Body Fluid Dynamics: Back to the Future

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ABSTRACT
Pioneering investigations conducted over a half century ago on tonicity, transcapillary fluid exchange, and the distribution of water and solute serve as a foundation for understanding the physiology of body fluid spaces. With passage of time, however, some of these concepts have lost their connectivity to more contemporary information. Here we examine the physical forces determining the compartmentalization of body fluid and its movement across capillary and cell membrane barriers, drawing particular attention to the interstitium operating as a dynamic interface for water and solute distribution rather than as a static reservoir. Newer work now supports an evolving model of body fluid dynamics that integrates exchangeable Na\(^+\) stores and transcapillary dynamics with advances in interstitial matrix biology.


Transcapillary movement of water and solute between cells and extracellular compartments interfaces with powerful physical forces residing in the interstitial matrix. A modern view of body fluid spaces hinges on reconnecting historical principles with this new and emerging dynamic.

Compartmentalization of Body Water
The content of total body water (TBW) is a physiologic function of tissue composition leading to qualitatively predictable alterations with age, gender, and body weight. Most tissues such as skin, muscle, visceral organs, and brain consist of 70 to 80% water by weight, whereas adipose tissue and bone are only 10 to 20% water. TBW reflects a weighted average of tissue water content with relatively lower values in subjects with greater adiposity or lower muscle mass. Relative to weight, women and elderly individuals generally have less body water because of higher content of body fat or preferential loss of muscle mass with age, respectively. TBW increases with obesity but decreases relative to body weight with the gain of relatively drier adipose tissue.1,2

Nephrologists routinely estimate TBW to gauge electrolyte and fluid deficits with hypovolemia or hypertonicity, assess dialytic adequacy using TBW as a surrogate for the volume of distribution of urea, guide drug dosing, and rationalize dialytic clearance of toxins. TBW is classically estimated as 60% of body weight in men and 50% of body weight in women deducting 5% for elderly patients.3 Given physiologic variation in body tissue composition, early investigators recognized that absolute weight-based rules of estimation apply only to a select population of healthy individuals4 and subsequently derived regression equations better predict TBW in a broader range of subjects. Anthropomorphic equations including age, gender, ethnicity, weight, and height are now available to im-

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The ECF compartment is further subdivided into interstitial fluid (ISF) and transcellular fluid. Skeletal muscle predominates the ICF. Percentages of total body water (TBW) are provided in Figure 1 and Table 1. The ECF is subdivided into five subcompartments: plasma volume; interstitial and lymph fluid; dense connective tissue and bone; transcellular fluid within body cavities such as the pleural space, cerebrospinal fluid; and adipose tissue. Scant adipose tissue water resides primarily in the ECF and tips compartmentalization toward the extracellular compartment with increasing obesity. Higher fat mass and lower skeletal muscle content raise the ratio of plasma to interstitial fluid volume. To clarify the compartmentalization of body water, we provide a balance sheet for body weight and water distribution among the major body tissues for men and women (Table 3).

Table 1. Tracer distributions for measurement of ECF volume

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Volume of Distribution (% TBW)</th>
<th>Plasma/Lymph/Interstitial</th>
<th>Connective Tissue</th>
<th>Bone</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inulin</td>
<td>25 to 33</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>sucrose</td>
<td>30 to 36</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>mannitol</td>
<td>33 to 39</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>glucose</td>
<td>42 to 46</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sulfate</td>
<td>33 to 39</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Chloride (or bromide)</td>
<td>46 to 52</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sodium</td>
<td>50 to 55</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>

Eadman and Leibman\(^2\) drew upon historic dissection data for skeletal water as 16% of body weight,\(^19\) skeletal water content as 25 to 30% by weight, and assumed skeletal water is >90% extracellular to calculate ECF bone water as 7.5% of TBW. Unfortunately, skeletal water is not >90% extracellular, because skeletal weight includes bone and enclosed marrow (Table 2).\(^17,18,24,25\) Normally active bone marrow is highly cellular, predominantly intracellular water.\(^25,26\) When bone and marrow are accounted for, skeletal water is only about 60% extracellular, reducing bone ECF to 3% of TBW (Table 2).

