CASE 21

A 23-year-old man has been admitted to the surgical floor after suffering multiple injuries in a motor vehicle accident. Plain film radiographs have not indicated any fractures. At the time of admission, his abdomen had some bruising but no distention or tenderness. After 8 hours of observation, the nurse calls the physician because the patient’s urine output has been decreasing steadily. His blood pressure is normal but lower than it was when he presented to the hospital, and he has a slightly increased heart rate. His abdomen is now distended and tender. An intravenous (IV) fluid bolus of 500 mL of normal saline is administered, and his urine output increases to a normal range. The surgeon makes a diagnosis of hypovolemia that probably is caused by intraabdominal hemorrhage and prepares the patient for exploratory surgery.

◆ What is the response of the juxtaglomerular cells to decreased extracellular fluid and arterial pressure?

◆ What are two effects of angiotensin II?

◆ What are two mechanism by which autoregulation of renal blood flow occurs?
ANSWERS TO CASE 21: RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Summary: A 23-year-old man has hypotension, tachycardia, and oliguria secondary to intraabdominal hemorrhage after a motor vehicle accident.

◆ Juxtaglomerular cells and decreased renal arterial perfusion: Release of renin.
◆ Two effects of angiotension II: Increases vascular smooth muscle tone and increases aldosterone production by the adrenal cortex.
◆ Mechanisms of autoregulation: Myogenic mechanism and tubuloglomerular feedback.

CLINICAL CORRELATION

Monitoring urine output is an easy way to assess a patient’s fluid status. Often after surgery or trauma, a Foley catheter is placed in the bladder to measure urine output accurately. Decreasing urine output may be because of hypovolemia or injury to the urinary tract system. In this case, the decreased urine output probably was secondary to hypovolemia, because the patient also has hypotension and tachycardia. The blood pressure remained relatively normal initially because of the renin-angiotensin system, which sensed the decreased blood flow to the renal artery, and the sympathetic nervous system, which sensed the decreased blood volume and pressure. The decreased blood flow through the renal artery will stimulate renin to be released, with the subsequent generation of angiotensin II, leading to increased systemic blood pressure and total peripheral resistance. Decreased blood volume and pressure will be sensed by volume and pressure receptors, leading to modest vasoconstriction and increased systemic blood pressure. With excessive blood loss (hypovolemic shock), the action of the autonomic (sympathetic) nervous system causes pronounced vasoconstriction of the renal arteries with shunting of blood to vital organs (brain, heart, lungs) and is seen clinically with decreased urine output. Replacement with crystalloid fluids and blood is necessary to maintain kidney perfusion and prevent acute tubular necrosis. If a patient is in shock and urine output is not responding to IV fluids and blood, low-dose dopamine often is used to cause renal artery dilation and increased renal blood flow. In any case, the source of bleeding must be addressed and intravascular volume must be replaced.

APPROACH TO GLOMERULAR FILTRATION RATE

Objectives

1. Know the concepts underlying regulation of renal artery blood flow.
2. Understand the concept of autoregulation.
3. Know the basics of how to measure the glomerular filtration rate (GFR).
Definitions

Renin: A proteolytic enzyme released from the juxtaglomerular cells of the afferent arteriole that splits off angiotensin I from angiotensinogen.

Angiotensin II: A potent vasoactive peptide produced by the conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme (ACE).

Antidiuretic hormone (ADH, vasopressin): A posterior pituitary peptide hormone that functions both as a regulator of osmotic balance and a vasoconstrictor.

Autoregulation: The maintenance of normal blood flow to an organ during periods of altered arterial pressure.

Tubuloglomerular feedback: The process by which alterations in renal tubular flow are sensed by specialized cells in the macula densa and signal the afferent arteriole to constrict or dilate to bring about alterations in GFR, thereby negating the alteration in tubular flow.

DISCUSSION

Urine output is regulated by numerous factors, including alterations in extracellular fluid volume and blood volume (volume expansion or depletion). Typically, under conditions of volume expansion (eg, drinking a liter of water), urine output is increased, whereas under conditions of volume depletion (eg, hemorrhage, profuse sweating) urine output is decreased. In this case, the patient probably has had an intraabdominal hemorrhage during trauma that has led to modest volume depletion. The renal system responds by reducing urine output in an attempt to maintain volume-water balance. As this case demonstrates, several mechanisms come into play to regulate urine output during volume depletion, including the sympathetic nervous system, volume-sensitive hormonal systems, and intrinsic autoregulator mechanisms.

