both by diffusion and through water efflux across aquaporin-1. This process is predicted to optimize urinary concentration by lowering blood flow to the inner medulla. To optimize urea trapping, DVR endothelia express the urea transporter-B (UT-B) to facilitate urea transportation (35). Angiotensin II might also induce vasodilatory paracrine agents generated in the vicinity of outer medullary vascular bundles. PG (34) and NO (36) are main vasodilators in the medullary interstitium to counteract the vasoconstrictor effect of angiotensin II. All these mechanisms work together to maintain the constant medullary microcirculation and form the major framework of medullary autoregulation (33, 37).

**Renal Hemodynamics and Progressive Renal Failure**

Arteriolar resistance and renal hemodynamics may also play an important role in patients with underlying chronic kidney disease (CKD). A large body of experimental and clinical evidence suggests that intraglomerular hypertension is partially responsible for the progression of CKD (38, 39).

According to this theory, the loss of nephrons leads to a compensatory rise in filtration in the remaining more normal nephrons. This is an appropriate response in the short run, as it tends to maintain the total GFR. It is driven by afferent arteriolar dilatation, which leads to a rise in both single nephron RBF and GFR (40). The elevation in intraglomerular pressure, however, appears to be maladaptive in the long run, since it tends to result in progressive glomerular damage (41). Similar findings are seen in diabetic nephropathy, except that renal vasodilatation is a primary event, induced in some way by hyperglycemia or insulin deficiency (42). In addition to glomerular alteration, CKD also activates the RAS to compromise the medullary microcirculation, which leads to tubulointerstitial injury and plays an important role in the progression of renal failure.

**Drug-Induced Renal Hemodynamic Alteration**

The GFR is normally maintained within relatively narrow limits to prevent inappropriate fluctuations in solute and water excretion. GFR regulation is primarily achieved by alterations in arteriolar tone, which influence both intraglomerular pressure and RBF. In normal subjects, the GFR is maintained by autoregulation, which is mediated by four kinds of messages: pressure, chemical, humoral, and neural messages, as described above. At the same time, medullary microcirculation is also strictly regulated to maintain the homeostasis.

Many drugs are highly concentrated in the kidney. High local renal drug concentration makes kidney a damage-prone organ for drugs. Some of these medications will affect the above renal hemodynamic regulation, which is essential for the maintenance of proper renal function. Long-term alterations of renal hemodynamic regulation might disturb the normal-functioning kidney. We will discuss some of the renal hemodynamic alterations induced by medications used and summarized into Table 2.
Table 2. Mechanisms and managements of drug induced alteration in renal hemodynamics

