

Disorders of Sodium Balance

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Sodium is the predominant cation in extracellular fluid (ECF); the volume of ECF is directly proportional to the content of sodium in the body. Disorders of sodium balance, therefore, may be viewed as disorders of ECF volume. The body must maintain ECF volume within acceptable limits to maintain tissue perfusion because plasma volume is directly proportional to ECF volume. The plasma volume is a crucial component of the blood volume that determines rates of organ perfusion. Many authors suggest that ECF volume is maintained within narrow limits despite wide variations in dietary sodium intake. However, ECF volume may increase as much as 18% when dietary sodium intake is increased from very low to moderately high levels [1,2]. Such variation in ECF volume usually is well tolerated and leads to few short-term consequences. In contrast, the same change in dietary sodium intake causes only a 1% change in mean arterial pressure (MAP) in normal persons [3]. The body behaves as if the MAP, rather than the ECF volume, is tightly regulated. Under chronic conditions, the effect of MAP on urinary sodium excretion displays a remarkable gain; an increase in MAP of 1 mm Hg is associated with increases in daily sodium excretion of 200 mmol [4].

Guyton [4] demonstrated the importance of the kidney in control of arterial pressure. Endogenous regulators of vascular tone, hormonal vasoconstrictors, neural inputs, and other nonrenal mechanisms are important participants in short-term pressure homeostasis. Over the long term, blood pressure is controlled by renal volume excretion, which is adjusted to a set point. Increases in arterial pressure lead to natriuresis (called *pressure natriuresis*), which reduces blood volume. A decrease in blood volume reduces venous return to the heart and cardiac output. Urinary volume excretion exceeds dietary intake until the blood volume decreases sufficiently to return the blood pressure to the set point.

Disorders of sodium balance resulting from primary renal sodium retention lead only to modest volume expansion without edema because increases in MAP quickly return sodium excretion to baseline

CHAPTER

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levels. Examples of these disorders include chronic renal failure and states of mineralocorticoid excess. In this case, the price of a return to sodium balance is hypertension. Disorders of sodium balance that result from secondary renal sodium retention, as in congestive heart failure, lead to more profound volume expansion owing to hypotension. In mild to moderate cases, volume expansion eventually returns the MAP to its set point; the price of sodium balance in this case is edema. In more severe cases, volume expansion never returns blood pressure to normal, and renal sodium retention is unremitting. In still other situations, such as nephrotic syndrome, volume expansion results from changes in both the renal set point and body volume distribution. In this case, the price of sodium balance may be both edema and hypertension. In each of these cases, renal sodium (and chloride) retention results from a discrepancy between the existing MAP and the renal set point.

The examples listed previously emphasize that disorders of sodium balance do not necessarily abrogate the ability to achieve sodium balance. When balance is defined as the equation of sodium intake and output, most patients with ECF expansion (and edema or hypertension) or ECF volume depletion achieve sodium balance. They do so, however, at the expense of expanded or contracted ECF volume. The *failure to achieve sodium balance at normal ECF volumes* characterizes these disorders.

Frequently, distinguishing disorders of sodium balance from disorders of water balance is useful. According to this scheme, disorders of water balance are disorders of body osmolality and usually are manifested by alterations in serum sodium concentration

(see Chapter 1). Disorders of sodium balance are disorders of ECF volume. This construct has a physiologic basis because water balance and sodium balance can be controlled separately and by distinct hormonal systems. It should be emphasized, however, that disorders of sodium balance frequently lead to or are associated with disorders of water balance. This is evident from Figure 2-24 in which hyponatremia is noted to be a sign of either ECF volume expansion or contraction. Thus, the distinction between disorders of sodium and water balance is useful in constructing differential diagnoses; however, the close interrelationships between factors that control sodium and water balance should be kept in mind.

