AJKD
Core Curriculum in Nephrology

The Role of the Kidney in Disorders of Volume: Core Curriculum 2016

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The human body uses exquisitely sensitive resistors to assess organ perfusion, yet caregivers can only infer this information on the physical examination from crude measurements of skin turgor, capillary refill in nail beds, orthostatic blood pressures, and weight. Despite efforts to measure these markers, only a postural pulse increment $>$ 30 beats/min has both sensitivity and specificity greater than 95% in the diagnosis of volume depletion. Our primitive measures are matched with vague language regarding "volume status." Patients with excess volume are often described as "tanked," "positive," or "ahead," whereas those who are volume depleted may be described as "down," "negative," or the even more inexact "dry" or "dehydrated." Because a specific description of the volume disorder will help guide therapy, it is best to start with consideration of how extracellular volume affects vital organ perfusion. Although the extracellular volume sensed by vital organs usually increases or decreases in parallel with the total extracellular volume, there are circumstances in which these do not correlate; thus, an understanding of the concepts of body fluid compartments and effective circulating intravascular volume are required to understand the renal response. The focus of this review is primarily on disorders that affect extracellular compartments, in contrast to disorders of osmoregulation, which primarily affect the intracellular compartment.

BODY FLUID COMPARTMENTS

Body fluid, which is primarily made of up sodium, potassium, chloride, and water, constitutes about two-thirds of body weight, with solid tissue (primarily bone) making up the remaining one-third. The 3 major fluid compartments are the intracellular, intravascular, and interstitial spaces. Cell membranes separate the intracellular space from the extracellular space, and the adenosine triphosphatase sodium/potassium pump (Na^+/K^+-ATPase) maintains a high intracellular potassium concentration and low intracellular sodium concentration; the opposite is found in the extracellular space. The osmolality of both compartments is the same. Most cell membranes are permeable to water, but functionally impermeable to sodium, potassium, and chloride. Thus, changes in water balance, as may occur in the setting of hyper- and hyponatremia, lead to alterations in cell size, whereas changes in isotonic fluid balance primarily affect the extracellular compartment. Because sodium is the major cation in the extracellular space, sodium and its accompanying anions represent the predominant osmoles in the extracellular space; thus, sodium and water accumulation in the extracellular compartment leads to volume expansion, hypertension, and edema, whereas loss of sodium and water leads to a decline in blood pressure and decrease in vital organ perfusion. Consequently, the kidney's response to disorders of volume is directed at sodium excretion or retention, and derangements in sodium regulation by the kidney can lead to disorders of volume homeostasis.

The Extracellular Compartment

The extracellular compartment comprises the intravascular space and the interstitium. Normally, the volume within the vasculature is about one-quarter of the extracellular volume. Traditionally, this volume is thought to remain restricted within the vasculature with help of the oncotic forces provided by plasma proteins, primarily albumin. However, emerging evidence suggests that some of the traditional mechanistic explanations used to support the concept of a distinct and definable "intravascular" volume need to be updated. Starling's law, which suggests that fluid movement across a semipermeable membrane is simply governed by the algebraic sum of outward hydraulic and inward oncotic pressure, is likely an oversimplification. The conventional model of the capillary wall was simply a fenestrated permeable barrier between interdigitating endothelial cells. Intravascular volume was thought to be maintained primarily due to a balance of venous pressure and plasma protein concentration. However, in the 1960s, increasing awareness of a "matrix of molecular fibers" that cover the endothelial lining emerged, and subsequently, the role of the endothelial glycocalyx as a determinant of transcapillary fluid movement has

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challenged the Starling model. More modern data suggest that the inward oncotic forces are much less significant than originally thought, and that filtered fluid likely does not return to postcapillary venules, but rather is absorbed by the lymphatic system. The endothelial glycocalyx contributes to the overall permeability of the capillary wall, and given its fragile and complex structure, it is disrupted by a range of acute illnesses. Accordingly, albumin infusion, once widely promoted in resuscitation, has more recently fallen out of favor compared with isotonic crystalloid solutions despite previous supportive data, though there is still an important role in the use of albumin infusions at the time of large-volume paracentesis for severe ascites. Nevertheless, a more updated fluid paradigm minimizes the importance of inward oncotic pressure and instead focuses on capillary permeability and outward hydraulic pressure.

In most capillary beds, there is an arterial limb and a venous limb, joined by a capillary plexus. However, in several organs, including the portal system and the kidney, there are additional capillary beds placed "in series" that further complicate the concept of a singular vascular volume, and the relationship between volume and pressure within these beds is complex. Mean arterial pressure, which reflects volume within the arterial limb, is affected by a host of regulatory mechanisms, including vascular tone, the sympathetic nervous system, and the renin-angiotensin-aldosterone system (RAAS). Central venous pressures are typically used to estimate filling of the venous system, but are affected by other factors, particularly right-sided cardiac function.