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<tr>
<th>Diuretics</th>
<th>Mechanism</th>
<th>Management</th>
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<tbody>
<tr>
<td>Loop diuretics</td>
<td>Affect tubuloglomerular feedback mechanism</td>
<td>Avoid volume depletion</td>
</tr>
<tr>
<td></td>
<td>Inhibit PGs and stimulate renin synthesis</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Induce hypovolemia and activate ADH</td>
<td>Avoid volume depletion and hypokalemia</td>
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<tr>
<td></td>
<td>Hypokalemia related impairment of vasorelaxation</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Block the vasoconstrictive effect of aldosterone</td>
<td>Avoid volume depletion</td>
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<tr>
<th>Antihypertensive agents</th>
<th>Mechanism</th>
<th>Management</th>
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<tbody>
<tr>
<td>ACEI / ARB</td>
<td>Reverse AII-induced vasoconstriction on efferent arteriole</td>
<td>Careful use in renovascular stenosis and patients with reduced renal perfusion pressure</td>
</tr>
<tr>
<td>Direct renin inhibitor (DRI)</td>
<td>Reverse AII-induced vasoconstriction on efferent arteriole</td>
<td>Careful use in renovascular stenosis and patients with reduced renal perfusion pressure</td>
</tr>
<tr>
<td>β-blocker</td>
<td>Effects on intrarenal adrenergic receptors</td>
<td>Avoid hypotension</td>
</tr>
<tr>
<td></td>
<td>Modest and clinical insignificant GFR reduction</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker (CCB)</td>
<td>Attenuate vascular smooth muscle contraction</td>
<td>Avoid hypotension</td>
</tr>
<tr>
<td></td>
<td>Different impacts between subtypes, often little clinical significance</td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory drugs (NSAID)</td>
<td>Block the production of vasodilatory PGs</td>
<td>Avoid in high risk patients and discontinue drug if GFR decline</td>
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</tbody>
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<tr>
<th>Immunosuppressants</th>
<th>Mechanism</th>
<th>Management</th>
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<tbody>
<tr>
<td>Calcineurin inhibitors</td>
<td>Vasoconstrictive effects</td>
<td>Minimize drug dose and careful monitor drug level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administrate vasodilatory CCB</td>
</tr>
<tr>
<td>Steroid</td>
<td>May increase GFR in short term but decrease GFR in long-term exposure</td>
<td>Avoid unnecessary long-term exposure</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>May reduce inflammation-related vasoconstriction</td>
<td>Beneficial effect on GFR</td>
</tr>
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<tr>
<th>Antibiotics</th>
<th>Mechanism</th>
<th>Management</th>
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<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Both tubular toxicity and vasoconstrictive effects</td>
<td>Drug level monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain patient’s hydration</td>
</tr>
<tr>
<td>Cephalosporin/Penicillin</td>
<td>No significant renal hemodynamic impact</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Constricting renal vessels directly</td>
<td>Sodium loading before and during treatment</td>
</tr>
<tr>
<td>Chinese herbs</td>
<td>Complex composition and variable biological activity</td>
<td>Avoid unnecessary exposure and identify contributing drug composition</td>
</tr>
</tbody>
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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; GFR, glomerular filtration rate; PGs, prostaglandins.
Antihypertensive Agent-Related Renal Hemodynamic Change

Blood pressure is a product of cardiac output and peripheral resistance. Antihypertensive agents are always targeting the above two factors, which also play key roles in determining renal hemodynamics. It is very likely that antihypertensive agents have a profound effect on renal hemodynamics. The condition becomes clinically significant if the perfusion pressure is markedly reduced as the ability of autoregulation to protect the GFR is impaired. Thus, any antihypertensive agent might produce acute kidney injury when there are severe and bilateral renovascular lesions or a marked unilateral lesion in a solitary kidney (11).

Diuretics

Diuretics prevent sodium reabsorption along the nephron. The common effect of diuretics is depletion of extracellular fluid. Over-diuresis will mimic the hypovolemic status and initiate the renal autoregulation mechanism. The mechanism falls apart and leads to renal injury, if the alteration of renal hemodynamics goes beyond the range of self-protective mechanism in the kidney. Furthermore, different diuretics will have different effects on renal hemodynamics.

Loop Diuretics

Loop diuretics, such as furosemide or bumetanide, inhibit the Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter in the thick ascending limb. The mechanism has two facets on renal hemodynamics. The decreased Na\(^+\) and Cl\(^-\) reabsorption by macula densa will mimic the hypovolemic status and increase the GFR via tubuloglomerular feedback. On the other hand, an inhibition of the Na\(^+\)-K\(^+\)-2Cl\(^-\) transporter in the thick ascending limb of the loop of Henle reduces by loop diuretics the delivery of NaCl to the medullary interstitium and results in a decrease in medullary hypertonicity (43). This is an inhibitory stimulus for synthesis of intramedullary PGs (44). Prostaglandin-mediated vasodilation is important for maintaining medullary perfusion (45). Loop diuretics also stimulate renin synthesis, increase generation of angiotensin II, and enhance vasconstrictor action (46), which might further compromise the medullary perfusion and counteract the tubuloglomerular feedback mechanism (47). The above harmful effect is noteworthy only in the volume depletion status, when medullary perfusion is jeopardized (44). Avoiding over-diuresis and volume depletion is the best way to prevent loop diuretics-induced acute kidney injury.