Skeletal muscle water is often underappreciated but accounts for 40 to 50% of TBW, nearly 75% of ICF and cell mass, and about 33% of interstitial fluid volume. Loss of muscle mass redistributes TBW from ICF to ECF and increases the ratio of plasma to interstitial fluid volume.\(^4,27\) To clarify the compartmentalization of body water, we provide a balance sheet for body weight and water distribution among the major body tissues for men and women (Table 3).

\[ P_{ic} - P_{ec} = \Pi_{ic} - \Pi_{ec} \]  

\(P_{ic}\) and \(P_{ec}\) represent intracellular and extracellular hydrostatic pressures, respectively, and \(\Pi_{ic}\) and \(\Pi_{ec}\) represent osmotic pressures.
Table 2. Distribution of water and Na\(^+\) within bone and marrow (skeleton)

<table>
<thead>
<tr>
<th>Skeletal Component</th>
<th>Water Content (L)</th>
<th>Relative Water (% of Tissue Mass)</th>
<th>ECF Water (L)</th>
<th>Relative ECF (% of TBW)</th>
<th>Na(^+) Content (mEq/kg of body weight)</th>
<th>Tissue [Na(^+)] (mEq/L H(_2)O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>0.9</td>
<td>15</td>
<td>0.9</td>
<td>2.1</td>
<td>18 to 20 (5)</td>
<td>-1500 (~400)</td>
</tr>
<tr>
<td>Active marrow</td>
<td>0.9</td>
<td>80</td>
<td>0.18</td>
<td>0.4</td>
<td>0.4</td>
<td>30</td>
</tr>
<tr>
<td>Inactive marrow</td>
<td>0.4</td>
<td>15</td>
<td>0.32</td>
<td>0.75</td>
<td>0.6</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>2.2</td>
<td>23</td>
<td>1.4</td>
<td>3.25</td>
<td>21 (6)</td>
<td>700 (200)</td>
</tr>
</tbody>
</table>

Tissue water (%) 63

The values are estimates for average adult man. The values in parentheses represent exchangeable Na\(^+\) as opposed to total Na\(^+\). Based on references 10,14,18,25,26,183. TBW, total body water; ECF, extracellular fluid.

Table 3. Body water distribution among tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Weight (kg)</th>
<th>Body Weight (%)</th>
<th>Water Content Fraction</th>
<th>ECF Fraction</th>
<th>ECF Water (L)</th>
<th>ICF Water (L)</th>
<th>Total Water (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>man 5.5</td>
<td>7.53</td>
<td>0.80</td>
<td>0.63</td>
<td>2.79</td>
<td>1.61</td>
<td>4.40</td>
</tr>
<tr>
<td></td>
<td>woman 4.1</td>
<td>6.83</td>
<td>0.80</td>
<td>0.68</td>
<td>2.23</td>
<td>1.05</td>
<td>3.28</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>man 28.5</td>
<td>39.04</td>
<td>0.76</td>
<td>0.16</td>
<td>3.47</td>
<td>18.19</td>
<td>21.66</td>
</tr>
<tr>
<td></td>
<td>woman 18</td>
<td>30</td>
<td>0.76</td>
<td>0.16</td>
<td>2.19</td>
<td>11.49</td>
<td>13.68</td>
</tr>
<tr>
<td>Skin</td>
<td>man 4.3</td>
<td>5.89</td>
<td>0.72</td>
<td>0.95</td>
<td>2.94</td>
<td>0.15</td>
<td>3.10</td>
</tr>
<tr>
<td></td>
<td>woman 3</td>
<td>5</td>
<td>0.72</td>
<td>0.95</td>
<td>2.05</td>
<td>0.11</td>
<td>2.16</td>
</tr>
<tr>
<td>Brain and viscera</td>
<td>man 6</td>
<td>8.22</td>
<td>0.72</td>
<td>0.35</td>
<td>1.51</td>
<td>2.81</td>
<td>4.32</td>
</tr>
<tr>
<td></td>
<td>woman 5.4</td>
<td>9</td>
<td>0.72</td>
<td>0.35</td>
<td>1.36</td>
<td>2.53</td>
<td>3.89</td>
</tr>
<tr>
<td>Bone</td>
<td>man 5.75</td>
<td>7.88</td>
<td>0.15</td>
<td>1.00</td>
<td>0.86</td>
<td>0.00</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>woman 4.2</td>
<td>7</td>
<td>0.15</td>
<td>1.00</td>
<td>0.63</td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td>Active Marrow</td>
<td>man 1.17</td>
<td>1.6</td>
<td>0.80</td>
<td>0.20</td>
<td>0.19</td>
<td>0.75</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>woman 0.9</td>
<td>1.5</td>
<td>0.80</td>
<td>0.20</td>
<td>0.14</td>
<td>0.58</td>
<td>0.72</td>
</tr>
<tr>
<td>Inactive Marrow</td>
<td>man 2.48</td>
<td>3.4</td>
<td>0.15</td>
<td>0.80</td>
<td>0.30</td>
<td>0.07</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>woman 1.8</td>
<td>3</td>
<td>0.15</td>
<td>0.80</td>
<td>0.22</td>
<td>0.05</td>
<td>0.27</td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>man 3.7</td>
<td>5.07</td>
<td>0.80</td>
<td>1.00</td>
<td>2.96</td>
<td>0.00</td>
<td>2.96</td>
</tr>
<tr>
<td></td>
<td>woman 3</td>
<td>5</td>
<td>0.80</td>
<td>1.00</td>
<td>2.4</td>
<td>0.00</td>
<td>2.4</td>
</tr>
<tr>
<td>Transcellular</td>
<td>man 1.1</td>
<td>1.51</td>
<td>0.95</td>
<td>1.00</td>
<td>1.05</td>
<td>0.00</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>woman 1.1</td>
<td>1.83</td>
<td>0.95</td>
<td>1.00</td>
<td>1.05</td>
<td>0.00</td>
<td>1.05</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>man 14.5</td>
<td>19.86</td>
<td>0.14</td>
<td>0.80</td>
<td>1.62</td>
<td>0.41</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>woman 18.5</td>
<td>30.83</td>
<td>0.13</td>
<td>0.85</td>
<td>1.97</td>
<td>0.35</td>
<td>2.31</td>
</tr>
<tr>
<td>Total</td>
<td>man 73</td>
<td></td>
<td>17.69</td>
<td>24</td>
<td>41.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>woman 60</td>
<td></td>
<td>14.23</td>
<td>16.15</td>
<td>30.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of TBW</td>
<td>man 42.43</td>
<td>57.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>woman 46.84</td>
<td>53.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of Body Weight</td>
<td>man 57.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>woman 50.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values shown are for an average adult man or an average adult woman. Adapted from references 1,2,4,10,14,18,25,26, and 184–186. TBW, total body water; ICF, intracellular fluid; ECF, extracellular fluid.