The figures herein describe characteristics of sodium homeostasis in normal persons and also describe several of the regulatory systems that are important participants in controlling renal sodium excretion. Next, mechanisms of sodium transport along the nephron are presented, followed by examples of disorders of sodium balance that illuminate current understanding of their pathophysiology. Recently, rapid progress has been made in unraveling mechanisms of renal volume homeostasis. Most of the hormones that regulate sodium balance have been cloned and sequenced. Intracellular signaling mechanisms responsible for their effects have been characterized. The renal transport proteins that mediate sodium reabsorption also have been cloned and sequenced. The remaining challenges are to integrate this information into models that describe systemic volume homeostasis and to determine how alterations in one or more of the well-characterized systems lead to volume expansion or contraction.

Normal Extracellular Fluid Volume Homeostasis

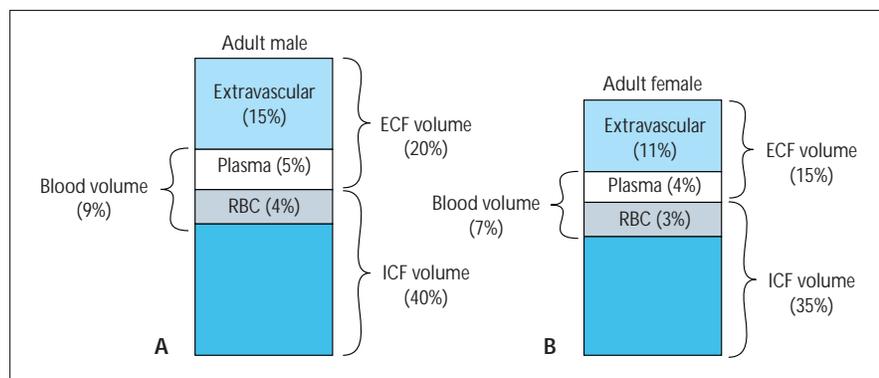
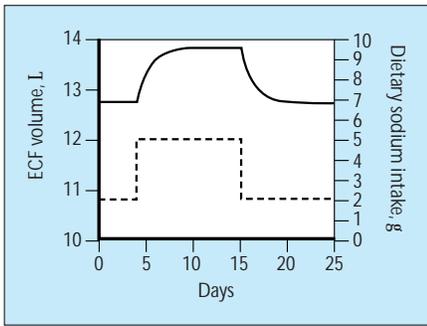


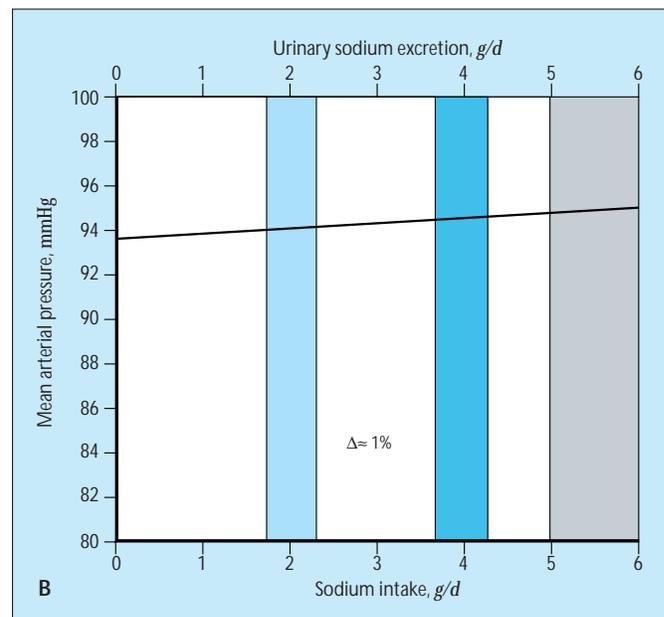
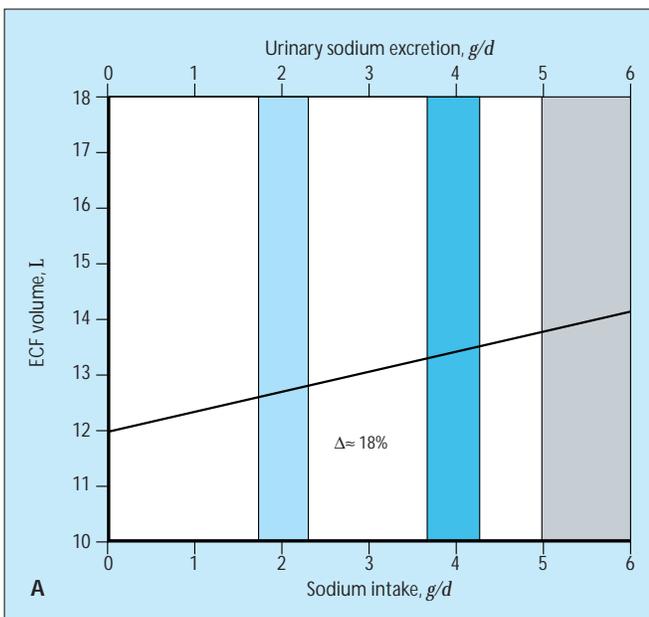
FIGURE 2-1