Thiazide Diuretics

In addition to the volume depletion-induced change in renal hemodynamics (48), thiazide diuretics is associated with mild hypokalemia and results in impaired endothelium-dependent vasorelaxation (49). Thiazide diuretics also preferentially induce hyponatremia via the volume-depletion mechanism, which enhances ADH secretion and subsequent water reabsorption regardless of decreased osmolarity. Loop diuretics are less likely to develop this complication, as the disturbance of countercurrent mechanism, which is essential for the maximal action of ADH (50). The alteration might compromise both renal hemodynamics and microcirculation (49). Hypovolemia, hypokalemia, and hyponatremia induced by thiazide may all compromise renal hemodynamics and its long-term usage should be monitored.

Aldosterone Antagonist

Aldosterone constricts preferentially renal efferent arterioles than afferent arterioles (26). Recent studies provide evidence that aldosterone accelerates hypertension, proteinuria and glomerulosclerosis in chronic renal failure (51). Although the underlying mechanisms are not well defined, aldosterone may exert these deleterious renal effects by elevating renal vascular resistance and glomerular capillary pressure via calcium channel activation (26) and NO secretion attenuation (52). The vasoconstrictive actions on glomerular capillary may play an important role in the progression of renal failure. Aldosterone antagonist blocks the vasoconstrictive effect of aldosterone and induces favorable effects in renal hemodynamics. However, its clinical use is limited by high risk of hyperkalemia.

Angiotensin Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB)

RAS plays an important role in the regulation of renal hemodynamics, both in the cortex and medulla. One of the major apparent preferential benefits of ACEI or ARB is the reversal of angiotensin II-induced vasoconstriction on efferent arterioles. Decreasing vascular resistance at efferent arterioles will directly lower the intraglomerular pressure, independent of the reduction in systemic blood pressure.

The risk of acute kidney injury after ACEI or ARB is not limited to renovascular disease, but can occur in any condition in which renal perfusion pressure is reduced (53). In some patients receiving ACEI/ARB, the GFR may fall presumably due to a reduction in intraglomerular pressure induced by efferent arteriolar dilation. This is most likely to occur in patients with a diastolic pressure below 70 mmHg who are being treated with high doses of
diuretics (54). Monitoring changes in GFR after initiating ACEI/ARB treatment is warranted to avoid unfavorable kidney injury.

**Direct Renin Inhibitor (DRI)**

DRI (55), as a newer agent of RAS blockade, are thought to have similar or even potentially superior renoprotective and hemodynamic effects as compared with ACEI and ARB (56). DRI reduces plasma renin activity and angiotensin II levels without compensatory elevation in angiotensin I and angiotensin II as seen with ACEI and ARB. Moreover, recent studies revealed that DRI reduces renal fibrosis and apoptosis in chronic ischemic renal failure rat model beyond its RAS blockade effect. The effect was thought to be mediated by blocking pro-renin receptor by this specific drug, which could enhance renal perfusion and renal plasma flow (57). However, the effect of this new agent on renal hemodynamics deserves more study and observation in clinical practice. As in the case of ACEI/ARB use, GFR should be monitored after initiation of DRI treatment, especially in high-risk patients.