motic pressures. Plants, fungi, and bacteria possess rigid cell walls that generate hydrostatic pressure to counteract osmotic pressure gradients. Animal cells shed these reinforced walls during evolution to gain flexibility, but the cost of this loss leaves cell volume regulation to the mercy of extracellular tonicity\(^{29,30}\);
where \([c]\) represents molal solute concentration, \(z\) is the valence for electrolyte solutes, and \(\varphi\) is the osmotic coefficient for nonideality (see supplemental material for further details and index of mathematical symbols).31,32

Osmotic water movement is directly proportional to hydraulic permeability \(I_p\) and solute concentration gradient \(\Delta[c]\) in the ideal situation of an impermeable solute33:

\[
\text{Osmotic Water Flux} = I_p \times \Delta\Pi_{\text{ideal}}
\]

\[
= I_p \times 19.34 \times \varphi \times z \times \Delta[c] \tag{6}
\]

Most solutes are partially permeable and undergo convective transport along with water. Staverman introduced the reflection coefficient, \(\sigma\), to relate the observed osmotic pressure gradient \(\Delta\Pi_{\text{obs}}\) to the ideal osmotic pressure gradient \(\Delta\Pi_{\text{ideal}}\) with an impermeable solute34:

\[
\sigma = \frac{\Delta\Pi_{\text{obs}}}{\Delta\Pi_{\text{ideal}}} \tag{7}
\]

Osmotic Water Flux

\[
= I_p \times \sigma \times 19.34 \times \varphi \times z \times \Delta[c] \tag{8}
\]

\(\sigma\) is a dimensionless number between 0 and 1. In the presence of a concentration gradient, a solute with \(\sigma = 1\) produces maximal osmosis, whereas a solute with \(\sigma = 0\) fails to generate osmotic water movement. Why is there no net water flux when \(\sigma = 0\) despite a large concentration gradient \(\Delta[c] \gg 0\)? Qualitatively, solute movement down its concentration gradient provides free energy for water to move against its osmotic gradient, which counteracts favorable water movement in the opposite direction; thus, no net water transport results. For solute to provide free energy for uphill water movement, both solute and water must move in a coupled fashion along the same pathway.35

Solute are often classified as effective or ineffective osmoles on the basis of their ability to generate osmotic water movement. Osmotic water flux requires a solute concentration gradient \(\Delta[c] \gg 0\) and a sizeable reflection coefficient \(\sigma \gg 0\); effective osmoles satisfy both requirements, whereas ineffective osmoles fail on one or both counts. Simplistically, a solute concentration gradient across a membrane barrier must be generated faster than the solute flux across the barrier to sustain a concentration gradient for osmosis. Flux of noncharged solutes is often divided into a diffusive component in the absence of water movement and a convective component, which occurs with water flux \(I_v\)33,36:

\[
P_{\text{ic}} - P_{\text{ec}} = 0 \tag{2}
\]

\[
\Pi_{\text{ic}} = \Pi_{\text{ec}} \tag{3}
\]

\[
\Pi(37^\circ\text{C};\text{mmHg}) = 19.34 \times \varphi \times z \times [c] \tag{4}
\]