In addition, the permeability of the capillary endothelium further complicates this issue. Administered isotonic fluid rapidly leaves the intravascular space for the interstitial space at a rate of 60 to 110 mL/min for apparently healthy volunteers, although somewhat less rapidly in ill patients. Thus, whereas volume resuscitation with intravenous saline solution improves arterial hydraulic pressure in certain conditions, such fluid eventually leaks into the interstitial space and gradually reaches equilibrium within the venous and arterial limbs.

The rapid movement between the interstitial and intravascular compartments is perhaps most exquisitely illustrated by ultrafiltration of isotonic fluid that occurs with a typical dialysis session in which 2 to 4 L of fluid are removed. Given that the circulating intravascular blood volume is typically 5 to 10 L, rapid redistribution must occur to avoid circulatory collapse. The plasma refill rate, which describes the rate of fluid movement from the interstitium into the intravascular compartment, is generally considered to be ~1 L/h in reasonably healthy patients, but somewhat less in those with heart failure.

In addition, newer considerations regarding sodium have challenged traditional Guytonian models of sodium homeostasis. It seems that sodium may bind polyanionic proteoglycans and glycosaminoglycans in the interstitium of the skin and serve as a "nonosmotic" reservoir of sodium. These nonosmotic sodium stores may contribute to the development of hypertension or lead to immunomodulation and activation of vascular endothelial growth factor. Thus, conceptually separating the intravascular compartment from the interstitial compartment is a physiologic oversimplification. However, for considerations of isotonic fluid and volume homeostasis in this Core Curriculum, there are only 2 body compartments, the intracellular and extracellular spaces.

Additional Readings

» Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370(15):1412-1421.
» Davison D, Basu RK, Goldstein SL, Chawla LS. Fluid management in adults and children: core curriculum 2014. *Am J Kidney Dis.* 2014;63(4):700-712.
» Mange K, Matsuura D, Cizman D, et al. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med.* 1997;127(9):848-853.
» Rabelink TJ, Rotmans JL. Salt is getting under our skin. *Nephrol Dial Transplant.* 2009;24(11):3282-3283.
» Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol.* 1896;19(4):312-326.

EFFECTIVE CIRCULATING BLOOD VOLUME

The intravascular fluid compartment is composed of 3 different vascular beds: the arteries, capillaries, and veins. Traditionally, arterial volume has received the greatest attention because along with vascular resistance, they are the major determinants of mean arterial pressure, the critical determinant of organ perfusion. Despite the importance of arterial volume, the body has no internal mechanism to accurately measure arterial volume, intravascular volume, or even extracellular volume. Instead, the body relies on surrogate measurements by pressure receptors within the vasculature and flow receptors within the kidney. These sensors trigger a coordinated response to changes in organ perfusion, even if these signals do not match total body volume. Thus, terms such as "intravascular volume" or "effective arterial blood volume" have been championed to describe the vascular (primarily arterial) volume critical for organ perfusion.

CARDIOVASCULAR BARORECEPTORS

High-pressure baroreceptors are stretch-sensitive fibers mainly in the aortic arch and carotid sinuses, near the common carotid artery bifurcation, that measure pressure indirectly based on stretch of this sensitive structure. Afferent fibers from the carotid

sinus baroreceptors connect to the medulla by cranial nerve IX, the glossopharyngeal nerve, whereas extracarotid and cardiac baroreceptors connect to the brainstem by the vagus nerve. Reduction in carotid sinus or aortic arch pressure can stimulate baroreceptors and lead to sympathetic nervous system activation. In addition to systemic effects of sympathetic nervous system activation, the efferent limb of the sympathetic nervous system can lead to a decrease in blood flow to the kidney, decrease in glomerular filtration, increase in renin release, and increases in sodium and water reabsorption throughout the nephron. The efferent nerves from sympathetic chains of the celiac plexus and thoracolumbar chain travel along the renal artery into the hilum of the kidney, divide into smaller bundles, and then follow the vascular tree as it branches into the renal parenchyma. Ultimately, these form discrete neuroeffector junctions. Stimulation by the autonomic nervous system has at least 3 effects in the kidney: at the afferent and efferent arterioles, stimulation leads to an increase in vascular tone; at the modified smooth muscle cells in the afferent arteriole, known as juxtaglomerular (JG) cells, stimulation leads to renin release (see text that follows); and at the proximal and distal tubules and thick ascending limb of the loop of Henle, there is direct activation of sodium reabsorption. Norepinephrine appears to be the major catecholamine at play at these neuroeffector junctions via β_1-adrenergic receptors on JG cells and α_1-adrenergic receptors on arterioles and tubular epithelium. Collectively, high-pressure stretch receptors have an efferent limb that regulates cardiac function, vascular smooth muscle cell contraction, and renal natriuresis.

Normally, small changes in blood volume have little effect on the release of vasopressin, but as the deficit increases and more severe volume depletion is sensed, activation of the sympathetic nervous system can also stimulate the nonosmotic release of vasopressin exponentially. Vasopressin's action on the V1 receptors on the smooth muscles of the vasculature give this hormone its original name, but its actions on the distal nephron in principal cells and cortical collecting duct cells explain this hormone's additional label as the antidiuretic hormone. When vasopressin activates the V2 receptors on the basolateral aspect of the collecting duct cells in the kidney, an intracellular cascade beginning with the activation of cyclic adenosine monophosphate allows aquaporins to cycle to the luminal membrane, which permits reclamation of water from the urinary space and creation of concentrated urine.

