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Chapter 8A: Effective circulating volume and the steady state Find Print

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INTRODUCTION — The maintenance of adequate tissue perfusion is essential for normal cellular metabolism by providing nutrients and by removing waste products. It is not surprising, therefore, that multiple sensors and multiple effectors are involved in this process. The presence of several levels of control illustrates an important difference between the regulation of volume and the regulation of osmolality or the concentration of a particular solute. Maintenance of concentration can often be achieved with only a single sensor (such as the hypothalamic osmoreceptors), since all tissues are perfused by the same arterial blood. In comparison, there may be marked variability in regional perfusion, necessitating the presence of local sensors.

A simple example is changing from the sitting to the standing position which, by gravity, tends to result in hyperperfusion of and fluid accumulation in the lower extremities, and hypoperfusion of the brain [1]. In this setting, activation of the carotid sinus baroreceptors with a subsequent increase in sympathetic activity helps to preserve cerebral perfusion (see below).

This chapter will review how the effective circulating volume is regulated, both in the face of changes in dietary Na+ intake and in disease states in which tissue perfusion is altered. In particular, it will show how the neurohumoral influences and the reabsorptive characteristics of the different nephron segments that have been discussed in Chaps. 3 to 5 are integrated in an appropriate fashion to maintain the steady state. The physiologic and clinical importance of the steady state will also be reviewed.

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DEFINITION — The **effective circulating volume** refers to that part of the extracellular fluid (ECF) that is in the arterial system (normally about 700 mL in a 70 kg man) and is effectively perfusing the tissues [2]. However, a better physiologic definition is the pressure perfusing the arterial baroreceptors in the carotid sinus and glomerular afferent arterioles, since it is changes in pressure (or stretch) rather than volume or flow that is generally sensed at these sites.

The effective circulating volume usually varies directly with the ECF volume. Both of these parameters are typically proportional to total body Na+ stores, since Na+ salts are the primary extracellular solutes that act to hold water within the extracellular space (see "Chapter 7A: Exchange of water between the cells and ECF"). As a result, the regulation of Na+ balance (by alterations in urinary Na+ excretion) and the maintenance of the effective circulating volume are closely related functions. Na+ loading will tend to produce volume expansion, whereas Na+ loss will lead to volume depletion.

In some settings, however, the effective circulating volume may be **independent** of the ECF volume, the plasma volume, or even the cardiac output (table 1). In congestive heart failure, for example, the effective circulating volume is reduced because a primary decrease in cardiac output lowers the pressure at the baroreceptors [2,3]. As will be discussed below, this decline in pressure and flow induces compensatory fluid retention by the kidney, leading to expansion of the extracellular fluid. The net result is effective volume depletion in association with increases in both the plasma and total ECF volumes.

The increase in volume in this setting is in part **appropriate** because the associated rise in intracardiac filling pressure can, by increasing cardiac stretch, improve cardiac contractility and raise the cardiac output and systemic blood pressure toward normal. On the other hand, the elevation in intravascular pressure can also be maladaptive in that it promotes fluid movement out of the vascular space, potentially leading to both pulmonary and peripheral edema.

The effective circulating volume may, in some cases, also be independent of the cardiac output. In addition

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ineffectively, since it bypasses the capillary circulation. Thus, the patient is normovolemic, despite the presence of a cardiac output that may be substantially elevated.

The potential dissociation between the effective circulating volume and the cardiac output can also be illustrated by the hemodynamic changes seen in patients with advanced cirrhosis and ascites (table 1) [2,3]. In this disorder, the ECF volume is expanded because of the ascites, the plasma volume is increased due in part to fluid accumulation in the markedly dilated but slowly circulating splanchnic venous circulation [5], and the cardiac output is often elevated because of multiple arteriovenous fistulas throughout the body such as the spider angiomas on the skin [6].

Despite all of these signs suggesting volume expansion, most of the excess fluid is hemodynamically ineffective and these patients behave as if they are volume depleted due to marked peripheral vasodilatation. (See "Hyponatremia in patients with cirrhosis".) This is exemplified by reductions in systemic vascular resistance and blood pressure, a very low rate of urinary Na+ excretion (often below 10 meq/day) [7], a reduction in the blood volume in the cardiopulmonary circulation [8], and a progressive increase in the secretion of the hormones typically released in response to hypovolemia: renin, norepinephrine, and antidiuretic hormone (ADH) [7-9].

