Pathophysiology and etiology of edema in adults

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INTRODUCTION

Edema is defined as a palpable swelling produced by expansion of the interstitial fluid volume. A variety of clinical conditions are associated with the development of edema, including heart failure, cirrhosis, and the nephrotic syndrome (table 1).

Some patients have localized edema. This can be caused by a variety of conditions, including venous obstruction, as occurs with deep vein thrombosis or venous stasis, and allergic reactions (such as laryngeal edema).

This topic will review the pathophysiology and etiology of generalized edematous states. The clinical manifestations, diagnosis, and therapy of edema are discussed separately. (See "Clinical manifestations and evaluation of edema in adults" and "General principles of the treatment of edema in adults" and "Treatment of refractory edema in adults".)

PATHOPHYSIOLOGY OF EDEMA FORMATION

There are two basic steps involved in edema formation:

- An alteration in capillary hemodynamics that favors the movement of fluid from the vascular space into the interstitium
- The retention of dietary or intravenously administered sodium and water by the kidneys

The importance of the kidneys in the development of edema should not be underestimated. Edema (other than localized edema as with an allergic reaction) does not become clinically apparent until the interstitial volume has increased by at least 2.5 to 3 liters. Since the normal plasma volume is only about 3 liters, it is clear that patients would develop marked hemoconcentration and shock if the edema fluid were derived only from the plasma.

Hemoconcentration and shock do not occur, because of the following sequence:

- The initial movement of fluid from the vascular space into the interstitium reduces the plasma volume and consequently reduces tissue perfusion.
- In response to these changes, the kidney retains sodium and water.
- Some of this fluid stays in the vascular space, returning the plasma volume toward normal. However, the alteration in capillary hemodynamics results in most of the retained fluid entering the interstitium and eventually becoming apparent as edema.

The net effect is a marked expansion of the total extracellular volume (as edema) with maintenance of the plasma volume at closer-to-normal levels. This pathophysiologic sequence also illustrates an important point that must be considered when treating a patient with edema. Renal sodium and water retention in most edematous states is an **appropriate** compensation in that it restores tissue perfusion, even though it also augments the degree of edema. Removing the edema fluid with diuretic therapy will improve symptoms due to edema but may diminish tissue perfusion, occasionally to clinically significant levels. (See "General principles of the treatment of edema in adults".)

The hemodynamic effects are different when the primary abnormality is **inappropriate** renal fluid retention. In this setting, both the plasma and interstitial volumes are expanded, and deleterious hemodynamic effects from removal of the excess fluid are much less likely. This is an example of overfilling of the vascular tree which most often occurs with primary renal disease.

Capillary hemodynamics — The exchange of fluid between the plasma and the interstitium is determined by the hydraulic and oncotic pressures in each compartment. The relationship between these parameters has traditionally been described by Starling's law [1,2]:

Net filtration = LpS x (delta hydraulic pressure - delta oncotic pressure)
= LpS x [(Pcap - Pif) - s(ecap - eif)]

where Lp is the unit permeability (or porosity) of the capillary wall, S is the surface area available for fluid movement, Pcap and Pif are the capillary and interstitial fluid hydraulic pressures, ecap and eif are the capillary and interstitial fluid oncotic pressures, and s represents the reflection coefficient of proteins across the capillary wall (with values ranging from 0 if completely permeable to 1 if completely impermeable).

Classically, it had been assumed and taught that outward filtration predominates at the arterial end of the capillary, while, in the venule, as hydrostatic pressure falls, fluid returns to the capillary from the interstitium, driven by the oncotic pressure gradient. However, subsequent observations have shown that, in most capillary beds, net filtration continues throughout the length of the capillary, and that many of the assumptions of the Starling relationship are invalid [3-6].

In the traditional model, the reflection coefficient of proteins across the capillary wall was assumed to be close to 1. However, owing to albumin diffusion through large capillary pores, approximately half of the body's albumin content is extravascular, and, when directly measured, interstitial oncotic pressure is 30 to 60 percent of plasma oncotic pressure [6].

Actual capillary hemodynamics differ from the classical Starling equation because the structure of the interstitial space and the capillary filtration barrier are much more complex than was once believed [3-6]. The interstitial space is not simply a protein-free ultrafiltrate of plasma. Rather, the interstitium is a triphasic system consisting of free-flowing fluid, a gel phase consisting of large polyanionic glycosaminoglycan (GAG) molecules, and a collagen matrix. Sodium ions bound to GAG exert osmotic pressure that promotes capillary filtration while the collagen matrix exerts hydrostatic pressure that opposes it [6]. Interstitial albumin is confined to the free-flowing fluid phase, and its concentration is determined by the relative rates of water and albumin flux through the capillary.