\[
\text{Osmolality (mOsm/kg)} = \varphi \times z \times [c] \tag{5}
\]

\[
J_s = P_D \times \Delta[c] + (1 - \sigma) \times J_v \times [c]_m \tag{9}
\]

where \(J_s\) is solute flux, \(P_D\) is diffusive permeability, and \([c]_m\) is mean solute concentration across the membrane. Generally, solutes with low reflection coefficients \((\sigma \to 0)\) have high \(P_D\), because the transport pathway allowing for convective solute transport with water also typically supports diffusive solute movement.37 The converse is not necessarily true because solutes with high reflection coefficients \((\sigma \to 1)\) may or may not exhibit low \(P_D\), depending on the characteristics of the independent pathway for solute diffusion. If the independent pathway is simple diffusion through the lipid bilayer, \(P_D\) is typically low.38 Alternatively, if the independent pathway is transporter facilitated, \(P_D\) is relatively high. For example, along inner medullary collecting ducts, urea and water move independently through urea transporter and aquaporin facilitated pathways during high ADH states; thus, \(P_D\) is high, but \(\sigma\) is near 1.39,40

Urea illustrates the relationship between solute osmotic efficacy and membrane permeability, diffusion surface area, and kinetics of solute generation or loss. Urea is relatively hydrophilic and exhibits low \(P_D\) \((\sim 1 \text{ to } 5 \times 10^{-6} \text{ cm/s})\) and a reflection coefficient near 1 in artificial lipid bilayers; thus, urea is quite effective at eliciting osmosis when urea concentration gradients are abruptly created in these experimental systems.41 This is in contrast to ethanol, which exhibits high \(P_D\) \((\sim 10^{-4} \text{ cm/s})\) even with model membranes.42 However, textbooks often suggest that urea is freely diffusible across membranes and therefore an ineffective osmole.3 Urea transporters facilitate urea diffusion across some biologic membranes, but even the low permeability of pure lipid bilayers is sufficient to minimize urea concentration gradients as total cell membrane surface area is quite large \((\sim1.2 \times 10^8 \text{ cm}^2\) or 12,000 m2), and urea generation rate is comparatively meager.43 Even if one assumes a robust urea generation rate of about 40 g/d, pure lipid bilayer permeability, and no urea excretion or metabolism, a transcellular urea gradient of only about 0.025 mM is expected (see supplemental material). Transcapillary urea gradients are also minimal for most capillary beds as a result of high diffusive permeability and a low reflection coefficient \((\sigma < 0.1)\) with urea easily traversing interendothelial pores.44–46 However, cerebral capillaries exhibit low urea permeability with a sizeable reflection coefficient of about 0.5.47,48 If blood urea nitrogen falls at a rate of 50 mg/dl/h during hemodialysis, a cerebral transcapillary urea gradient of about 0.25 mM can develop leading to a \(\sim 2.4 \text{ mmHg}\) (19.34 * 0.5 * 0.25 mOsm/kg) osmotic pressure favoring capillary filtration (see supplemental material). Cerebral interstitial edema or dialysis disequilibrium may ensue from such a rapid fall in blood urea nitrogen.49

At the capillary-interstitial interface, plasma proteins are excluded from interendothelial pores and act as effective osmoles, whereas small solutes such as Na+, Cl−, and urea are ineffective osmoles freely moving across interendothelial spaces.44,50 Oncotic and colloid osmotic pressure (COP) are used to describe protein-generated osmotic pressure, but these
Inflammatory hypoalbuminemia behaves similarly as $\alpha_1$ and $\alpha_2$ fractions—the acute phase proteins—dramatically rise, but differs compared to analbuminemia because the $\beta$ fraction is unchanged, and the $\gamma$ fraction often increases with chronicity. Thus, globulin osmotic efficiency improves but slightly less compared with analbuminemia with a fall in globulin $\text{MW}_{av}$ from $\sim 150$ kD to $\sim 120$ kD (see supplemental material). The larger osmotic contribution of plasma globulins facilitates a robust defense of plasma COP in inflammatory states and explains the superior correlation of plasma total protein concentration with plasma COP compared with serum albumin in critically ill, hypoalbuminemic patients.

**Cell Volume Homeostasis and Body Na$^+$ and K$^+$ Distribution**

Tonicity is shorthand for the action of effective osmolality across a barrier and in this context traditionally refers to the volume behavior of cells in a solution. Osmolality, on the other hand, measures both effective and ineffective osmoles in a kilogram of body fluid. For instance, ethanol elevates plasma osmolality but does not affect tonicity by rapidly permeating lipid bilayers. Thus, estimates of tonicity are physiologically relevant, whereas osmolality is an imperfect surrogate for tonicity and requires appropriate discounting of ineffective osmoles.