In summary, the effective circulating volume is an unmeasured entity that reflects tissue perfusion and may be independent of other hemodynamic parameters [2]. The diagnosis of effective volume depletion is usually made by demonstrating renal Na+ retention as evidenced by a urine Na+ concentration below 15 to 20 meq/L. This relationship is generally true as long as there is neither renal Na+ wasting (most often due to diuretic therapy or underlying renal disease) nor selective renal or glomerular ischemia (as with bilateral renovascular disease or acute glomerular disease). In the latter setting, urinary Na+ excretion may be low without systemic hypoperfusion, whereas obligatory Na+ wasting can prevent the renal Na+ retention that is normally associated with volume depletion [10].

EFFECTIVE CIRCULATING VOLUME, RENAL

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attempt to lower the volume toward normal. Conversely, the kidney retains Na+ in the presence of effective volume depletion. This system of volume regulation must be very efficient, since small alterations in Na+ intake necessitate parallel changes in Na+ excretion that involve less than 1 percent of the filtered Na+ load (see "Chapter 8C: Regulation of renal Na+ excretion", section on 'Day-to-day regulation').

The time course of the response to variations in Na+ intake is illustrated in Figure 1 (figure 1) [11]. If dietary intake is abruptly increased in a patient on a low-sodium diet, only about one-half of the excess intake is excreted on the first day. The remainder is retained, augmenting body Na+ stores. This elevates the plasma osmolality, which stimulates both thirst and the secretion of ADH (see page 000). The increments in water intake and renal water reabsorption produce water retention, resulting in increases in the effective circulating volume and body weight and the return of the plasma osmolality to normal. (See "Chapter 9A: Water balance and regulation of plasma osmolality".)

On subsequent days, a progressively greater fraction of the excess intake is excreted (and less retained) until, by three to four days, a new steady state is achieved in which renal Na+ excretion matches intake [12]. This new steady state is characterized by a mild increase in the effective circulating volume due to the Na+ and water retained on the first four days [12-15]. The total quantity of Na+ retained is directly related to the increment in Na+ intake above the previous baseline. Thus, the greater the increase in intake, the greater the increase in steady state extracellular volume (figure 2).

The same sequence occurs, in reverse, if Na+ intake is now reduced. Negative Na+ balance occurs until there has been enough loss of volume to lower Na+ excretion to the reduced level of intake.

Thus, a high-sodium diet is characterized by increases in volume and Na+ excretion and a low-sodium diet by decreases in volume and Na+ excretion. The changes in volume are essential, since they constitute the signal that allows urinary Na+ excretion to vary appropriately with fluctuations in Na+ intake. Let us assume, for the sake of simplicity, that Na+ excretion in normal subjects is primarily determined by the Na+-retaining

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level if Na+ excretion is to remain at 350 meq/day (figure 3). The signal for the continued suppression of aldosterone and stimulation of ANP is the persistent volume expansion.

Clinical implications — In addition to its role in volume regulation in normal subjects, the steady state also has important implications in the pathogenesis and treatment of disease states. As an example, diuretics inhibit Na+ reabsorption at different sites in the nephron; they are most often given to patients with edema or hypertension to lower the ECF volume. The initial volume loss activates Na+-retaining mechanisms, such as the renin-angiotensin system, that act to limit further losses. These counterregulatory forces are so efficient that, assuming diuretic dose is constant, all of the fluid and electrolyte losses occur in the first 7 to 14 days of therapy, with the maximum natriuretic response being induced by the first dose. (See "Time course of loop and thiazide diuretic-induced electrolyte complications".)

A steady state is also achieved with changes in intake of other electrolytes. If, for example, K+ intake is increased, the new steady state will be characterized by a limited elevation in body K+ stores and a small rise in the plasma K+ concentration [16]. The latter change will be the stimulus to maintain an increased rate of K+ excretion, a response that is mediated in part by enhanced secretion of aldosterone (see Chap. 12).

These observations have important implications for the development of many fluid and electrolyte disorders. The capacity to excrete Na+, K+, HCO3-, and H2O is so great in normal subjects that too much Na+ (edema), too much K+ (hyperkalemia), too much HCO3- (metabolic alkalosis), and too much H2O (hyponatremia) will not persist unless there is an abnormality in the renal excretion of that substance. The excretion of H2O, for example, occurs via the suppression of the release of antidiuretic hormone, resulting in the formation of a dilute urine. Thus, the differential diagnosis of hyponatremia primarily consists of those disorders in which ingested water cannot be excreted normally, usually due to an inability to suppress the release of antidiuretic hormone. (See "Causes of hyponatremia".)

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