JG cells can also function independently from systemic baroreceptors as sensors of kidney perfusion. When pressure to glomeruli is low, these cells release renin from secretory granules with the help of a complex intracellular cascade. When pressure is high, renin release is suppressed.

The opposite arrangement is present in the cardiac atria and large central veins; when low-pressure baroreceptors in these regions sense stretch, there is a reflex inhibition of sympathetic tone. In addition, stretch in the cardiac atria stimulates the release of natriuretic peptides that favor renal sodium excretion. One of the best characterized of these is atrial natriuretic peptide (ANP) released from atrial and ventricular myocytes in response to cardiac wall stretch and other factors. It is activated by the serine protease corin, present on myocytes, and then ANP binds to ANP receptors found in the glomerulus, proximal tubule, thick ascending limb, and collecting duct. It appears that ANP has direct effects on the glomerulus to increase filtration by increasing glomerular permeability. In the proximal tubule, ANP appears to limit sodium reabsorption by antagonizing angiotensin II (Ang II). In the thick ascending limb and collecting duct, ANP limits sodium retention by inhibiting Na^+/K^+-ATPase activity in the former and luminal Na^+ channel in the latter. However, resistance to ANP and other natriuretic peptides is common, and several mechanisms have been postulated, including natriuretic peptide receptor desensitization, corin deficiency, and RAAS activation.

The JG Apparatus

In addition to responding to changes in pressure, the kidneys can also respond to changes in tubular flow. The JG apparatus (JGA) has 3 components: the macula densa, the extraglomerular mesangium, and a vascular element involving terminal parts of the afferent arteriole that holds renin-producing JG cells. The macula densa is composed of a group of 20 to 30 modified epithelial cells in the thick ascending limb of the renal tubule. These cells are equipped with the $Na^+/K^+/2Cl^-$-cotransporter (NKCC2) and are affected by luminal chloride concentration. Because the predominant determinant of chloride delivery is tubular flow, the macula densa cells can respond to changes in tubular flow. In turn, tubular flow is primarily determined by glomerular filtration rate and proximal sodium reclamation. Thus, in settings of decreased kidney perfusion and consequent decreased renal tubular flow, the macula densa is activated. Upon activation, the macula densa stimulates paracrine release of renin from the neighboring cells of the JGA to increase glomerular pressure and therefore maintain filtration by Ang II (see text that follows). In contrast, when tubular flow is increased, an opposing response ensues by several mediators, including adenosine, which appear to lead to vasoconstriction of the afferent arteriole and a decrease in glomerular filtration, seemingly to limit losses. This process of sampling the flow

in the distal nephron to alter glomerular filtration is known as tubuloglomerular feedback.

Additional Reading

» Schrier RW. Decreased effective blood volume in edematous disorders: what does this mean? *J Am Soc Nephrol.* 2007;18(7):2028-2031.

SODIUM HANDLING IN THE NEPHRON

Because sodium is central to the maintenance of normal volume homeostasis, the kidney is designed to excrete only a very small percentage of the filtered load of sodium. This mandate translates into an extraordinary task:

$$[Na^+] \times \text{GFR} = \text{sodium filtered}$$

$$140\ \text{mEq/L} \times 180\ \text{L/d} = 25,200\ \text{mEq/d}$$

Thus, each day, >99% of the filtered sodium is absorbed and the remaining sodium is excreted. To achieve this end, >65% is typically reabsorbed in the proximal tubules, 25% in the loops of Henle, ~6% in the distal convoluted tubules, and the remaining 3% in the collecting ducts. The key sodium transporters in the nephron are shown in Fig 1.

Reabsorption of sodium throughout the nephron is facilitated by an array of luminal sodium transporters along the nephron, which take advantage of low concentrations within the cells maintained by Na^+/K^+-ATPase on the basolateral membrane. In the proximal tubule, the bulk of the sodium is reabsorbed with the help of the sodium/hydrogen exchanger NHE3, which also plays a major role in reabsorption of the filtered load of bicarbonate. Reabsorption in this segment is iso-osmotic, but can be altered by several factors. When the glomerular filtration fraction is increased, peritubular protein concentration is increased, which will favor increased fluid reabsorption in the proximal tubule. This phenomenon is called glomerular tubular balance and highlights when increased filtration is matched with increased reabsorption. NHE3 expression and activity in the proximal tubule can be increased by Ang II. This means that activation of Ang II will lead to a further increase in proximal sodium reabsorption and decrease distal delivery of sodium and water. Because this action is linked to bicarbonate reabsorption,

