Chapter 41: Edema

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PLASMA AND INTERSTITIAL FLUID EXCHANGE

Approximately two-thirds of total body water is intracellular and one-third is extracellular. One-fourth of the latter is in the plasma, and the remainder comprises the interstitial fluid. Edema represents an excess of interstitial fluid that has become evident clinically.

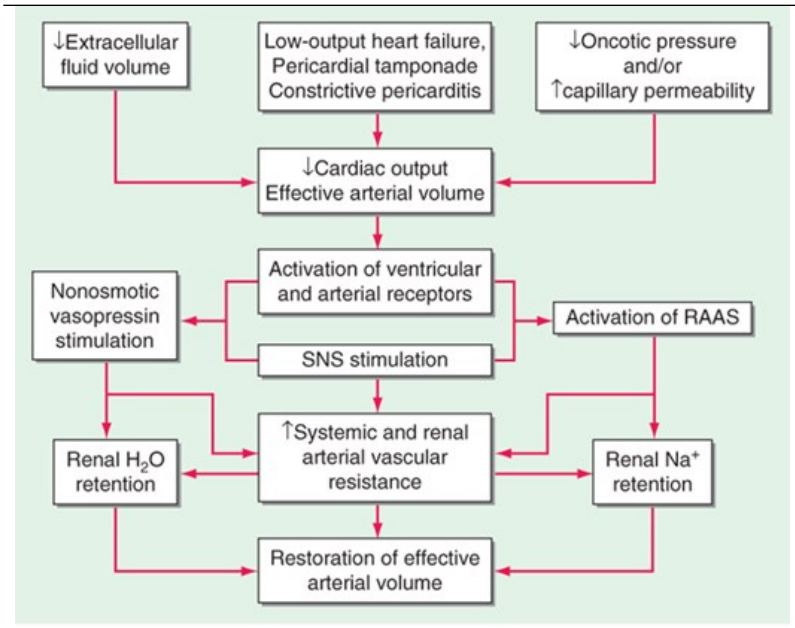
There is constant interchange of fluid between the two compartments of the extracellular fluid. The hydrostatic pressure within the capillaries and the colloid oncotic pressure in the interstitial fluid promote the movement of water and diffusible solutes from plasma to the interstitium. This movement is most prominent at the arterial origin of the capillary and falls progressively with the decline in intracapillary pressure and the rise in oncotic pressure toward the venular end. Fluid is returned from the interstitial space into the vascular system largely through the lymphatic system. These interchanges of fluids are normally balanced so that the volumes of the intravascular and interstitial compartments remain constant. However, a net movement of fluid from the intravascular to the interstitial spaces takes place and may be responsible for the development of edema under the following conditions: (1) an increase in intracapillary hydrostatic pressure; (2) inadequate lymphatic drainage; (3) reductions in the oncotic pressure in the plasma; (4) damage to the capillary endothelial barrier; and (5) increases in the oncotic pressure in the interstitial space.