**β-Blocker**

β-blockers exert their antihypertensive effects through antagonism of β-adrenergic receptors. Beyond the effects on cardiac output and blood pressure, β-blockers also influence renal plasma flow and GFR through their direct effects on intrarenal adrenergic receptors. The intrarenal α-, β1- and β2-adrenergic receptors mediate vasoconstriction, renin secretion and vasodilation respectively. Various β-blockers differ in their β1 selectivity (cardioselectivity), intrinsic partial agonist activity and vasodilatory properties. Therefore, they have different effects on renal hemodynamics and renal function. In general, acute administration of most β-blockers reduces both RBF and GFR, whether they are cardioselective or not. Exceptions include nebivolol, carvedilol and ciliprolol, which increase or maintain effective RBF possibly through their vasodilatory effects (58-60). Cardioselective agents tend to produce less significant reductions in effective renal plasma flow and GFR after their long-term oral administration (61). It is possible that β-blockers reduce renal hemodynamics mainly through β1 blockade effect. Mostly, the degree of reduction in GFR and renal plasma flow is modest without clinical significance (62). Maintaining adequate systemic blood pressure in chronic β-blocker treatment can minimize undesirable effects on renal hemodynamics and prevent kidney injury.

**Calcium Channel Blocker (CCB)**

CCBs attenuate contraction of vascular smooth muscle through the inhibition of the entry of calcium or its mobilization from intracellular space. They uniformly lower peripheral vascular resistance and decrease vascular responsiveness to angiotensin II. Most CCBs influence renal microcirculation with a predominant vasodilatory action on afferent arterioles, whereas efferent arterioles are relatively refractory to CCBs. Subsequently, they reduce renal vascular resistance, improve RBF, maintain or increase GFR, increase filtration fraction, and have natriuresis effects. These renal hemodynamic effects of CCBs are maximal in the presence of vasocostricators norepinephrine and angiotensin II (63). Hypertensive patients appear to be more sensitive, especially with advanced kidney disease (64). In contrast to acute administration, chronic administration of CCBs does not change significantly renal hemodynamic status and its effect in hypertensive patients are variable (65). Some patients exhibit exaggerated improvement in GFR whereas others have no change in GFR and renal plasma flow (66). It is possible that significant clinical changes are counteracted by the reduction in blood pressure and renal perfusion pressure.

Newly developed CCBs have been found to exert different impacts on renal hemodynamics. Unlike conventional CCBs acting exclusively on L-type Ca channels, newly developed CCBs such as mibefradil and efonidipine also exert blocking action on T-type Ca channels. These T-type CCBs cause lower increase in filtration fraction because T-type Ca channels not only mediate aldosterone release but also presence on both afferent and efferent arterioles (67). Furthermore, N-type CCBs (e.g., cilnidipine) reduce glomerular pressure by inhibiting neurotransmitter release and dilating both afferent and efferent arterioles (68). These newly developed CCBs lead to more detailed understanding of different Ca channel subtypes in the kidney. Conclusively, CCBs tend to increase RBF, GFR and filtration fraction with different effects between subtype selectivities. Hypotension will counteract these hemodynamic effects and should be avoided.

**Others**

Central α2-adrenergic agonists, peripheral α1-adrenergic antagonists, and direct vasodilators all decrease renal vascular resistance by decreasing circulating levels of catecholamines, inhibition of preglomerular α1-mediated vasoconstriction, and direct relaxation of resistance vessels respectively (69-71). These antihypertensive agents preserve RBF and have little clinically important effects on GFR.
Nonsteroidal Antiinflammatory Drugs (NSAID)

The production of vasodilatory PGs is blocked by non-selective cyclooxygenase inhibitors such as indomethacin, ibuprofen, or other NSAID. These drugs should not be administered to individuals with renal insufficiency to prevent the loss of this crucial protective mechanism. Similar to non-selective NSAIDs, selective COX2 inhibitors also impact negatively on renal function in those with impaired kidneys (72) because the key isozyme enzyme in the kidney is COX2.

The NSAID can produce an acute decline in both GFR and renal plasma flow when given to patients with high angiotensin II and norepinephrine levels. This most often occurs with effective circulating volume depletion due, for example, to heart failure or cirrhosis. In these conditions, prostaglandin synthesis is appropriately enhanced and administration of a NSAID can lead to unopposed action of the vasoconstrictors and acute renal failure (73, 74). However, these agents, which are widely used in the treatment of arthritis and other disorders, have little effect on renal function when given to normovolemic subjects in whom the baseline level of renal prostaglandin production is relatively low. Once acute kidney injury occurred after NSAID administration, discontinuation of NSAID can usually reverse GFR and RBF. Careful monitoring of GFR changes in high-risk patients is recommended.