Capillary lumens are lined with a glycocalyx consisting of a complex network of GAG molecules and other glycoproteins, forming a filtration barrier that is interrupted by clefts through which capillary filtration occurs [3-5]. Because albumin is excluded from the luminal surface of these filtration clefts, intravascular albumin exerts much more oncotic pressure than would be predicted from direct measurements of interstitial albumin concentrations; ie, the true net filtration force across the capillary membrane depends not so much upon interstitial oncotic pressure as upon the colloid oncotic pressure of fluid just below the endothelial glycocalyx.

Fluid accumulating in the interstitial space is returned to the circulation by lymphatics [3-6]. The capacity for lymph flow varies among tissues, and there is emerging evidence that lymphangiogenesis may be regulated by interstitial sodium bound to GAG molecules [7].

Capillary dynamics differ substantially among the vascular beds of different organs [8]. As an example, hepatic sinusoids are highly permeable to proteins; as a result, the capillary and interstitial oncotic pressures are roughly equal, and there is little transcapillary oncotic pressure gradient [2]. The net effect is that the hydraulic pressure gradient favoring filtration is essentially unopposed. To some degree, filtration is minimized by a lower capillary hydraulic pressure than in skeletal muscle since approximately two-thirds of hepatic blood flow is derived from the portal vein, a low-pressure system. In addition, ascites does not normally develop, because the filtered fluid is removed by the lymphatics.

The alveolar capillaries also have a relatively low capillary hydraulic pressure (due to perfusion from the low-pressure system in the right ventricle) and are more permeable than skeletal muscle to proteins. This results in smaller transcapillary hydraulic and oncotic pressure gradients [9]. The clinical significance of this difference will be discussed below.

Edema formation — The development of edema requires an alteration in capillary dynamics in a direction that favors an increase in net filtration and also inadequate removal of the additional filtered fluid by lymphatic drainage. Edema may form in response to an elevation in capillary hydraulic pressure (which increases the "delta hydraulic pressure") or increased capillary permeability (Lp), or it can be due to disruption of the endothelial glycocalyx, decreased interstitial compliance, a lower plasma oncotic pressure (which reduces the "delta oncotic pressure"), or a combination of these changes (table 1). Edema can also be induced by lymphatic obstruction since the fluid that is normally filtered is not returned to the systemic circulation.

Increased capillary hydraulic pressure — Capillary hydraulic pressure, although generated by cardiac contraction, is relatively insensitive to alterations in arterial pressure. This stability is due to autoregulatory changes in resistance at the precapillary sphincter, which determine the extent to which the arterial pressure is transmitted to the capillary. If the arterial pressure is increased, for example, the sphincter constricts, minimizing the elevation in capillary hydraulic pressure and preventing the development of edema.

By contrast, the resistance at the venous end of the capillary is not well regulated. Consequently, changes in venous pressure result in parallel alterations in capillary hydraulic pressure. The venous pressure is increased in two settings: (1) when the blood volume is expanded, augmenting the volume in the venous system; and (2) when there is venous obstruction. Examples of edema due to volume expansion include heart failure and renal disease; edema due to effective venous obstruction is commonly seen with cirrhosis of the liver, in which there is a marked increase in hepatic sinusoidal pressure, and with deep venous thrombosis in the lower extremities. Diastolic dysfunction due to decreased compliance of the heart (which results in pulmonary edema) and right heart failure and pericardial disease (which result in peripheral edema) are other causes of effective venous obstruction.

Hypoalbuminemia — Hypoalbuminemia due to albumin loss in the urine in the nephrotic syndrome or to decreased hepatic albumin synthesis also contributes to edema formation. However, chronic hypoalbuminemia alone may be insufficient to induce edema. (See 'Compensatory factors' below.)

Increased capillary permeability — An increase in capillary permeability due to vascular injury promotes the development of edema for several reasons. With vascular injury, the unit permeability (porosity, or "Lp" in the equation above) of the capillary wall increases, which tends to increase net filtration. In addition, the reflection coefficient of proteins across the capillary wall ("s" in the equation above) decreases, and disruption of the glycocalyx narrows the difference between the oncotic pressure of the capillary and the oncotic pressure of fluid just below the endothelial glycocalyx, thereby reducing the oncotic pressure gradient.

Increased capillary permeability contributes to edema in the following clinical settings:

- Burns, in which both histamine and oxygen free radicals can induce microvascular injury in addition to the direct physical action of the injury [10].

- Therapy with recombinant human interleukin-2 or vascular endothelial growth factor, which appear to directly increase capillary permeability [11,12].