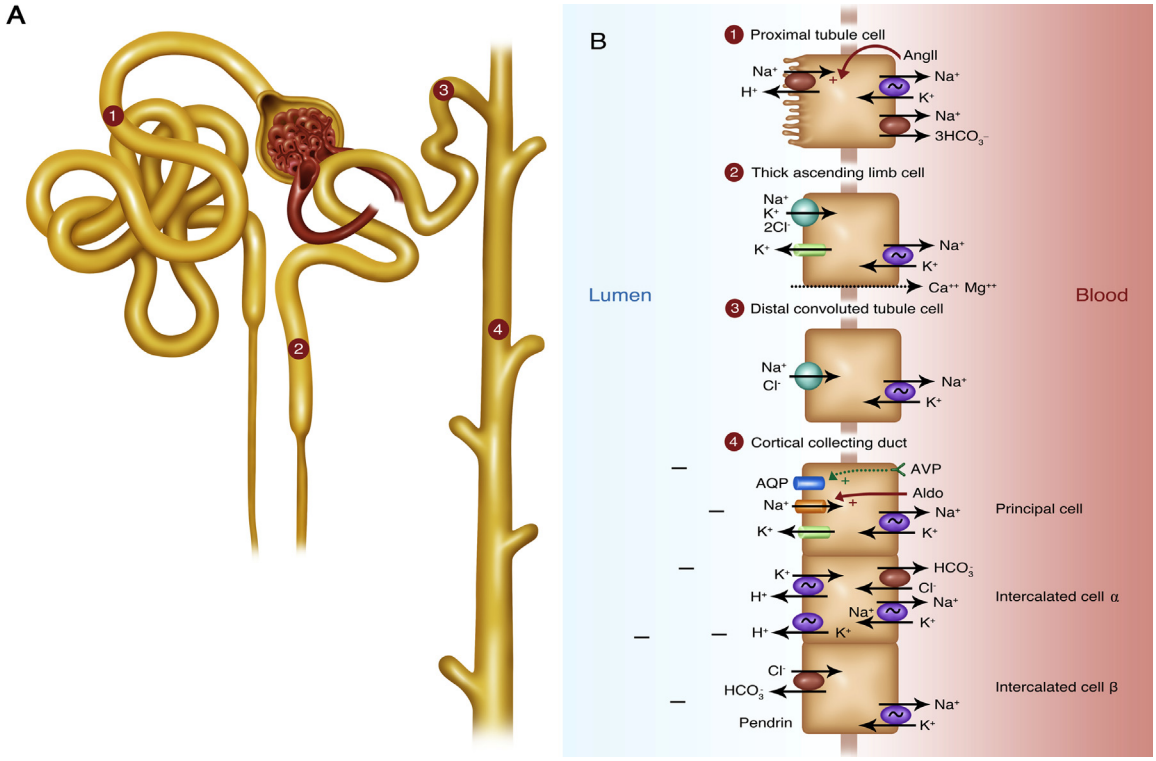

Figure 1. The key transporters for sodium reabsorption along the nephron. (A) The nephron. Note the intimate relationship of the terminal portion of the thick ascending limb of Henle with the afferent arteriole of the glomerulus. (B) Major cell types of each nephron segment. The luminal membrane is on the left, and the basolateral membrane, on the right, with the Na^+/K^+-ATPase on each cell. In the proximal tubule, angiotensin II (AngII) increases sodium reabsorption by the sodium/hydrogen exchanger and likely throughout the nephron. The $Na^+/K^+/2Cl^-$-cotransporter in the thick ascending limb of Henle is the primary transporter in the macula densa to coordinate tubuloglomerular feedback. In the collecting duct, aldosterone (Aldo) activity promotes sodium reabsorption and vasopressin activity promotes reabsorption of water. See text for additional details. Abbreviations: AQP, aquaporin; AVP, arginine vasopressin.

increased sodium reabsorption may affect bicarbonate levels and alter the usual threshold for bicarbonate reabsorption. Other ions also depend on sodium reabsorption in the proximal tubule, including cotransporters for glucose and phosphate, but these contribute relatively little to normal sodium reabsorption because these molecules are present in much smaller concentrations in serum. For example, the normal glucose concentration at 100 mg/dL represents only 5 mmol/L of glucose. Thus, the coupling of glucose transport with sodium results in a relatively small amount of the total filtered load of reabsorbed sodium.

In the loop of Henle, the majority of the sodium is reabsorbed by NKCC2. Sodium, but not water, is reabsorbed in the ascending limb, whereas water is reabsorbed in the thin limb; together, this arrangement creates the concentrated medulla necessary for creation of a concentrated urine later in the nephron. The terminal aspect of the thick ascending limb greets its own glomerulus with the specialized macula densa cells. These cells feature most of the transport properties of the thick ascending limb, but have the ability to generate a signal cascade that can influence glomerular filtration (see previous text). In the distal convoluted tubule, sodium and chloride are reabsorbed without water with the Na^+/Cl^- cotransporter.