Immunosuppressive Agents in Intrarenal Hemodynamics

Calcineurin Inhibitors

Cyclosporine A (75) is nephrotoxic and responsible for progressive renal failure in some kidney transplant patients (76). Acute CsA nephrotoxicity has been shown to enhance renal arterial vasoconstriction and decrease RBF (77), in part by altering the balance between vasodilating and vasoconstricting mediators, such as endothelin, NO, and eicosanoids (78, 79). CsA also activates the RAS system (80, 81), sodium reabsorption (82) and sympathetic nervous system (83, 84). The vasoconstrictive effect of CsA occurs preferentially in the afferent arterioles, but also in adjacent small arteries (85). This change is mostly functional and reversible in acute administration, but may cause ischemia in the long run, contributing to chronic nephropathy. Tacrolimus is another calcineurin inhibitor increasingly used in organ transplantation patients with the main advantage of less acute allograft rejection. Tacrolimus also induced renal vasoconstriction and acute nephrotoxicity (86). Renal graft histology after long term tacrolimus treatment showed similar structural injury with CsA (87). Most studies currently available favor the nephrotoxic effects of tacrolimus being identical to that of CsA, but solid controlled data are limited. To prevent long-term nephrotoxicity of calcineurin inhibitors, minimization of drug dose and careful monitoring of plasma levels are the most important measures. If complete withdrawal is not allowed to ensure adequate immunosuppression, administration of vasodilatory calcium channel blockers have been demonstrated to preserve renal plasma flow and GFR in transplanted kidney (88).

Steroid

Glucocorticoids (GCs) affect kidney function directly via tubular effects and indirectly via cardiovascular system effects. Excess glucocorticoids including endogenous Cushing syndrome and exogenous administration can cause hypertension (89). It is observed that cardiac output, total peripheral resistance, and renal vascular resistance are elevated (90). There may be many interacting pathophysiological pathways. First, glucocorticoids can exert mineralocorticoid activity via binding of mineralocorticoid receptors and result in sodium and water retention. Second, glucocorticoids change vascular tonicity control balance by increasing vascular sensitivity to angiotensin II and noradrenaline (91, 92), increasing level of endothelin-1 (93) downregulating of the Na+/Ca2+-exchanger in vascular smooth muscle cells (94), inactivating the NO system, and inhibiting production of vasodilators, such as prostacyclin, PGE2 and kallikrein (95).

Acute and chronic administration of corticosteroids in humans differ in overall effects on RBF and GFR. Short-term administration of adrenocorticotropic hormone (ACTH) or GCs increases RBF and GFR. Plasma volume expansion, efferent arteriolar vasoconstriction, glomerular blood pressure elevation, rise in filtration fraction, elevation of plasma amino acid levels due to catabolic effects, and increased plasma level of ANP may all play a role (96-98). In contrast, Haentjens et al. found that Cushing’s patients had lower GFR possibly due to permanent alterations of vessel remodeling (99). Long-term effects of excess GCs in humans may decrease GFR. Avoid unnecessary long-term exposure to GCs is suggested.

Mycophenolate

Mycophenolate mofetil (MMF) is an anti-lymphocyte drug with immunosuppressive and anti-inflammatory properties. Animal studies had revealed the renal protective effect of MMF in several renal
failure models such as glomerulonephritis (100), diabetic nephropathy (101), hypertension (102) or remnant kidney (103). In vitro study also suggested that MMF can attenuate the RAS system activity (104). Treatment with MMF did not change directly blood pressure or glomerular hemodynamics. Instead, the anti-inflammatory effects of MMF that reduced vasoconstriction induced by inflammation may explain why MMF can prevent the reduction of GFR.