- Episodic idiopathic **capillary leak** syndromes, which may be mediated by increased expression of interleukin-2 receptors on circulating mononuclear cells or by increased generation of kinins [13-15]. Affected patients often have an associated monoclonal gammopathy and, during episodes, have a massive leak of proteins and fluids out of the vascular space with the hematocrit rising acutely to as high as 70 to 80 percent [15]. The mortality rate is high in this disorder. Preliminary evidence suggests that the combination of aminophylline (an inhibitor of phosphodiesterase) and terbutaline (a relatively selective beta-2-adrenergic agonist) may prevent episodes [15,16] and therefore improve survival [13,16]. It is not clear, however, why these drugs are effective. The associated monoclonal gammopathy may progress to overt multiple myeloma among those patients with capillary leak syndrome who survive long enough. In one series of 11 patients followed for a mean of 6.4 years, three died, one during an attack and two from multiple myeloma [13]. (See "Idiopathic systemic capillary leak syndrome".)

- Any of the conditions associated with the adult respiratory distress syndrome. In this disorder, ischemia- or sepsis-induced release of cytokines, such as interleukin-1 or tumor necrosis factor, may play an important role in the increase in pulmonary capillary permeability, at least in part via the recruitment of neutrophils [17,18].

- Capillary permeability is moderately increased in patients with diabetes mellitus [19,20]. This abnormality may be mediated in part by hyperglycemia-induced accumulation of advanced glycosylation end products derived from the combination of glucose with circulating proteins [21]. The net effect is to enhance the severity of edema which, in these patients, is usually due to heart failure or the nephrotic syndrome.

- The malnutrition syndrome, kwashiorkor, may be another example of edema due in part to increased capillary permeability. Although edema has often been ascribed to hypoalbuminemia, increased generation of cysteinyl leukotrienes that increase capillary permeability may be of primary importance in the edema of kwashiorkor [22]. (See 'Compensatory factors' below.)

Lymphatic obstruction (lymphedema) — Lymphatic obstruction is an unusual cause of edema (called lymphedema). It is most often due to radical lymph node dissection for malignancy (eg, breast cancer). Lymphatic obstruction may also play a pivotal role in the development of "nephrogenic ascites" [23,24]. (See "Clinical features and diagnosis of peripheral lymphedema"

and "Unique aspects of gastrointestinal disease in dialysis patients", section on 'Hemodialysis-associated ascites'.)

Myxedema — Hypothyroidism leads to a marked accumulation of interstitial albumin and other proteins [25]. Although this may be due in part to an elevation in capillary protein permeability, the excess interstitial protein and fluid would normally be returned to the systemic circulation by the lymphatics. However, lymphatic flow is low or normal in patients with myxedema [25] and not increased as in other edematous states [26]. This may be due to binding of the filtered proteins to excess interstitial mucopolysaccharides, thereby preventing their removal by the lymphatics [25].

Compensatory factors — Since there is normally a small gradient favoring filtration, it might be expected that only a minor change in these hemodynamic forces would lead to edema. However, experimental and clinical observations indicate that there must be at least a **15 mmHg** increase in the gradient favoring filtration before edema can be detected [1,2]. Two factors contribute to this protective response:

- Lymphatic flow and contractility increase in the presence of tissue edema and remove some of the excess filtrate [27,28]. With pulmonary edema due to heart failure, for example, accumulation of lung liquid at any given elevation in pulmonary capillary pressure is related to the functional capacity of the lymphatics which, in turn, is influenced by both individual factors and the acuteness of the hemodynamic change [29]. With acute rises in pulmonary capillary pressures, the pulmonary lymphatic system does not have an increased capacity to remove fluid; as a result, pulmonary edema occurs at pulmonary artery capillary pressures as low as 18 mmHg. By contrast, patients with chronic heart failure have an increased lymphatic capacity and do not develop pulmonary edema until much higher pulmonary capillary pressures (eg, >25 mmHg) are reached.

- Fluid entry into the interstitium will eventually raise the interstitial hydraulic pressure, reducing the pressure gradient favoring filtration [1].

In contrast to the systemic vasculature, glycocalyx GAGs of the pulmonary vessels do not appear to contribute to the pulmonary endothelial barrier to fluid and protein [30]. Instead, the alveolar capillaries appear to have a greater baseline permeability to albumin [2,9], which leads to increased protection against edema due to hypoalbuminemia than seen in skeletal muscle. Thus, in the absence of a concurrent rise in left atrial and pulmonary capillary pressures, pulmonary edema is not usually seen with hypoalbuminemia, even at a plasma albumin concentration acutely low enough to induce peripheral edema [31].

The response is appreciably different after the rapid administration of large volumes of saline to patients with marked hypovolemia, a condition in which a low plasma albumin concentration can predictably cause edema. In this setting, there is acute dilutional hypoalbuminemia without time for the interstitial albumin concentration to fall. As a result, the transcapillary oncotic pressure gradient

is reduced, and pulmonary edema can occur before the restoration of normal intracardiac filling pressures.