The relative abundance of effective osmoles in intracellular and extracellular compartments dictates body water distribution between ICF and ECF. All cells contain largely fixed or poorly permeable anions such as metabolites (ATP, phosphocreatine, and sulfate), nucleotides, and proteins. $K^+$ acts as the primary counter-ion and serves optimal ribosomal protein synthesis requiring high intracellular $K^+$ concentrations. The fixed intracellular anions and $K^+$ counter-ions create a Donnan effect-related osmotic gradient favoring persistent water entry. To counteract this osmotic gradient, Na$^+$-K$^+$-ATPases actively extrude Na$^+$ ions producing a double-Donnan effect. $\text{Cl}^-$ passively moves with Na$^+$ to maintain electroneutrality leading to osmotic equilibrium (Figure 2). In essence, the cells expend ATP to convert permeable Na$^+$ and K$^+$ ions into impermeable, effective osmoles sequestered in the ECF and ICF, respectively. Similarly, $\text{Cl}^-$ concentrates in the ECF, whereas fixed anions predominate in the ICF. Water passively distributes into the ECF or ICF compartments in proportion to the effective Na$^+$ and K$^+$ content to reach effective osmotic equilibrium (tonicity) and establish cell volume.

Almost 98% of total body Na$^+$ is distributed among the ECF subcompartments (Table 4). Total body Na$^+$ is often divided into exchangeable (Na$^+$$_{ex}$) and nonexchangeable domains on the basis of the extent of radioisotope Na$^+$ equilibration with the body pool. About 20 to 30% of total body Na$^+$ is nonexchangeable, residing in anhydrous bone matrix. Total body K$^+$ diametrically mirrors Na$^+$ with about 95% located intracellularly (Table 4). Unlike Na$^+$, however, over 90% of body K$^+$ is exchangeable.
Body Sodium and Potassium Distribution

### Table 4.

<table>
<thead>
<tr>
<th></th>
<th>PlasmaContent (mEq/kg)</th>
<th>PlasmaConcentration (mEq/kg H₂O)</th>
<th>InterstitialContent (mEq/kg)</th>
<th>InterstitialConcentration (mEq/kg H₂O)</th>
<th>Bone and Connective TissueContent (mEq/kg)</th>
<th>Bone and Connective TissueConcentration (mEq/kg H₂O)</th>
<th>IntracellularContent (mEq/kg)</th>
<th>IntracellularConcentration (mEq/kg H₂O)</th>
<th>TotalExchangeable (mEq/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>6</td>
<td>150</td>
<td>18</td>
<td>148.5</td>
<td>28 (14)</td>
<td>400 (200)</td>
<td>2</td>
<td>6</td>
<td>54</td>
</tr>
<tr>
<td>K⁺</td>
<td>0.2</td>
<td>4.2</td>
<td>0.5</td>
<td>4</td>
<td>3.3</td>
<td>4.8</td>
<td>52.6 (49.3)</td>
<td>160 (150)</td>
<td>56.6</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>3.6</td>
<td>60</td>
<td>20</td>
<td>110</td>
<td>30</td>
<td>90</td>
<td>120</td>
<td>150</td>
<td>70</td>
</tr>
<tr>
<td>A⁻</td>
<td>24.7</td>
<td>350</td>
<td>32</td>
<td>330</td>
<td>32</td>
<td>33</td>
<td>32</td>
<td>33</td>
<td>32</td>
</tr>
</tbody>
</table>

The values are estimates for an average adult man. The parentheses indicate exchangeable cation opposed to total cation content and concentration. Adapted from references 2,14,183, and 187.

Historically dominated investigation, interstitial balance equally depends on lymphatic function. The modified Starling relationship mathematically delineates water flux between capillary plasma and interstitium:

\[
\text{Net Capillary Filtration (J_ν)} = \frac{I_p \ast ([P_c - P_i]) - \sigma (\Pi_c - \Pi_i)}{L_p}
\]

where \(I_p\) is hydraulic permeability, \(P_c\) and \(P_i\) are capillary and interstitial hydrostatic pressures, \(\Pi_c\) and \(\Pi_i\) are capillary and interstitial colloid osmotic pressures, and \(\sigma\) represents the osmotic reflection coefficient. At steady state, capillary filtration must equal lymphatic flow. The magnitude of hydrostatic and osmotic pressures and their balance across capillaries has been debated continuously over the last century. Physiology textbooks still present a framework where filtration predominates at the arterial end and reabsorption occurs at the venous end of the capillary with falling capillary hydrostatic pressure and constant capillary osmotic pressure (Figure 3). Recent studies, however, point to low net filtration with net filtration pressures \((J/V/L_p)\) of 0.5 to 1 mmHg across the entire length of the capillary in most vascular beds (Figure 3). A better understanding of interstitial matrix and reassessment of \(\Pi_c\) and \(P_i\) has driven this paradigm shift.