REDUCTION OF EFFECTIVE ARTERIAL VOLUME

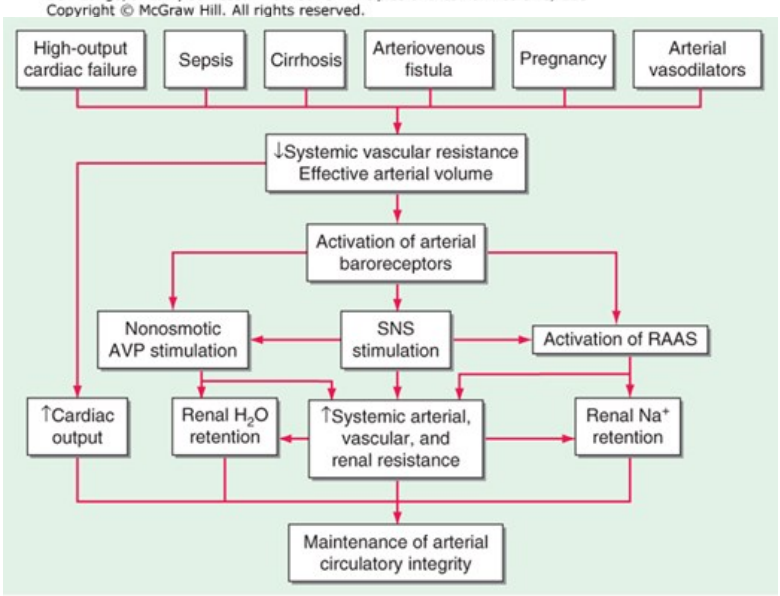
In many forms of edema, the effective arterial blood volume, a parameter that represents the filling of the arterial tree and that effectively perfuses the tissues, is reduced. Underfilling of the arterial tree may be caused by a reduction of cardiac output and/or systemic vascular resistance, by the pooling of blood in the splanchnic veins (as in cirrhosis), and by hypoalbuminemia **(Fig. 41-1A)**. As a consequence of this underfilling, a series of physiologic responses designed to restore the effective arterial volume to normal are set into motion. A key element of these responses is the renal retention of sodium and, therefore, water, thereby restoring effective arterial volume, but sometimes also leading to the development or intensification of edema.

FIGURE 41-1

Clinical conditions in which a decrease in cardiac output (*A*) and systemic vascular resistance (*B*) cause arterial underfilling with resulting neurohumoral activation and renal sodium and water retention. In addition to activating the neurohumoral axis, adrenergic stimulation causes renal vasoconstriction and enhances sodium and fluid transport by the proximal tubule epithelium. AVP, arginine vasopressin; RAAS, renin-angiotensin aldosterone system; SNS, sympathetic nervous system. *(From Annals of Internal Medicine, RW Schrier: Body fluid volume regulation in health and disease: A unifying hypothesis. 113(2):155-159, 1990. Copyright © 1990, American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.)*



A



B

RENAL FACTORS AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The diminished renal blood flow characteristic of states in which the effective arterial blood volume is reduced is translated by the renal juxtaglomerular cells (specialized myoepithelial cells surrounding the afferent arteriole) into a signal for increased renin release. Renin is an enzyme with a molecular mass of about 40,000 Da that acts on its substrate, angiotensinogen, an α_2-globulin synthesized by the liver, to release angiotensin I, a decapeptide, which in turn is converted to angiotensin II (AII), an octapeptide. AII has generalized vasoconstrictor properties, particularly on the renal efferent arterioles. This action reduces the hydrostatic pressure in the peritubular capillaries, whereas the increased filtration fraction raises the colloid osmotic pressure in these vessels, thereby enhancing salt and water reabsorption in the proximal tubule as well as in the ascending limb of the loop of Henle.

The renin-angiotensin-aldosterone system (RAAS) operates as both a hormonal and paracrine system. Its activation causes sodium and water retention and thereby contributes to edema formation. Blockade of the conversion of angiotensin I to AII and blockade of the AII receptors enhance sodium and water excretion and reduce many forms of edema. AII that enters the systemic circulation stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone in turn enhances sodium reabsorption (and potassium excretion) by the collecting tubule, further favoring edema formation. Blockade of the action of aldosterone by spironolactone or eplerenone (aldosterone antagonists) or by amiloride (a blocker of epithelial sodium channels) often induces a moderate diuresis in edematous states.

ARGININE VASOPRESSIN

(See also Chap. 381) The secretion of arginine vasopressin (AVP) by the posterior pituitary gland occurs in response to increased intracellular osmolar concentration; by stimulating V_2 receptors, AVP increases the reabsorption of free water in the distal tubules and collecting ducts of the kidneys, thereby increasing total-body water. Circulating AVP is elevated in many patients with heart failure secondary to a nonosmotic stimulus associated with decreased effective arterial volume and reduced compliance of the left atrium. Such patients fail to show the normal reduction of AVP with a reduction of osmolality, contributing to edema formation and hyponatremia.

ENDOTHELIN-1

This potent peptide vasoconstrictor is released by endothelial cells. Its concentration in the plasma is elevated in patients with severe heart failure and contributes to renal vasoconstriction, sodium retention, and edema.