Renal sodium retention — As noted above, the retention of fluid by the kidney in edematous states can represent an appropriate compensatory response to reduced effective arterial blood volume (also called effective circulating volume depletion) or an inappropriate manifestation of renal disease [31,32]. In most instances, the effective arterial blood volume is directly proportional to the cardiac output. Thus, when the cardiac output is reduced because of underlying cardiac disease, the kidney serves to restore the effective arterial blood volume by retaining sodium and water.

However, effective tissue perfusion and the cardiac output are not always related, since the former can also be reduced by a decrease in peripheral vascular resistance [33]. As an example, experimental creation of an arteriovenous fistula is associated with no initial change in cardiac output, yet tissue perfusion is reduced since the blood flowing through the fistula is bypassing the capillary circulation. In response to this hemodynamic change, the kidney retains sodium and water, thereby increasing the blood volume and cardiac output [34]. The new steady state is characterized by a cardiac output that exceeds the baseline level by an amount equal to the flow rate through the fistula.

A common clinical correlate of this experiment occurs in patients with cirrhosis and ascites, who frequently have an elevated cardiac output [35]. Despite this, they behave as if they are volume depleted, as evidenced by avid renal sodium retention and a progressive rise in secretion of the three hypovolemic hormones (renin, norepinephrine, and antidiuretic hormone [ADH]) [33,36,37]. (See "Hyponatremia in patients with cirrhosis".)

The disparity between the high cardiac output and the renal and neurohumoral responses in cirrhosis is due both to splanchnic vasodilatation and to the presence of multiple arteriovenous fistulas throughout the body, such as spider angiomata in the skin. The net effect is a marked fall in systemic vascular resistance and a reduction in systemic blood pressure [33,38]. Much of the cardiac output is circulating ineffectively, as there is a progressive reduction in renal and eventually musculocutaneous perfusion [39].

The renal sodium and water retention seen in heart failure or cirrhosis results from both a hypovolemia-induced fall in glomerular filtration rate (GFR) and, more importantly, an increase in tubular reabsorption. The latter is mediated by increases in the activity of the renin-angiotensin-aldosterone and sympathetic nervous systems [33,40,41].

The compensated state — Although the renin-angiotensin-aldosterone system undoubtedly contributes to sodium retention in disorders such as heart failure and cirrhosis, the plasma renin activity is normal in some patients with these disorders [41,42]. A partial explanation for this seemingly paradoxical finding is that the patient has entered a compensated state in which the

initial fluid retention has increased venous return to the heart, thereby allowing systemic hemodynamics to be stabilized (at least in the resting state) and removing the stimulus for continued renin release [40,41]. This sequence is depicted in the figure, which shows the changes that occur with chronic thoracic inferior vena cava constriction, an experimental model that simulates the changes seen in heart failure in humans (figure 1) [40]. The new steady state seen after six to seven days is characterized by plasma volume expansion but normalization of the systemic blood pressure, urinary sodium excretion, and renin and aldosterone release.

In many patients, however, stable heart failure is associated with a persistent reduction in cardiac output, and it is not clear why renin levels should be normal [40]. One possible explanation is that circulating levels may not reflect the degree of activation of tissue renin-angiotensin systems. (See "Actions of angiotensin II on the heart".)

ETIOLOGY

The most common causes of generalized edema seen by the clinician are:

- Heart failure
- Cirrhosis
- Nephrotic syndrome and other forms of renal disease
- Premenstrual edema and pregnancy

The pathogenesis of edema in heart failure will be reviewed here because it illustrates many of the mechanisms described above [43]; the unusual causes of drug-induced edema and refeeding edema will also be briefly reviewed. However, the pathogenesis of edema in cirrhosis, renal disease, and premenstrual or pregnant women is discussed separately. The pathogenesis of the uncommon condition idiopathic edema, which is generally seen in young women, is also presented separately. (See "Pathogenesis of ascites in patients with cirrhosis" and "Pathophysiology and treatment of edema in patients with the nephrotic syndrome" and "Preeclampsia: Clinical features and diagnosis" and "Idiopathic edema".)

Heart failure — Heart failure can be produced by a variety of disorders, including coronary artery disease, hypertension, the cardiomyopathies, valvular disease, and cor pulmonale. The edema in the different causes of heart failure is due to an increase in venous pressure that produces a parallel rise in capillary hydraulic pressure and to renal sodium retention due to reduced perfusion of the kidneys. Despite the similarity in pathogenesis, the **site** of edema accumulation is variable and is dependent upon the nature of the cardiac disease [44]:

- Coronary heart disease, hypertensive heart disease, and left-sided valvular disease tend to preferentially impair left ventricular function. As a result, patients with one of these disorders typically present with pulmonary but not peripheral edema.