Interstitial and connective tissues are typically modeled as triphasic systems: free flowing fluid with albumin, a gel phase with glycosaminoglycans (GAGs), and a collagen-based matrix. Water and small solutes \((Na^+, Cl^-,\) and urea) move easily between all compartments according to prevailing osmotic, hydrostatic, and electrochemical forces. Albumin is excluded from the GAG compartment, and both GAGs and albumin are excluded from the collagen matrix. GAGs generate osmotic pressure \((\Pi_{GAG})\) both in proportion to concentration and negative charge density as the latter attracts cations.
Paradigm shift in transcapillary fluid exchange. (A and B) Classic view of transcapillary Starling forces with $\Pi_i$ and $P_i$ ignored leading to predominant filtration on the arterial end giving way to absorption on the venous end. (C and D) $\Pi_i$ is a nonlinear function of filtration rate ($J_v$). Filtration rate is the intersection of this function and $\Pi_i$ as a function of Starling forces. The Starling relationship is linear with a slope equal to $1/\alpha_{K_C}$ and y intercept of $\Pi_i + P_i/\sigma - P_C/\sigma$. As $P_C$ falls along the capillary, the linear Starling curve left shifts as the y intercept increases. The left shift is blunted by a decrease in $P_i$. $\Pi_i$ increases with falling filtration, and the relative steepness of the nonlinear $\Pi_i$ ($J_v$) function maintains filtration along the capillary.

Interstitial hydrostatic pressure ($P_i$) is slightly negative to zero ($-4$ to $0 \text{ mmHg}$). At euvolemia, the interstitium behaves as a low compliance system; small increases in interstitial volume or capillary filtration rate are met with a steep increase in $P_i$ which counteracts capillary filtration and edema. However, once interstitial volume rises by approximately 50% to 60% of albumin content resides in the extravascular compartment at a concentration of about $1$ to $1.5 \text{ g/dl}$ with $10$ g of albumin moving from plasma to lymph per hour. Because GAGs and collagen exclude albumin from about 25 to 50% of the interstitial volume, the effective albumin concentration in the interstitium approaches $2$ to $3 \text{ g/dl}$. $\Pi_i$ is 30 to 60% of $\Pi_i$ when directly measured and mirrors effective albumin concentration. Filtration rate dynamically regulates $\Pi_i$ with increased filtration diluting interstitial albumin and lowering $\Pi_i$ and absorption raising $\Pi_i$. $\Pi_i$ changes steeply with filtration rate as water flux outstrips albumin flux, and albumin exclusion falls producing a disproportionate decline in effective albumin concentration compared with dilution alone.

Interstitial protein gradients produce an even steeper nonlinear fall in $\Pi_i$ with filtration rate. In a two-pore model, most filtration occurs through small pores with $\sigma_{\text{albumin}} \approx 0.95$, whereas large pores transport a minute fraction of water but allow for significant albumin convection with large pore $\sigma_{\text{albumin}} \approx 0.05$. Effective albumin concentration in close proximity to small pores determines filtration as albumin infusion into the general pericapillary interstitium minimally affects filtration. Albumin gradients develop with high concentrations around large pores and low concentrations near small pores (Figure 5). Whether diffusion between pore regions is limited enough to sustain substantial protein concentration gradients is unclear. A variation of the theme proposes endothelial glycocalyx as the primary interendothelial, small pore permeability barrier with subglycocalyx $\Pi$ as the primary determinant of filtration; restricted access to the subglycocalyx space may further limit albumin diffusion to amplify interstitial concentration gradients.

and increases tissue $\text{Na}^+$ concentration. The collagen matrix generates a hydrostatic pressure that typically opposes GAG osmotic swelling ($P_{\text{collagen}}$). Except for hyaluronan, most GAGs are proteoglycans consisting of a carbohydrate GAG attached to a core protein that interacts with the collagen matrix. Measured $P_i$ reflects a balance between matrix hydrostatic and osmotic pressures (Figure 4):

$$P_i \approx P_{\text{collagen}} - \Pi_{\text{GAG}} \quad \text{(Eq. 12)}$$
Imminently increase $P_i$ leading to unabated capillary filtration and edema (Figure 6). Interstitial cells dynamically regulate $P_i$ shifting the entire $P_i$-interstitial volume curve. Cells loosen or tighten their grip on collagen matrix through cell surface integrin receptors, which interact with the extracellular matrix and the force-generating actin cytoskeleton. Reducing collagen $\beta$1-integrin receptor interactions and/or cytoskeletal depolymerization dramatically shifts the $P_i$-volume curve rightward (Figure 6). Inflammatory states and thermal injury decrease $P_i$ as a result of reduced integrin binding of collagen and/or thermal denaturation of collagen. A fall in $P_i$ may play a critical role in the early phase of sepsis and burn-induced edema. A fall in $P_i$ may play a critical role in the early phase of sepsis and burn-induced edema. Nephrotic syndrome demonstrates the interplay between serum albumin, $P_i$, capillary filtration, and $\Pi_i$. Unlike other hypoalbuminemic states, in nephrotic syndrome the globulin $M_{Wav}$ rises significantly to $\sim 215$ kD because of a preferential