In collecting ducts, water can be reabsorbed without sodium under the influence of vasopressin, and sodium can be reabsorbed without water by the epithelial sodium channel (ENaC) under the influence of aldosterone; if both hormones are active, both sodium and water will be retained. However, creation of maximally concentrated urine depends on more than just the presence of vasopressin. Vasopressin achieves its maximal effect on collecting ducts in the presence of a concentrated medulla. Patients who habitually have very little solute intake or those who have significant pathology of the medulla, such as those with sickle cell anemia, sickling in the renal medulla, and resultant papillary necrosis, may not be able to make urine that is maximally concentrated and instead can achieve only isosthenuria.

Additional Readings

» Roy A, Al-bataineh MM, Pastor-Soler NM. Collecting duct intercalated cell function and regulation. *Clin J Am Soc Nephrol.* 2015;10(2):305-324.

» Theilig F, Wu Q. ANP-induced signaling cascade and its implications in renal pathophysiology. *Am J Physiol Renal Physiol.* 2015;308(10):F1047-F1055.

DISORDERS OF EFFECTIVE CIRCULATING VOLUME

Left and Right Ventricular Dysfunction

Cardiac output is an important determinant of organ perfusion and hence of effective circulating volume. An impaired left ventricle, as might occur with myocardial ischemia, leads to a decrease in effective perfusion of central and renal baroreceptors, sympathetic nervous system activation, and RAAS activation. Sodium retention by the kidney and isotonic volume expansion will increase end-diastolic volume and may shift the Starling curve sufficiently to improve cardiac function. As effective circulating volume improves, improved baroreceptor perfusion normalizes sodium avidity. However, if cardiac function does not improve with an increase in end-diastolic volume, the resultant higher filling pressures will lead to an increase in pulmonary filling pressures, which may lead to pulmonary hypertension and right ventricular failure. Unfortunately, fluid retention may not improve cardiac function or organ perfusion, and effective circulating volume may remain reduced despite marked extracellular volume overload.

Although left ventricular function has received most of the attention as a determinant of effective circulating volume, increasing data suggest that the right ventricle is of independent importance. The right ventricle is morphologically different than its larger thicker counterpart. Unlike the higher systemic pressures facing the left ventricle, the right ventricle pumps into the low pressure of the pulmonary vasculature and is consequently less muscular and contractile. In scenarios of increasing pulmonary vasculature resistance, as with sleep apnea, pulmonary disease, or primary pulmonary hypertension, the right ventricle's thin walls fail to compensate, instead dilating into the pericardial sac, causing both paradoxical movement of the septa into the left ventricle, decreased left ventricular function, and primary right ventricular dysfunction. This is manifested as elevated central venous pressure and peripheral edema.

More recently, additional disorders associated with right ventricular dysfunction have been shown to lead to decreased effective circulating volume and consequently lead to sodium retention. Hypoxia, as commonly occurs in primary pulmonary disease, has been associated with renal sodium avidity. Obesity, a common cause of pulmonary hypertension, and cor pulmonale are both sodium-avid states and are associated with low urinary sodium excretion, greater need for diuretics, and higher risk for kidney injury. Animal models of right ventricular function through graded valvular damage display a reduction in renal blood flow and intense sodium retention. In addition, clinical data suggest that right ventricular function and central venous pressures are important independent determinants of kidney function, presumably through either direct venous congestion or an effect on cardiac output. Further research on this important physiologic axis is needed.

Pinpointing the ideal volume status in patients with either left or right heart failure is one of the most challenging and complex aspects of nephrology and leads to significant disagreement among consultant services in the care of patients. The complex physiology of fluid retention in patients with heart failure is illustrated in Fig 2.

Decreased Systemic Vascular Resistance

A decrease in systemic vascular resistance can lead to a decline in effective circulating volume. In normal pregnancy, systemic vasodilation is matched with volume expansion; a variety of mediators, including progesterone, prostacyclins, and relaxin, appear to contribute to the observed peripheral vasodilation. Although there is marked upregulation in the RAAS, there is insensitivity to Ang II, which may also contribute to the vasodilated state. In cirrhosis, vasodilation of the splanchnic and systemic circulation has been attributed to an increase in cytokines and vasodilating mediators, as well as splanchnic pooling as a result of the higher resistance within the cirrhotic liver. Together, these lead to a compensatory increase in the RAAS and nonosmotic stimulation of vasopressin, which leads to sodium and water retention. Profound vasodilation in sepsis along with endovascular injury can also lead to a decline in kidney perfusion.