- Cor pulmonale, by contrast, is initially associated with pure right ventricular failure, resulting in prominent edema in the lower extremities and, perhaps, ascites.

- Cardiomyopathies tend to produce equivalent involvement of both the right and left ventricles, often leading to the simultaneous onset of pulmonary and peripheral edema.

In acute pulmonary edema due to a myocardial infarction or ischemia, the left ventricular disease results in elevations in left ventricular end-diastolic and left atrial pressures, which are transmitted **back** through the pulmonary veins to the pulmonary capillaries. In general, the pulmonary capillary pressure must exceed 18 to 20 mmHg (normal equals 5 to 12 mmHg) before acute pulmonary edema occurs [45].

The pathogenesis of edema formation is somewhat different in chronic heart failure. In this setting, the increase in capillary pressure is a result of plasma volume expansion, not solely the obstructive effect of a diseased heart. This is called the **forward** hypothesis of heart failure, in which the primary event is a reduction in cardiac output [33,46]. This decrease in tissue perfusion leads to activation of the sympathetic and renin-angiotensin systems, which tend to promote sodium and water retention; they also tend to increase vascular resistance and cardiac inotropy, which maintain the systemic blood pressure [47,48]. (See "Pathophysiology of heart failure with reduced ejection fraction: Hemodynamic alterations and remodeling" and "Pathophysiology of heart failure: Neurohumoral adaptations", section on 'Neurohumoral adaptations'.)

The net effect in patients with relatively well-preserved cardiac function is an initially mild impairment in sodium-excretory ability. Edema is often absent at this time, unless there is a high level of sodium intake [49]. With more advanced disease, however, forward output can be restored only by plasma volume expansion and intracardiac filling pressures that are high enough to promote edema formation.

Similar considerations apply to high-output heart failure due, for example, to hyperthyroidism (where the hypermetabolic state leads to an increase in energy requirements) or to arteriovenous fistulas (where blood flowing through the fistulas is bypassing the capillary circulation). In these conditions, the patients still behave as if they are effectively volume depleted since the cardiac output is inappropriately low in relation to tissue needs [34,50].

The effect of fluid retention on cardiac function is illustrated in the following figure (figure 2) [43]. The left ventricular end-diastolic pressure (LVEDP) is a function of the plasma and extracellular fluid volumes and is increased or decreased by expanding or reducing those fluid spaces. The upper curve represents the normal Frank-Starling relationship between stroke volume and LVEDP and shows how increasing cardiac stretch enhances cardiac contractility [39] (see "Pathophysiology of heart failure with reduced ejection fraction: Hemodynamic alterations and remodeling"). The development of mild cardiac failure (middle curve) will, if the sympathetic stimulation of cardiac function is insufficient, lower both stroke volume and cardiac output (line

AB). The ensuing renal sodium and water retention can reverse these abnormalities since the increments in plasma volume will increase the LVEDP, and this augments cardiac contractility (line BC).

At this point, the patient is in a new steady state of compensated heart failure in which the stroke volume and cardiac output are normal, sodium excretion matches sodium intake, and the activity of the renin-angiotensin-aldosterone system has returned to normal (figure 1) [40,41]. The restoration of tissue perfusion in this setting has occurred only after there has been an elevation in the LVEDP, perhaps to a level sufficient to produce pulmonary edema.

There are several points that deserve emphasis in this simple example of mild to moderate heart failure:

- It demonstrates again the dual effects of fluid retention in edematous states: a beneficial increment in cardiac output and a potentially harmful elevation in venous pressure.
- It illustrates that vascular congestion (that is, an elevated LVEDP) and a low cardiac output do not have to occur together in patients with heart disease. At point B, the patient is in a low-output state, but there is no congestion; at point C, the patient is congested but has a normal cardiac output.
- The Frank-Starling relationship varies with exercise. Patients with moderate heart disease may have a normal cardiac output at rest but may be unable to increase it adequately with even mild exertion [51]. This relative decrease in tissue perfusion can lead sequentially to further neurohumoral activation, renal vasoconstriction and ischemia, sodium retention, and ultimately edema [52,53].
- Patients with mild to moderate heart disease may have no edema with dietary sodium restriction but may retain sodium and possibly become edematous if given a sodium load [49]. Suppose points A and C in the figure reflect the hemodynamic state on a low-sodium diet (figure 1). An increase in sodium intake will initially expand the intravascular volume and raise the LVEDP. In the normal subject (point A) who is still on the ascending limb of the Frank-Starling curve, the increase in filling pressure will enhance stroke volume and cardiac output, which will then promote the excretion of the excess sodium. By contrast, a similar elevation in the LVEDP in the patient with heart failure (point C), who is on a flatter part of the curve, will produce less of an increment both in cardiac output and consequently in sodium excretion. Limiting dietary sodium intake in this setting may be sufficient to alleviate the edema.