Fluid volumes in typical adult men and women, given as percentages of body weight. In men (A), total body water typically is 60% of body weight (Total body water = Extracellular fluid [ECF] volume + Intracellular fluid [ICF] volume). The ECF volume comprises the plasma volume and the extravascular volume. The ICF volume comprises the water inside erythrocytes (RBCs) and inside other cells. The blood volume comprises the plasma volume plus the RBC volume. Thus, the RBC volume is a unique component of ICF volume that contributes directly to cardiac output and blood pressure. Typically, water comprises a smaller percentage of the body weight in a woman (B) than in a man; thus, when expressed as a percentage of body weight, fluid volumes are smaller. Note, however, that the percentage of total body water that is intracellular is approximately 70% in both men and women [5].

**FIGURE 2-2**

Effects of changes in dietary sodium (Na) intake on extracellular fluid (ECF) volume. The dietary intake of Na was increased from 2 to 5 g, and then returned to 2 g. The relationship between dietary Na intake (dashed line) and ECF volume (solid line) is derived from the model of Walser [1]. In this model the rate of Na excretion is assumed to be proportional to the content of Na in the body (A_t) above a zero point (A_0) at which Na excretion ceases. This relation can be expressed as $dA_t/dt = I - k(A_t - A_0)$, where I is the dietary Na intake and t is time. The ECF volume is approximated as the total body Na content divided by the plasma Na concentration. (This assumption is strictly incorrect because approximately 25% of Na is tightly bound in bone; however, this amount is nearly invariant and can be ignored in the current analysis.) According to this construct, when dietary Na intake changes from level 1 to level 2, the ECF volume approaches a new steady state exponentially with a time constant of k according to the following equation:

$$A_2 - A_1 = \frac{I_2}{k} + \frac{I_1 - I_2}{k} e^{-kt}$$

**FIGURE 2-3**

Relation between dietary sodium (Na), extracellular fluid (ECF) volume, and mean arterial pressure (MAP). **A**, Relation between the dietary intake of Na, ECF volume, and urinary Na excretion at steady state in a normal person. Note that 1 g of Na equals 43 mmol (43 mEq) of Na. At steady state, urinary Na excretion essentially is identical to the dietary intake of Na. As discussed in Figure 2-2, ECF volume increases linearly as the dietary intake of Na increases. At an ECF volume of under about 12 L, urinary Na excretion ceases. The gray bar indicates a normal dietary intake of Na when consuming a typical Western diet. The dark blue bar indicates the range of Na

intake when consuming a “no added salt” diet. The light blue bar indicates that a “low-salt” diet generally contains about 2 g/d of Na. Note that increasing the dietary intake of Na from very low to normal levels leads to an 18% increase in ECF volume. **B**, Relation between the dietary intake of Na and MAP in normal persons. MAP is linearly dependent on Na intake; however, increasing dietary Na intake from very low to normal levels increases the MAP by only 1%. Thus, arterial pressure is regulated much more tightly than is ECF volume. (**A**, Data from Walser [1]; **B**, Data from Luft and coworkers [3].)