NATRIURETIC PEPTIDES

Atrial distention causes release into the circulation of atrial natriuretic peptide (ANP), a polypeptide. A high-molecular-weight precursor of ANP is stored in secretory granules within atrial myocytes. A closely related natriuretic peptide (pre-prohormone brain natriuretic peptide [BNP]) is stored primarily in ventricular myocytes and is released when ventricular diastolic pressure rises. Released ANP and BNP (which is derived from its precursor) bind to the natriuretic receptor-A, which causes (1) excretion of sodium and water by augmenting glomerular filtration rate, inhibiting sodium reabsorption in the proximal tubule, and inhibiting release of renin and aldosterone; and (2) dilation of arterioles and venules by antagonizing the vasoconstrictor actions of AII, AVP, and sympathetic stimulation. Thus, elevated levels of natriuretic peptides have the capacity to oppose sodium retention in hypervolemic and edematous states.

Although circulating levels of ANP and BNP are elevated in heart failure and in cirrhosis with ascites, these natriuretic peptides are not sufficiently potent to prevent edema formation. Indeed, in edematous states, resistance to the actions of natriuretic peptides may be increased, further reducing their effectiveness.

Further discussion of the control of sodium and water balance is found in **Chap. S1**.

CLINICAL CAUSES OF EDEMA

A weight gain of several kilograms usually precedes overt manifestations of generalized edema. *Anasarca* refers to gross, generalized edema. *Ascites* **(Chap. 50)** and *hydrothorax* refer to accumulation of excess fluid in the peritoneal and pleural cavities, respectively, and are considered special forms of edema.

Edema is recognized by the persistence of an indentation of the skin after pressure known as “pitting” edema. In its more subtle form, edema may be detected by noting that after the stethoscope is removed from the chest wall, the rim of the bell leaves an indentation on the skin of the chest for a few minutes. Edema may be present when the ring on a finger fits more snugly than in the past or when a patient complains of difficulty putting on shoes, particularly in the evening. Edema may also be recognized by puffiness of the face, which is most readily apparent in the periorbital areas owing to relative tissue laxity.

GENERALIZED EDEMA

The differences among the major causes of generalized edema are shown in **Table 41-1**. Cardiac, renal, hepatic, or nutritional disorders are responsible for a large majority of patients with generalized edema. Consequently, the differential diagnosis of generalized edema should be directed

toward identifying or excluding these several conditions.

TABLE 41-1

Principal Causes of Generalized Edema: History, Physical Examination, and Laboratory Findings

ORGAN SYSTEM	HISTORY	PHYSICAL EXAMINATION	LABORATORY FINDINGS
Cardiac	Dyspnea with exertion prominent—often associated with orthopnea—or paroxysmal nocturnal dyspnea	Elevated jugular venous pressure, ventricular (S_3) gallop; occasionally with displaced or dyskinetic apical pulse; peripheral cyanosis, cool extremities, small pulse pressure when severe	Elevated urea nitrogen-to-creatinine ratio common; serum sodium often diminished; elevated natriuretic peptides
Hepatic	Dyspnea uncommon, except if associated with significant degree of ascites; most often a history of ethanol abuse	Frequently associated with ascites; jugular venous pressure normal or low; blood pressure lower than in renal or cardiac disease; one or more additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren's contracture, spider angiomata, male gynecomastia; asterixis and other signs of encephalopathy) may be present	If severe, reductions in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); liver enzymes elevated, depending on the cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; macrocytosis from folate deficiency
Renal (CRF)	Usually chronic: may be associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs, or myoclonus; dyspnea can be present, but generally less prominent than in heart failure	Elevated blood pressure; hypertensive retinopathy; nitrogenous fetor; pericardial friction rub in advanced cases with uremia	Elevation of serum creatinine and cystatin C; albuminuria; hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)
Renal (NS)	Childhood diabetes mellitus; plasma cell dyscrasias	Periorbital edema; hypertension	Proteinuria (≥3.5 g/d); hypoalbuminemia; hypercholesterolemia; microscopic hematuria

Abbreviations: CRF, chronic renal failure; NS, nephrotic syndrome.