The situation is somewhat different with severe heart failure (figure 2). At this time, the plateau in stroke volume occurs earlier and at a lower level than in mild heart failure, and increasing the LVEDP cannot normalize the stroke volume. Two factors appear to account for this plateau:

- The heart may simply have reached its maximum capacity to increase contractility in response to increasing stretch. In vitro studies suggest that this abnormality may result from decreased calcium affinity for and therefore binding to troponin C and from decreased calcium availability within the myocardial cells [54]. (See "Excitation-contraction coupling in myocardium".)

- The Frank-Starling relationship actually applies to left ventricular end-diastolic **volume** since it is the stretching of cardiac muscle that is responsible for the enhanced contractility. The more easily measured LVEDP is used clinically since, in relatively normal hearts, pressure and volume vary in parallel. However, cardiac compliance may be greatly reduced with severe heart disease [55]. As a result, a small increase in volume produces a large elevation in LVEDP but no substantial stretching of the cardiac muscle and therefore little change in cardiac output [56].

Drug-induced edema — Certain drugs can induce edema by enhancing renal sodium reabsorption (table 1). In the past, this was most likely to occur with potent direct vasodilators such as minoxidil and diazoxide, which are now infrequently used [57-59]. Patients treated with minoxidil, for example, often require therapy with high doses of a loop diuretic (such as 160 to 240 mg of furosemide) to prevent edema formation.

The mechanism by which these agents stimulate sodium retention is uncertain. The fall in blood pressure itself probably plays an important role both directly and by activating the renin-angiotensin-aldosterone and sympathetic nervous systems, both of which stimulate sodium retention [57,60]. The ability of sympatholytic agents to directly diminish renin release and of angiotensin-converting enzyme (ACE) inhibitors to diminish angiotensin II production may explain why these drugs do not produce edema even though they lead to an equivalent reduction in blood pressure.

Peripheral edema occurs in 4 to 6 percent of diabetic patients treated with a thiazolidinedione such as pioglitazone or rosiglitazone (compared with 1 to 2 percent with placebo) and in a higher percentage of patients with a history of heart failure or those also treated with insulin. The mechanism is stimulation of sodium reabsorption by the sodium channels in the luminal membrane of collecting tubule cells, which is the same site stimulated by aldosterone. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Fluid retention/heart failure'.)

Other causes of drug-induced edema include:

- Calcium channel blockers, particularly the dihydropyridines, can result in leakage of fluid out of the capillary due primarily to dilatation of the precapillary sphincter [61]. (See "Major side effects and safety of calcium channel blockers".)

- Nonsteroidal antiinflammatory drugs inhibit renal prostaglandin synthesis and can exacerbate edema in patients with underlying heart failure or cirrhosis [62]. (See "NSAIDs: Electrolyte

complications".)

- Fludrocortisone, a synthetic mineralocorticoid used in the treatment of hypoaldosteronism and orthostatic hypotension, initially causes fluid retention, but edema is unusual because of the phenomenon of mineralocorticoid escape. (See "Pathophysiology and clinical features of primary aldosteronism".)

- Estrogens (alone or in oral contraceptives) may promote sodium retention, primarily in patients with impaired estrogen metabolism due to hepatic disease [63,64].

- Pramipexole, a dopamine agonist used in the treatment of Parkinson disease and restless legs syndrome, causes peripheral edema in approximately 5 percent of patients; this effect appears to be dose related, but the mechanism is uncertain [65].

- Docetaxel, used in the treatment of metastatic breast cancer, produces fluid retention that is cumulative and often dose limiting [66-68]. However, with appropriate premedication (three to five days of oral corticosteroids, beginning 24 hours prior to dosing), higher cumulative doses can be administered before fluid retention occurs [68].

Refeeding edema — Patients who have fasted for as little as three days retain sodium and may become edematous after refeeding with carbohydrates [69-74]. Insulin levels, which increase in response to the renewed intake of carbohydrates, result in enhanced reabsorption of sodium, thereby causing edema [72].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Edema (swelling) (Beyond the Basics)").