$$\pi_{\text{small}} = 0-5 \text{ mm Hg}$$

$$\pi_{\text{large}} = 15-25 \text{ mm Hg}$$

Dynamic interstitial forces play a critical part in regulating plasma-interstitial fluid balance in pathologic states. In hypovolemia, $P_i$ falls in vasoconstricted vascular beds leading to transient interstitial fluid absorption in a process known as transcapillary refill. Subsequent loss of interstitial volume concentrates albumin, increases $\pi_i$, decreases $P_i$, and thus limits transcapillary refill at approximately 75 to 80% of lost plasma volume (Figure 7).

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Figure 7. Transcapillary dynamics in hypovolemia and nephrotic syndrome. (A) Vasoc- 
striction with hypovolemia decreases $P_c$ and left shifts the Starling $I_\Pi$ curve with an 
increased $y$ intercept. Transient interstitial fluid absorption occurs increasing $I_i$ and 
restoring a lower level of steady-state filtration. $F$ also decreases leading to a small right 
shift in linear Starling relationship (not shown). Transcapillary refill of plasma volume 
occurs with absorption but may continue to occur if lymphatic flow is slow to match the 
lower steady-state filtration rate. (B) $I_\Pi$ falls in nephrotic syndrome leading to a right shift 
of the $I_i$ Starling curve and transiently increased filtration. The subsequent fall in $I_\Pi$ 
reduces filtration to a new steady state. $F$ would increase slightly producing a left shift of 
the Starling linear curve to further minimize a rise in filtration (not shown).

urinary loss of osmotically efficient low molecular weight proteins along with albumin and an accumulation of high molecular proteins such as $\alpha$-1-macroglobulin, fibrinogen, haptoglobin multimers, and $\beta$ lipoproteins (see supplemental material). Thus, nephrotic patients are unable to defend $I_i$ despite a reasonable serum total protein concentration as the globulin fraction consists of large, osmotically inefficient proteins. $I_c$ declines proportionately with falling plasma albumin as opposed to analbuminemic patients who exhibit approximately 50% of normal $I_c$ without plasma albumin. Capillary filtration rises with falling $I_c$, but the subsequent fall in $I_i$ and rise in $P_i$ tends to normalize filtration and minimize edema (Figure 7). The difference between $I_i$ and $I_c$ remains constant at about 50% of $I_i$ or about 12 mmHg, essentially negating the tendency for low $I_c$ to produce edema. Of course, because the floor for $I_i$ is zero, once $I_c$ falls below 10 to 14 mmHg (around 1.5 to 2 g/dl plasma albumin), edema is inevitable. A rapid fall in $I_c$ as seen in pediatric nephrotic crises with minimal change disease may kinetically outstrip the compensatory fall in $I_i$, leading to intravascular volume depletion and hemodynamic compromise.

Whether a fall in $I_c$ is the primary determinant of nephrotic edema is controversial, because several investigators have demonstrated autonomously enhanced sodium reabsorption in the distal nephron and diminished sodium excretion preceding hypoproteminemia. Proponents of the overfill hypothesis suggest that renal sodium retention is the primary abnormality in nephrotic syndrome, whereas others support the underfill theory wherein low $I_i$ leads to intravascular volume depletion and secondary renal sodium retention. Increased capillary permeability measured as albumin extravasation (increased $I_p$ and/or decreased $\sigma$) may also contribute to intravascular volume depletion. As in all controversies, individual patients may demonstrate overfill, underfill, or mixed physiology. Severe or rapidly developing hypoproteminemia and clinical features of volume depletion support underfilling, whereas hypertension, renal dysfunction, and mild to moderate hypoalbuminemia (serum albumin > 2 g/dl) suggest overfilling. Minimal change disease more commonly presents with underfill physiology, but whether histologic disease is an independent predictor of volume homeostasis or simply reflects more severe or rapid hypoproteminemia with maintained GFR is unclear.