Source: Reproduced with permission from GM Chertow, in E Braunwald, L Goldman (eds): Approach to the patient with edema, in Primary Cardiology, 2nd ed. Philadelphia, Saunders, 2003.

Heart Failure

(See also Chap. 257) In heart failure, the impaired systolic emptying of the ventricle(s) and/or the impairment of ventricular relaxation promotes an accumulation of blood in the venous circulation at the expense of the effective arterial volume. In addition, the activation of the sympathetic nervous system and the RAAS (see above) acts in concert to cause renal vasoconstriction and reduction of glomerular filtration and salt and water retention. Sodium and water retention continue, and the increment in blood volume accumulates in the venous circulation, raising venous and intracapillary pressure and resulting in edema (Fig. 41-1).

The presence of overt cardiac disease, as manifested by cardiac enlargement and/or ventricular hypertrophy, together with clinical evidence of cardiac failure, such as dyspnea, basilar rales, venous distention, and hepatomegaly, usually indicates that edema results from heart failure. Noninvasive tests

such as electrocardiography, echocardiography, and measurements of BNP (or N-terminal proBNP [NT-proBNP]) are helpful in establishing the diagnosis of heart disease. The edema of heart failure typically occurs in the dependent portions of the body.

Edema of Renal Disease

(See also Chap. 314) The edema that occurs during the acute phase of glomerulonephritis is characteristically associated with hematuria, proteinuria, and hypertension. In most instances, the edema results from primary retention of sodium and water by the kidneys owing to renal dysfunction. This state differs from most forms of heart failure in that it is characterized by a normal (or sometimes even increased) cardiac output. Patients with *chronic* renal failure may also develop edema due to primary renal retention of sodium and water.

Nephrotic Syndrome and Other Hypoalbuminemic States

The primary alteration in the nephrotic syndrome is a diminished colloid oncotic pressure due to losses of large quantities (≥3.5 g/d) of protein into the urine and hypoalbuminemia (<3.0 g/dL). As a result of the reduced colloid osmotic pressure, the sodium and water that are retained cannot be confined within the vascular compartment, and total and effective arterial blood volumes decline. This process initiates the edema-forming sequence of events described above, including activation of the RAAS. The nephrotic syndrome may occur during the course of a variety of kidney diseases, including glomerulonephritis, diabetic glomerulosclerosis, and hypersensitivity reactions. The edema is diffuse, symmetric, and most prominent in the dependent areas; periorbital edema is most prominent in the morning.

Hepatic Cirrhosis

(See also Chap. 344) This condition is characterized, in part, by hepatic venous outflow obstruction, which in turn expands the splanchnic blood volume, and hepatic lymph formation. Intrahepatic hypertension acts as a stimulus for renal sodium retention and causes a reduction of effective arterial blood volume. These alterations are frequently complicated by hypoalbuminemia secondary to reduced hepatic synthesis, as well as peripheral arterial vasodilation. These effects reduce the effective arterial blood volume, leading to activation of the sodium- and water-retaining mechanisms described above **(Fig. 41-1B)**. The concentration of circulating aldosterone often is elevated by the failure of the liver to metabolize this hormone. Initially, the excess interstitial fluid is localized preferentially proximal (upstream) to the congested portal venous system, causing ascites **(Chap. 50)**. In later stages, particularly when there is severe hypoalbuminemia, peripheral edema may develop. A sizable accumulation of ascitic fluid may increase intraabdominal pressure and impede venous return from the lower extremities and contribute to the accumulation of the edema.

Drug-Induced Edema

A large number of widely used drugs can cause edema **(Table 41-2)**. Mechanisms include renal vasoconstriction (nonsteroidal anti-inflammatory drugs and cyclosporine), arteriolar dilation (vasodilators), augmented renal sodium reabsorption (steroid hormones), and capillary damage.