Antibiotics

Aminoglycosides

Aminoglycosides is well known for their nephrotoxicity mainly by their tubular cytotoxicity. The shading necrotic tubular cells obstruct tubule, increase tubular hydrostatic pressure, and reduce filtration pressure gradient, thus reduced GFR (105). Moreover, the impairment of proximal reabsorption leads to excessive delivery of water and solutes to the distal nephron. This activates the TGF mechanism and subsequently decreases the GFR (106). However, these tubular effects cannot fully explain the reduction of GFR which happens before tubular obstruction and persists after TGF adaptation period. Aminoglycosides also exhibit glomerular and vascular effects in altering filtration and perfusion.

In nephrotoxicity experiments, Gentamicin can reduce GFR directly by triggering mesangial contraction (107), neutralizing glomerular negative charges and eliminating glomerular filtration barrier selectivity (108). Gentamicin also increases renal vascular resistance and decreases RBF by increasing vasoconstrictors, blocking synthesis of vasodilatory PGs (109), and inducing leukocyte margination, thus leading to vascular plugging (110). To prevent the negative impact of aminoglycosides on renal hemodynamics, careful monitoring of drug level and maintenance of patient’s hydration are warranted. Currently new strategies involving specific mechanisms of action, such as cotreatment with antioxidant or vasodilators, are mostly at the preclinical level of development (111).

Cephalosporin/Penicillin

The nephrotoxicity of beta-lactam antibiotics is rare with the penicillins, uncommon with the cephalosporins, and slightly more common with penems. The renal toxic beta-lactam antibiotics cause acute proximal tubular necrosis, resulting from the direct toxicity to tubular cells (112). No significant renal hemodynamic influence had been documented.

Amphotericin B

Amphotericin B (AmB) is very effective for treatment of severe fungal infection, but its clinical use is limited by the high prevalence of nephrotoxicity. AmB causes transporting defects due to tubular dysfunction. AmB also reduces RBF and GFR by constricting renal vessels directly (113). Recent studies revealed that AmB can change vascular smooth muscle cell membrane permeability by binding to mammalian sterol molecules forming intramembrane pores (114). This change depolarizes cell, activates voltage-dependent calcium channels, makes a surge in intracellular calcium concentration, and then leads to smooth muscle contraction. Increased intracellular calcium concentration also activates arachidonic acid metabolism, leading to accumulation of vasoactive substances with a net vasoconstrictive effect. However, reversing AmB-induced vasoconstriction with vasodilatory CCB was only limited to anecdotal reports and not firmly recommended. More evidences supported utilizing sodium loading orally or intravenously before starting and during AmB treatment in patients without contraindications to reduce AmB-induced nephrotoxicity (115).

Chinese Herbs

The use of herbal or botanical medicine is ancient and world-wide. The compositions of numerous herbs are very complex. Most of them contain undetermined compounds with variable biological activity. Moreover, many herbal products contain heavy metals or undisclosed additive drugs. Therefore some herbal medicines cause various kidney syndromes such as acute tubular necrosis, Faconi’s syndrome, interstitial nephritis/fibrosis, papillary necrosis and urinary tract carcinoma (116). Among such numerous compounds, some may exhibit vasoactivity and affect renal hemodynamics. An example is Ma huang, an ephedrine-containing herb with sympathomimetic activity. Ephedrine can induce hypertension and increase urine flow rate (117). We suggest avoiding unnecessary exposure to herbal medicines with unknown compositions. Once acute kidney injury happened, one should identify the possible contributing drug composition for further specific management.

Summary

Drugs can affect renal hemodynamics via variable pathways of both systemic and intrarenal effects. Changes in renal hemodynamics can be clinically evident with significant GFR decline and some of these changes may be irreversible. By reviewing the mechanisms controlling renal hemodynamics and medications known to affect renal hemodynamics, clinicians should be more cautious when administering medications.
References


Drug and Renal Hemodynamics