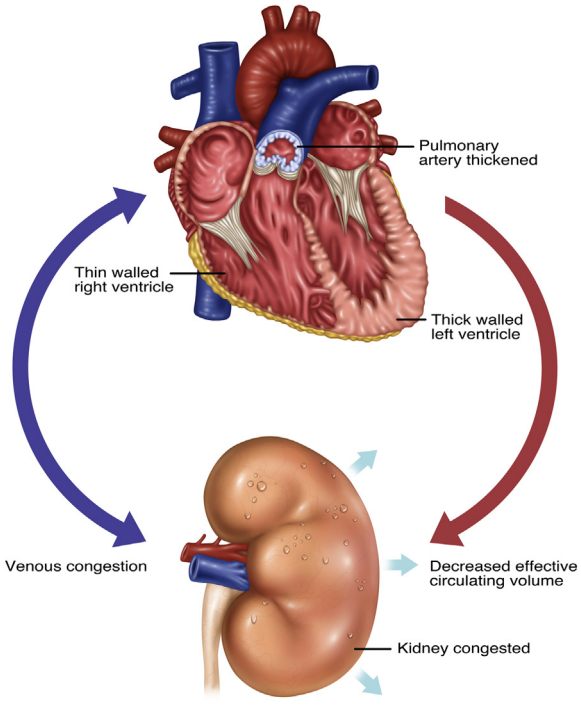

Figure 2. In heart failure, both the left and right ventricle can independently impair glomerular filtration and cause sodium avidity, likely due to important structural differences between the 2 chambers. The thin-walled right ventricle is ill equipped to deal with pressure afterload and instead dilates. This further impairs cardiac output, as well as causing increased venous congestion, which ultimately leads to renal venous congestion. The thick-walled left ventricle, although capable of responding to changes in afterload, does so at the expense of higher filling pressures, which can lead to pulmonary congestion and decreased circulating effective arterial volume.

Although nephrotic syndrome features edema and low serum albumin levels, just as with cirrhosis of the liver, the mechanism of extracellular volume expansion is entirely different. Historically, it had been postulated that the edema seen with nephrosis developed secondary to the low serum albumin level and the movement of intravascular fluid to the interstitium with secondary activation of the RAAS from effective volume depletion (the "underfill" theory). However, with the exception of children who have massive proteinuria from minimal change disease, RAAS activation is typically not observed in nephrotic syndrome. Instead, it appears that the sodium-avid state is related to a direct effect of proteinuria on renal tubular cells (the overfill theory). The nephrotic urine can induce ENaC activity in cultured collecting duct cells and, in an experimental model with unilateral proteinuria, sodium retention is observed only in the distal nephron of the affected side.

Extracellular Volume Depletion

Hemorrhage is essentially the only circumstance in which the volume lost is identical to extracellular fluid with respect to both sodium concentration and other serum components. Losses from the skin, gastrointestinal tract, or kidney can result in extracellular volume depletion in conjunction with disorders of osmolality, acid-base, and potassium homeostasis. It is worth noting that all extrarenal fluids lost from the body are either isotonic (blood) or hypotonic (sweat and gastrointestinal losses). Skin losses can result from burns or sweat, though losses from burns represent a special circumstance in which the integrity of blood vessel walls in the peripheral circulation may be altered such that there can be marked loss of both fluid and proteins into the interstitium.

Normal perspiration facilitates heat dissipation by evaporation in hyperthermic conditions and in nonthermal conditions such as exercise. Secretory cells from these glands release an isotonic precursor fluid that becomes hypotonic as sodium and chloride are reabsorbed along the ducts to the skin surface. This is influenced by the sweat rate; if the rate is slower, more sodium and chloride are reabsorbed, whereas if the rate is more rapid, there is less time for absorption. Thus, sodium concentration in sweat is highly variable and may range from as low as 5 mmol/L to as high as 90 mmol/L, and volume losses may be as great as 1 to 3.5 L/h depending on the temperature and physical exertion level. In contrast, normal insensible losses from skin are usually

relatively small and in the range of 400 mL daily and respiratory losses are typically ~500 mL (usually more in ventilated patients). These losses are offset by roughly 500 cc generated from cellular metabolism.

Losses from the gastrointestinal tract can be considerable. These losses can be proportional to intake or considerably greater in the setting of gastrointestinal epithelial lining dysfunction or a disruption in normal flow through the gastrointestinal tract. For example, each salivary gland can produce up to 1 L a day. Gastric juice typically includes up to 2 L, pancreatic and biliary fluids are usually higher, and the small intestines contribute ~1 L as well. Thus, there is the potential for up to 9 L of fluid lost each day by the gastrointestinal tract. Fortunately, the bulk of this fluid is reabsorbed in the small intestines and colon, the final step in the formation of solid feces. Electrolyte contents of the intraluminal fluid of these segments of the bowel vary physiologically based on the local transporters of gastrointestinal epithelial cells and can also vary based on dietary and pharmacologic interventions. For example, stomach secretions, when maximally stimulated, can approach pH of 1. With use of a proton pump inhibitor, pH may be closer to 7 and the gastric secretion flow rate may decrease considerably.

Renal losses do not occur physiologically, but may be sizable in tubular disorders that are inherited or induced pharmacologically. Individuals with defects in tubular function, such as proximal renal tubular acidosis, Bartter syndrome, or Gitelman disorder, all have considerable urinary sodium losses that can lead to volume depletion and chronic hypertrophy of the JGA. Pharmacologic therapy can also lead to urinary sodium losses. Examples include the use of diuretics directed at any site or excretion of an osmotic load as with mannitol infusion, glycosuria from poorly controlled diabetes mellitus or pharmacologic use of the sodium glucose transport inhibitors, and urea excretion after release of an acute urinary tract obstruction (though osmotic diuresis from urea excretion may be compounded by volume overload that developed before relief of the obstruction and tubular dysfunction if the obstruction was chronic). A range of electrolyte losses typically accompanies the losses from osmotic diuresis, and electrolyte abnormalities from diuretics depend on the site of action of each medication.