TABLE 41-2

Drugs Associated with Edema Formation

Nonsteroidal anti-inflammatory drugs
Antihypertensive agents
Direct arterial/arteriolar vasodilators
Hydralazine
Clonidine
Methyldopa
Guanethidine
Minoxidil
Calcium channel antagonists
α-Adrenergic antagonists
Thiazolidinediones
Steroid hormones
Glucocorticoids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
Interleukin 2
OKT3 monoclonal antibody

Source: Reproduced with permission from GM Chertow, in E Braunwald, L Goldman (eds): Approach to the patient with edema, in Primary Cardiology, 2nd ed. Philadelphia, Saunders, 2003.

Edema of Nutritional Origin

A diet grossly deficient in calories and particularly in protein over a prolonged period may produce hypoproteinemia and edema. The latter may be intensified by the development of beriberi heart disease, which also is of nutritional origin, in which multiple peripheral arteriovenous fistulae result in reduced effective systemic perfusion and effective arterial blood volume, thereby enhancing edema formation **(Chap. 333)** (Fig. 41-1B). Edema develops or becomes intensified when famished subjects are first provided with an adequate diet. The ingestion of more food may increase the quantity of sodium ingested, which is then retained along with water. So-called refeeding edema also may be linked to increased release of insulin, which directly increases tubular sodium reabsorption. In addition to hypoalbuminemia, hypokalemia and caloric deficits may be involved in the edema of starvation.

LOCALIZED EDEMA

In thrombophlebitis, varicose veins, and primary venous valve failure, the hydrostatic pressure in the capillary bed upstream (proximal) of the obstruction increases so that an abnormal quantity of fluid is transferred from the vascular to the interstitial space, which may give rise to localized edema. The latter may also occur in lymphatic obstruction caused by chronic lymphangitis, resection of regional lymph nodes, filariasis, and genetic (frequently called primary) lymphedema. The latter is particularly intractable because restriction of lymphatic flow results in both an increase in intracapillary pressure and increased protein concentration in the interstitial fluid, which act in concert to aggravate fluid retention.

Other Causes of Edema

These causes include hypothyroidism (myxedema) due to deposition of hyaluronic acid; hyperthyroidism (pretibial myxedema secondary to Graves' disease), in which edema is typically nonpitting and, in Graves' disease, exogenous hypercortisolism; pregnancy; and administration of estrogens and vasodilators, particularly dihydropyridines such as nifedipine.

DISTRIBUTION OF EDEMA

The distribution of edema is an important guide to its cause. Edema associated with heart failure tends to be more extensive in the legs and to be accentuated in the evening, a feature also determined largely by posture. When patients with heart failure are confined to bed, edema may be most prominent in the presacral region.

Edema resulting from hypoproteinemia, as occurs in the nephrotic syndrome, characteristically is generalized, but it is especially evident in the very soft tissues of the eyelids and face and tends to be most pronounced in the morning owing to the recumbent posture assumed during the night. Less common causes of facial edema include trichinosis, allergic reactions, and myxedema. Edema limited to one leg or to one or both arms is usually the result of venous and/or lymphatic obstruction. Unilateral paralysis reduces lymphatic and venous drainage on the affected side and may also be responsible for unilateral edema. In patients with obstruction of the superior vena cava, edema is confined to the face, neck, and upper extremities in which the venous pressure is elevated compared with that in the lower extremities.

APPROACH TO THE PATIENT WITH EDEMA

An important first question is whether the edema is localized or generalized. If it is localized, the local phenomena that may be responsible should be identified. If the edema is generalized, one should determine if there is serious hypoalbuminemia, e.g., serum albumin <3.0 g/dL. If so, the history, physical examination, urinalysis, and other laboratory data will help evaluate the question of cirrhosis, severe malnutrition, or the nephrotic syndrome as the underlying disorder. If hypoalbuminemia is not present, it should be determined if there is evidence of heart failure severe enough to promote generalized edema. Finally, it should be ascertained as to whether or not the patient has an adequate urine output or if there is significant oliguria or anuria. **These abnormalities are discussed in Chaps. 52, 310, and 311.**

FURTHER READING

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