Renal autoregulation is an intrinsic property of the renal vasculature that serves to maintain renal blood flow and the GFR at nearly normal levels in the presence of alterations in renal arterial pressure. Although the mechanism of this response is not fully understood, it appears to be predominantly related to myogenic stretch receptors in the wall of the afferent arteriole, similar to what is observed in precapillary sphincters in muscle capillaries during autoregulation of muscle blood flow. The efferent arteriole does not appear to be involved in the autoregulation mechanisms. Under conditions of elevated mean arterial pressures, such as observed during volume expansion, hydrostatic pressures along the renal vasculature will be elevated, leading to an initial increase in renal blood flow and the GFR (secondary to elevation of glomerular capillary hydrostatic pressure). The elevated pressure in the afferent arteriole stretches the arteriole, causing the arteriole to respond, inducing constriction. This constriction returns blood flow to near normal and glomerular hydrostatic pressure and, hence GFR, to near normal. Conversely, under conditions of depressed mean arterial pressure, such as observed
During volume depletion, hydrostatic pressure along the renal vasculature is decreased, leading to an initial decrease in renal blood flow and GFR (secondary to reduction of glomerular capillary hydrostatic pressure). The reduced pressure decreases the stretch of the afferent arteriole, causing the arteriole to respond, inducing *dilation*. This returns blood flow and GFR to near normal. Maximum dilation is approached when renal perfusion pressures decrease to 70 to 80 mm Hg so that further decreases in renal arterial pressure will lead to parallel decreases in renal blood flow and GFR.

**Tubuloglomerular feedback** also serves to autoregulate renal blood flow and GFR through a mechanism induced by alterations in tubular flow rate (chloride delivery) that is sensed by specialized cells in the *macula densa segment* of the *cortical thick ascending limb*. These cells are juxtapositioned to their own afferent arteriole and control constriction of the arteriole. Under conditions of an elevated GFR, for example, volume expansion, the tubular flow rate (chloride delivery) will increase; this will be sensed by the macula densa cells, and this leads to constriction of the afferent arteriole, bringing about a reduction in GFR and tubular flow rate. Conversely, under conditions of a reduced GFR, for example, volume depletion, the reduced tubular flow rate will be sensed by the macula densa cells, leading to dilation of the afferent arteriole, bringing about an increase in GFR and tubular flow rate. Hence, the tubuloglomerular feedback mechanism works in parallel with the normal autoregulatory process in an attempt to maintain renal blood flow and GFR at nearly normal levels.

**Extrinsic factors** play a significant role in regulating renal function during both hypo- and hypervolemia and normally overpower the intrinsic autoregulatory mechanisms. The *renin-angiotensin-aldosterone system* can play a major role in this process. In hypovolemic states, the reduction in blood volume results in reduced renal blood flow and reduced hydrostatic pressure along the renal vasculature. The decrease in pressure in the afferent arteriole is sensed by baroreceptors in the afferent arteriole, leading to stimulation of renin release from the juxtaglomerular cells of the afferent arteriole (increased sympathetic activity also increases renin release).

\[
\text{Renin} \quad \text{ACE} \\
\text{Angiotensinogen} \rightarrow \text{Angiotensin I} \rightarrow \text{Angiotensin II}
\]

Renin is a proteolytic enzyme that works on a plasma $\alpha_2$-globulin, angiotensinogen, to produce angiotensin I, which in turn is converted to angiotensin II by ACE, which is present predominantly at the luminal surface of endothelial cells in the lungs, although significant levels are present in the renal afferent and efferent arterioles.

**Angiotensin II** is a *potent vasoactive peptide* that leads to vasoconstriction, elevating mean arterial pressure toward normal. **Angiotensin II** also leads to vasoconstriction of both the afferent and efferent arterioles, increasing renal vascular resistance and reducing renal blood flow. This leads to a modest decrease in glomerular capillary hydrostatic pressure and, in turn, GFR. The reduced GFR will contribute to a reduction in urine output (see below).
In a similar manner, hypervolemic states lead to elevated mean arterial pressure, bringing about an increase in renal blood flow and pressure along the renal vasculature. The afferent arteriole baroreceptors sense this change and signal to reduce renin release from the afferent arteriole, resulting in a reduction in angiotensin II and causing vasodilation and a reduction in mean arteriole pressure. A dilatation of both the afferent and efferent arterioles will accompany the reduced angiotensin II levels, causing an increase in renal blood flow and a modest increase in GFR. This in turn contributes to an increase in urine output.

Angiotensin II plays a secondary role in volume regulation by regulating the synthesis of aldosterone, a mineralocorticoid hormone, by the zona glomerulosa cells of the adrenal cortex. Aldosterone, in turn, acts on the renal distal tubule and cortical collecting ducts to enhance sodium (and chloride) reabsorption, leading to salt retention and an associated retention of water with a corresponding decrease in urine output. Hence, adaptive responses to elevation of angiotensin II during volume depletion lead to aldosterone synthesis and thus increased fluid retention. The opposite occurs in volume expansion.

The sympathetic nervous system also is intimately involved in regulating renal function during alterations in volume balance. Volume depletion will be accompanied by a decrease in blood volume and venous return to the heart that will be sensed by baroreceptors (volume receptors) in the atria and pulmonary veins and pressure receptors in the renal afferent arteriole, leading to increased sympathetic activity. This will result in sympathetically mediated vasoconstriction and partial return of mean arterial pressure toward normal. If blood volume depletion is modest—less than 10% of blood volume—the changes are modest, but will help maintain blood pressure near normal. With more severe cases of hypovolemia (15% to 25% blood loss), there is a more pronounced sympathetic-mediated vasoconstriction. Increased sympathetic activity also will lead to constriction of both the afferent and efferent arterioles, which, like angiotensin II, will reduce renal blood flow and modestly reduce GFR (subsequent to a modest reduction in glomerular capillary hydrostatic pressure) and contribute to reduced urine output. Conversely, during volume expansion, baroreceptors will sense an increase in blood volume and mean arterial pressure, leading to a decrease in sympathetic activity which, in turn, will lead to vasodilation and a return of blood pressure toward normal. Dilation of both the afferent and efferent arterioles will bring about an increase in renal blood flow and a modest increase in GFR and urine output. Again, the response is to return blood volume toward normal.