Extracellular Volume Expansion

Volume expansion from increased sodium ingestion or intravenous fluid infusion can initiate a program of responses that are designed to induce saluresis. These responses have also been studied using "head-out-of-water immersion" experiments because this model favors movement of fluid from the peripheral to the central circulation. In the setting of normal kidney function, effective circulating volume expansion is typically short lived.

The kidney can also be the cause of extracellular volume expansion. Activation of ENaC either from Liddle syndrome, in which ENaC is constitutively active, or from aldosterone or apparent aldosterone excess, leads to sodium retention, hypertension, and edema. These scenarios are usually resistant to the "pressure natriuresis" that occurs in the setting of normal kidney function and the ability to suppress the RAAS.

Additional Readings

» F Gnanaraj J, von Haehling S, Anker SD, Raj DS, Radhakrishnan J. The relevance of congestion in the cardio-renal syndrome. *Kidney Int.* 2013;83(3):384-391.
» Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol.* 2006;1(5):1066-1079.

RENAL RESPONSE TO VOLUME DEPLETION

Angiotensin

Secretory granules from JG cells release the protease renin. Renin can convert angiotensinogen to angiotensin I (Ang I), and then Ang I is converted to Ang II by angiotensin-converting enzyme. Ang II is most often recognized for its role in stimulating aldosterone by the Ang II receptor 1, but Ang II is a hormone of considerable importance in its own right. Ang II is one of the most potent vasoconstrictive substances in the body; in addition, Ang II has a direct effect on sodium reabsorption throughout the nephron and particularly in the proximal tubule by increasing NHE3 on the luminal membrane. This results in an increase in reabsorption of sodium and ultimately bicarbonate, even if metabolic alkalosis is present, and explains the "maintenance phase" or persistence of metabolic alkalosis in volume or chloride depletion.

Although loop diuretics can induce significant renal losses and also block the NKCC on the macula densa, limiting tubuloglomerular feedback, a renal response is still possible. The ensuing volume depletion can still activate the RAAS and lead to an increase in proximal tubule sodium reabsorption, which will limit distal delivery and further losses.

Role of Aldosterone in the Distal Nephron

When Ang II simulates aldosterone release from zona glomerulosa cells of the adrenal glands, aldosterone binds to the mineralocorticoid receptor in the distal nephron cells and acts as a transcription factor to increase expression of ENaC and the renal outer medulla K^+ channel (ROMK). In addition, aldosterone leads to ENaC deployment to the luminal

membrane from intracellular stores. When ENaC is active, sodium reabsorption by this highly selective channel is increased. This movement of sodium from the filtrate into the cell down its chemical gradient leads to a lumen-negative transepithelial membrane potential difference, which favors potassium movement down its electrochemical gradient out of the cell by ROMK. Neighboring intercalated cells are also affected by aldosterone; when the mineralocorticoid receptors in these cells are not phosphorylated, aldosterone stimulates H^+-ATPase. When Ang II is present, the mineralocorticoid receptors in these cells are not phosphorylated and aldosterone stimulates the luminal H^+-ATPase. When Ang II is absent, this does not occur.

This molecular pathway provides a complementary detail to the previous understanding of the "aldosterone paradox." The paradox is aldosterone's apparent disparate roles: aldosterone appears to be a sodium-retaining hormone in the setting of sensed volume depletion and a potassium-secreting hormone in the setting of hyperkalemia. This phenomenon has historically been explained by the difference in distal sodium delivery in the 2 settings. When there is sensed volume depletion and the RAAS is activated, Ang II−stimulated sodium reabsorption in the proximal nephron limits distal delivery and therefore limits potassium secretion, whereas when aldosterone is stimulated directly by hyperkalemia without Ang II, distal delivery is maintained and potassium can be secreted in tandem with sodium retention.

In addition, the observation that hypoaldosteronism does not predictably lead to hypotension emphasizes the fact that complementary pathways exist to defend volume homeostasis. Hypoaldosteronism can be inherited as an isolated defect in aldosterone synthase or acquired as part of primary adrenal insufficiency (Addison disease). In these scenarios, patients have sodium wasting, volume depletion, and hyperkalemia. In contrast, in the clinical disorder hyporeninemic hypoaldosteronism, hypotension is not a feature. This discrepancy highlights the redundant pathways available to maintain volume outside the RAAS.