SUMMARY

- There are two basic steps involved in edema formation (see 'Pathophysiology of edema formation' above):
  - An alteration in capillary hemodynamics that favors the movement of fluid from the vascular space into the interstitium
  - The retention of dietary or intravenously administered sodium and water by the kidneys
- The following sequence occurs (see 'Pathophysiology of edema formation' above):
  - The initial movement of fluid from the vascular space into the interstitium reduces the plasma volume, and consequently reduces tissue perfusion.
  - In response to these changes, the kidney retains sodium and water.
  - Some of this fluid stays in the vascular space, returning the plasma volume toward normal. However, the alteration in capillary hemodynamics results in most of the retained fluid entering the interstitium and eventually becoming apparent as edema.
- Renal sodium and water retention in most edematous states is an **appropriate** compensation in that it restores tissue perfusion, even though it also augments the degree of edema. The hemodynamic effects are different when the primary abnormality is **inappropriate** renal fluid retention. In this setting, both the plasma and interstitial volumes are expanded. (See 'Pathophysiology of edema formation' above.)
- The exchange of fluid between the plasma and the interstitium is determined by the hydraulic and oncotic pressures in each compartment. (See 'Capillary hemodynamics' above.)
- The development of edema requires an alteration in one or more of the Starling forces in a direction that favors an increase in net filtration and also inadequate removal of the additional filtered fluid by lymphatic drainage. This can be produced by (table 1) (see 'Edema formation' above):
  - An elevation in capillary hydraulic pressure
  - Increased capillary permeability
  - Higher interstitial oncotic pressure
  - A lower plasma oncotic pressure
  - Lymphatic obstruction
  - A combination of these changes
- Three factors protect against edema formation; these include (see 'Compensatory factors' above):
  - Lymphatic flow and contractility increase in the presence of tissue edema and remove some of the excess filtrate

- Fluid entry into the interstitium will eventually raise the interstitial hydraulic pressure, reducing the pressure gradient favoring filtration
- Fluid entry into the interstitium also lowers the interstitial oncotic pressure, both by dilution and by lymphatic-mediated removal of interstitial proteins

- The most common causes of generalized edema seen by the clinician are (see 'Etiology' above):

  - Heart failure (see 'Heart failure' above)
  - Cirrhosis (see "Pathogenesis of ascites in patients with cirrhosis")
  - Nephrotic syndrome and other forms of renal disease (see "Pathophysiology and treatment of edema in patients with the nephrotic syndrome")
  - Premenstrual edema and pregnancy (see "Preeclampsia: Clinical features and diagnosis")

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Topic 2309 Version 17.0

GRAPHICS

Major causes of edema by primary mechanism

Increased capillary hydraulic pressure
Increased plasma volume due to renal sodium retention
Heart failure, including cor pulmonale
Primary renal sodium retention
▪ Renal disease, including the nephrotic syndrome
▪ Drugs:* Nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, fludrocortisone, thiazolidinediones (glitazones), insulins, estrogens, progestins, androgens, testosterone, aromatase inhibitors, tamoxifen; and by multiple mechanisms: vasodilators (hydralazine, minoxidil, diazoxide) and calcium channel blockers (particularly dihydropyridines, ie, amlodipine, nifedipine); also refer to "Arteriolar vasodilation" below
▪ Refeeding edema
▪ Early hepatic cirrhosis
Pregnancy and premenstrual edema
Idiopathic edema, when diuretic induced
Sodium or fluid overload: Parenteral antibiotics or other drugs with large amounts of sodium, sodium bicarbonate, or excessive or overly rapid fluid replacement
Venous obstruction or insufficiency
Cirrhosis or hepatic venous obstruction
Acute pulmonary edema
Local venous obstruction
▪ Venous thrombosis
▪ Venous stenosis
Chronic venous insufficiency - post-thrombotic syndrome
Arteriolar vasodilation
Drugs:* Frequent - vasodilators (hydralazine, minoxidil, diazoxide), dihydropyridine calcium channel blockers; less frequent - alpha1 blockers, sympatholytics (ie, methyldopa), nondihydropyridine calcium channel blockers[1]
Idiopathic edema (?)
Hypoalbuminemia
Protein loss
Nephrotic syndrome
Protein-losing enteropathy
Reduced albumin synthesis
Liver disease
Malnutrition
Increased capillary permeability
Idiopathic edema (?)
Burns
Trauma
Inflammation or sepsis
Allergic reactions, including certain forms of angioedema
Adult respiratory distress syndrome

Diabetes mellitus
Interleukin-2 therapy
Malignant ascites
Lymphatic obstruction or increased interstitial oncotic pressure
Lymph node dissection
Nodal enlargement due to malignancy
Hypothyroidism
Malignant ascites
Other drugs* (uncertain mechanism)
Anticonvulsant: Gabapentin, pregabalin
Antineoplastic: Docetaxel, cisplatin
Antiparkinson: Pramipexole, ropinirole

* Patients with decreased cardiac output, preexisting renal insufficiency, and/or receiving higher doses are more likely to experience edema and edema-associated adverse events. This is not a complete list of drugs associated with edema. For additional information, refer to the Lexicomp individual drug monographs included with UpToDate.