A final modulator of water and volume balance is ADH. Although alterations in plasma osmolarity are the main factor regulating ADH release from the posterior pituitary, alterations in blood volume also are part of the response (see Case 24). During volume depletion, volume receptors lead to increased release of ADH into plasma. The ADH binds to receptors on the renal collecting ducts, leading to the insertion of water channels (aquaporins) into the luminal cell membrane, increasing cell water permeability and, in turn, stimulating water reabsorption from the tubule lumen. Water is retained, and
urine output is reduced. Conversely, during volume expansion, volume receptors sense the change, leading to a decrease in ADH secretion with a subsequent decrease in the water permeability and hence, water reabsorption by the collecting ducts. Water is lost, and urine output is elevated.

**GFR** is a major factor controlling the function of the kidney and is a major indicator of abnormal functions of the renal system. Hence, estimating GFR in the clinical setting is critical to understanding the status of the kidney. GFR typically is estimated in the clinic by measuring **creatinine clearance** or is estimated indirectly from the **plasma levels of creatinine and blood urea nitrogen (BUN)**. Both of these components are filtered at the glomerulus and excreted in the urine. As a result, both are inversely related to GFR. A reduction in GFR leads to reduced filtration and, in turn, excretion of these substances, resulting in elevated plasma levels. Hence, the time course of kidney diseases that affect GFR often can be monitored over years by following the changes in plasma levels of BUN and creatinine. A more direct assessment of GFR can be obtained by measuring the clearance of creatinine (see the references at the end of this case).

**COMPREHENSION QUESTIONS**

[21.1] An individual is known to be suffering from diabetes mellitus. Recently, he has developed hypertension. His doctor suspects that the patient may be developing renal insufficiency that is leading to a reduced glomerular filtration and, as a result, hypervolemia and hypertension. The doctor wishes to evaluate kidney function by measuring the glomerular filtration rate (GFR). She can estimate GFR best by performing a urine clearance study of which of the following substances?

A. Creatinine  
B. Para-aminohippuric acid (PAH)  
C. Urea  
D. Glucose  
E. Sodium

[21.2] A 21-year-old man has been vomiting to the point where he has become hypovolemic, as evidenced by an accompanying decrease in blood pressure and a feeling of light-headedness. The kidneys respond by reducing urinary volume flow, thus limiting the potential extent of hypovolemia. Increases in the plasma levels of which of the following hormones will bring about the most dramatic decrease in urinary volume flow rate?

A. Angiotensin II  
B. Atrial natriuretic peptide  
C. Parathyroid hormone  
D. Aldosterone  
E. Arginine vasopressin (ADH)
[21.3] A 56-year-old woman is diagnosed with small-cell carcinoma of the lung. She has a paraneoplastic effect from the cancer, with release of an ADH-like agent. Which of the following is most likely to be seen?

A. Elevated serum sodium
B. Elevated serum osmolarity
C. Elevated urine sodium
D. Elevated urine catecholamines

Answers

[21.1] A. Creatinine is a normal end product of muscle metabolism. It is freely filtered at the glomerulus and excreted in the urine. Although creatinine is not reabsorbed by the kidney tubules, it is partially secreted so that the rate of urinary excretion of creatinine overestimates the rate of filtration by a small percentage in healthy individuals (it overestimates more in individuals with a compromised GFR). Nonetheless, in the clinic the clearance of creatinine can provide a reasonable estimate of GFR.

[21.2] E. Increases in plasma levels of arginine vasopressin, or ADH, lead to water reabsorption by the collecting ducts, decreasing urine output.

[21.3] C. ADH allows for increased reabsorption of water from the collecting system, and thus decreases serum sodium and serum osmolarity. The urine is concentrated with high sodium and high osmolarity.

---

**PHYSIOLOGY PEARLS**

- Baroreceptors in the renal afferent arteriole sense low blood pressure in the arteriole and induce release of renin from the juxtaglomerular cells of the arteriole.
- Both the renal afferent and efferent arterioles are innervated with sympathetic nerves that regulate contraction and dilation of the arterioles.
- Autoregulation in the kidney maintains constancy of both renal blood flow and GFR during periods of altered renal arterial pressure.
- Aldosterone regulates the reabsorption of sodium (and chloride) from the distal tubule and the cortical collecting duct, bringing about retention of salt and water and an increase in extracellular fluid volume.
- ADH acts on the collecting ducts to increase their water permeability, leading to an increase in water reabsorption from the tubular fluid, bringing about retention of water and an increase in extracellular fluid volume.
REFERENCES