The Role of Chloride in Disorders of Volume

The role that chloride plays in volume homeostasis is less clear. Historically, sodium has been considered the main factor in volume homeostasis. Volume depletion and volume excess are inextricably linked to sodium depletion and excess. The terms salt and sodium are often used interchangeably. However, there is ongoing interest in the role of chloride. For example, metabolic alkalosis in the setting of volume depletion is known to be "chloride responsive," and the alkalosis can be mitigated by the addition of chloride without sodium. In several rat models of salt-sensitive hypertension, selective sodium loading without chloride fails to produce hypertension. This has been observed clinically because supplementation with sodium bicarbonate in the treatment of patients with chronic kidney disease and metabolic acidosis does not worsen hypertension and edema, whereas high sodium chloride intake in those with chronic kidney disease often does. Furthermore, the chemoreceptor macula densa cells of the JGA detect chloride flow in the distal nephron, not sodium. Defects in the pendrin transporter SLC26A4 (solute carrier family 26, member 4), a chloride/bicarbonate antiporter on the luminal membrane of type B intercalated cells, limit chloride reabsorption and may confer resistance to hypertension.

EFFECTIVE CIRCULATING VOLUME DEPLETION AND CLINICAL INDEXES

In the setting of volume depletion, the kidney can limit output considerably to prevent further losses as outlined above. A volume of just 500 mL is typically sufficient to excrete daily waste in a healthy individual. When volume depletion persists, kidney function may appear to decline based on further decrement in urine output and increase in serum creatinine level. This normal response to a low effective volume is called prerenal azotemia, a term that reflects the fact that the problem does not lie in the kidney and serum urea nitrogen level may be elevated out of proportion to creatinine level.

In the setting of extracellular volume depletion or a scenario in which the kidneys sense low volume such as congestive heart failure or cirrhosis, the kidneys are sodium avid. Urine sodium excretion is typically well $<$20 mEq/L, except when urine is extremely concentrated. In this case, the absolute value for urinary sodium excretion may not be $<$20 mEq/L, but fractional excretion of urinary sodium is still low and typically $<$1%. Urine creatinine excretion is likely to be high in this scenario so that the urine to plasma creatinine ratio is typically $>$20. Urine osmolality will also be high, though the absolute value depends on additional factors: individuals on a long-term low-solute diet may only be able to concentrate urine to osmolality of $\sim$300 mOsm/kg, whereas young healthy individuals may be able to concentrate urine to nearly 1,000 mOsm/kg. Because diuretics can increase urine sodium excretion, when diuretics are in use, fractional excretion of urea can be assessed. In prerenal azotemia, with or without diuretics, this value would be expected to be $<$35%. A urinary sodium to potassium ratio $<$ 0.25 has also been touted as an indicator of aldosterone effect, but this appears to have limited clinical utility. The increase in creatinine and decrease in urine output that accompanies

the kidney's ability to limit losses in the setting of volume depletion, as well as losses with kidney injury and decreased function, is called acute kidney injury, but is actually a remarkable adaptation and an "acute kidney success."

Additional Readings

» Friis UG, Madsen K, Stubbe J, et al. Regulation of renin secretion by renal juxtaglomerular cells. *Pflugers Arch.* 2013;465(1):25-37.
» Johns EJ, Kopp UC, DiBona GF. Neural control of renal function. *Compr Physiol.* 2011;1(2):731-767.
» Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical renin-angiotensin system in kidney physiology. *Compr Physiol.* 2014;4(3):1201-1228.
» Thurau K, Boylan JW. Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med.* 1976;61(3):308-315.

TREATMENT OF DISORDERS OF VOLUME

Treatment of volume depletion is directed at addressing the underlying disorder and restoring normal perfusion to vital organs. Extracellular volume loss is the most straightforward; normal saline solution (0.9% NaCl) is traditionally used to replace extracellular fluid loss and restore normal hemodynamics, though there is increasing interest in balanced solutions that have lower and more physiologic chloride concentrations, along with buffer such as lactate or acetate, which can be metabolized to bicarbonate.

When there is discordance between extracellular volume and effective circulating volume, treatment is more complex. Congestive heart failure and liver disease are characterized by sodium-avid states due to long-term activation of the sympathetic nervous system and RAAS. Not surprisingly, treatment with intravenous fluids is likely to lead to further volume retention rather than promoting an improvement in effective circulating volume, kidney function, and the desired subsequent diuresis. Thus, whereas traditional paradigms have focused on expanding the intravascular volume to maximize kidney function, a more comprehensive physiologic approach acknowledges that isotonic fluid dynamically distributes across the extracellular space, and that the volume within both the arterial and venous limbs might have important clinical consequences. In the case of cardiac dysfunction, therapy is directed at improving cardiac hemodynamics. This is achieved with a multitargeted approach, which may include several strategies: inotropic support, diuretics, RAAS blockade, and, more recently, therapies targeted at neprilysin, the enzyme that degrades ANP. In addition, therapies that affect renalase, the enzyme that metabolizes catecholamines, is likely to be another treatment avenue in the future. In hepatic failure, treatment is directed at decreasing splanchnic bed vasodilation with somatostatin analogues and increasing blood pressure with alpha-antagonists.

Regardless of the cause of effective volume depletion, when perfusion is restored, the kidneys can address the gamut of electrolyte abnormalities and excrete excess water, potassium, base, or acid.

Additional Readings

» Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. *J Am Coll Cardiol.* 2015;65:1029-1041.
» Desir GV, Peixoto AJ. Renalase in hypertension and kidney disease. *Nephrol Dial Transplant.* 2014;29:22-28.

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