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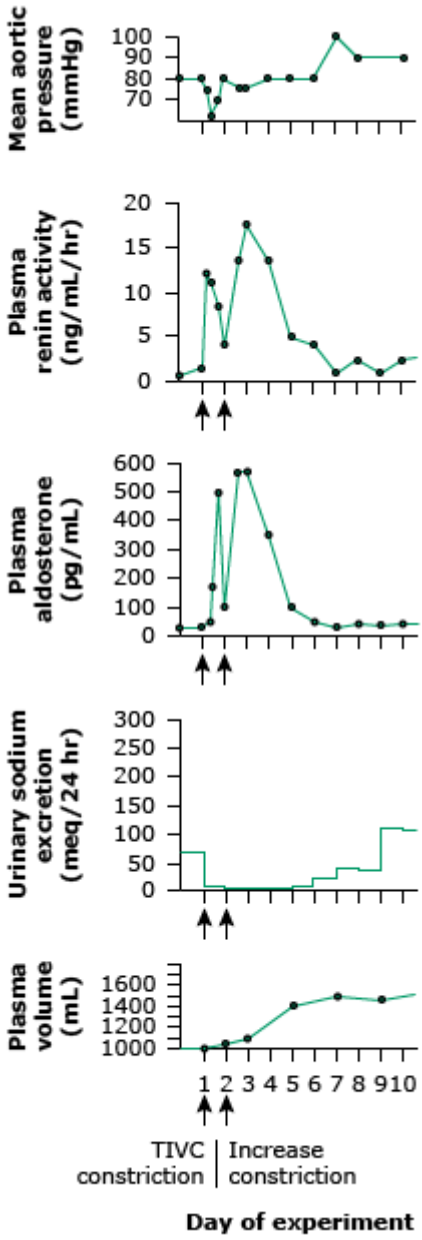
1. *Messerli FH. Vasodilatory edema: A common side effect of antihypertensive therapy. Curr Cardiol Rep 2002; 4(6):479.*

Graphic 53550 Version 9.0

Humoral adaptation to experimental heart failure

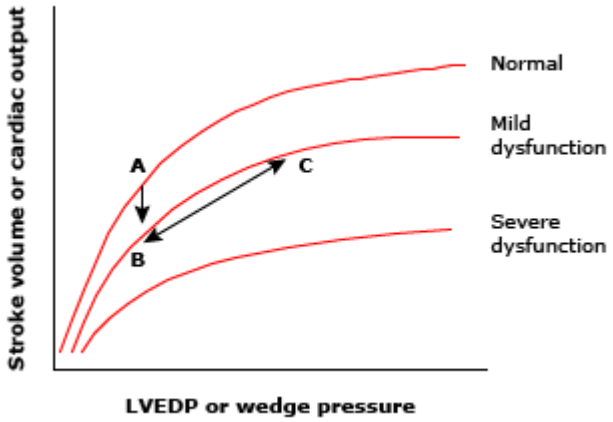


Sequential changes in mean aortic pressure, plasma renin activity, plasma aldosterone concentration, urinary sodium excretion, and plasma volume in a dog with moderate thoracic inferior vena cava constriction. There is initial hypotension, activation of the renin-angiotensin-aldosterone system, and a marked reduction in urinary Na+ excretion. By day 7, however, a new steady state is achieved in which renin and aldosterone levels and Na+ excretion have returned to baseline levels. The associated plasma volume expansion is responsible for restoring venous return to the heart, thereby allowing systemic hemodynamics to be normalized.

Watkins L Jr, Burton JA, Haber E, et al. J Clin Invest 1976; 57:1606. Copyright permission of the American Society for Clinical Investigation.

Graphic 52302 Version 3.0

Frank-Starling curves in heart failure



Idealized family of Frank-Starling curves produced by worsening ventricular function in heart failure. In ventricles with normal cardiac performance, there is a steep and positive relationship between increased cardiac filling pressures (as estimated from the LVEDP or pulmonary capillary wedge pressure) and increased stroke volume or cardiac output (top curve). By comparison, during progression from mild to severe myocardial dysfunction, this relationship is right shifted (ie, a higher filling pressure is required to achieve the same cardiac output) and flattened so that continued increases in left heart filling pressures lead to minimal increases in cardiac output at the possible expense of pulmonary edema. The onset of mild heart failure results in an initial reduction in cardiac function (from point A to point B), a change that can be normalized, at least at rest, by raising the LVEDP via fluid retention (point C). Diuretic therapy reduces left ventricular filling pressure at the expense of mildly decreased cardiac output (moving from point C to point B). By comparison, normalization of stroke volume is not attainable in severe heart failure (bottom curve).

LVEDP: left ventricular end-diastolic pressure.

Graphic 58693 Version 8.0

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Conflict of interest policy