**Total Body and Compartmental Tonicity**

Animal cells are largely in osmotic equilibrium with their surrounding environment; thus, intracellular tonicity equals interstitial tonicity. Clinicians estimate plasma tonicity, which may not equal interstitial and intracellular tonicity except in the case of red blood cells ($I_{RIC} = I_{PLASMA}$). Fortunately, in most body tissues, the difference between plasma and interstitial osmolality is minimal. A direct experimental measurement of the plasma to interstitial osmolality gradient is the difference in COP, which accounts for both protein and Donnan small ion effects:

$$\Pi_c - \Pi_i \approx 10-20 \text{ mmHg} \approx 0.5-1 \text{ mOsm/kg} \quad (\text{Eq. 13})$$

The tonicity gradient between plasma and interstitium is quite small, and we can hypothesize that tonicity is equal across all body compartments:

$$\text{Plasma Tonicity} \approx \text{Interstitial Tonicity} \approx \text{Total Body Tonicity} \quad (\text{Eq. 14})$$

In addition, if we assume the vast majority of effective body osmoles are exchangeable $\text{Na}^+$ and $\text{K}^+$ and their counter-ions and glucose, the following idealized relationship is derived (see supplemental material):

$$P_Na = f_{PW} \times \frac{\text{Na}^{\text{ex}} + \text{K}^{\text{ex}}}{\text{TBW}} - (G_{Na} \times \Delta[\text{Glucose}]_P) - P_K \quad (\text{Eq. 15})$$

where $f_{PW}$ is the plasma water fraction, and $G_{Na}$ is a correction factor for hyperglycemia related translocational hyponatremia that has been proposed to range from 1.5 to 2.4 mEq/L per 100 mg/dl rise in plasma glucose.
states have found that $P_{Na}$ may be delineated as follows (see supplemental material):

$$P_{Na} = 1.03 \ast f_{PW} \frac{Na_{ex}^+ + K_{ex}^+ - 250}{TBW} - (G_{Na} \ast \Delta [Glucose])_p - P_K \quad (Eq. 16)$$

Because total exchangeable cation ($Na_{ex}^+ + K_{ex}^+$) is in the order of 90 mEq/kg, the ideal relationship is a good approximation because 250 mEq pales in comparison and 1.03 is also quite close to 1. The 250 mEq deviation from ideality relates to a small osmotic gradient between plasma and total body osmolality, non-$Na^+$ and $K^+$ osmoles besides glucose, and exchangeable excess $Na^+$ and $K^+$ (see supplemental material). The nonideal quantity of 250 mEq in the derived $P_{Na}$ relationship applies only to well represented pathologic states within patient cohort data (congestive heart failure, cirrhosis, and low $Na^+$ diet). Whether this quantity is similar in other disease states such as syndrome of inappropriate anti-diuretic hormone (SIADH), volume depletion, and high $Na^+$ diet is unknown and potentially limits the accuracy of the idealized $P_{Na}$ approximation in these situations.\textsuperscript{137}

Broadly speaking, excess $Na^+$ and $K^+$ refer to any compartment where exchangeable $Na^+$ and $K^+$ concentration exceeds plasma water [$Na^+ + K^+$]. Often, excess $Na^+$ and $K^+$ is used interchangeably with osmotically inactive, although the two are not mechanistically synonymous. Some inaccurately suggest that a compartment with osmotically active $Na^+$ and $K^+$ in excess of plasma should accrue water until equilibrium with plasma is reached and excess cation is eliminated; thus, the persistence of a concentration gradient can only occur if excess cation is osmotically inactive. But excess cation may be osmotically active while maintaining a concentration gradient in two ways: a counteracting hydrostatic pressure balances the osmotic gradient, allowing compartment osmolarity to differ from plasma osmolarity or excess $Na^+$ and $K^+$ is counterbalanced by loss of non-$Na^+$ and $K^+$ osmoles maintaining plasma and total body tonicity. Of course, a portion of excess $Na^+$ and $K^+$ may truly be osmotically inactive ($\varphi = 0$). Bone and a small fraction of intracellular cation probably represent the osmotically inactive pool. Some may argue that the distinction between excess and osmotically inactive cation is pure semantics, but a growing literature on cartilage suggests otherwise. Cartilage is hypertonic, yet inelastic cartilage swelling is prevented by a counteracting collagen-based hydrostatic pressure.\textsuperscript{91,138}

Significant attention has historically focused on the dynamics of $Na^+$ balance given its prominent role in hypertension and edematous states. When positive $Na^+$ balance occurs, $Na^+$ is handled in several ways: $Na^+$ accumulates in the extracellular space with water such that plasma tonicity and $Na^+$ concentration remain constant; $Na^+$ is retained in excess of water with a resulting increase in plasma $Na^+$ concentration and tonicity along with a parallel rise in total body tonicity; or $Na^+$ is retained in excess of water with little or no change in plasma tonicity often termed excess $Na^+$ storage (or inaccurately as osmotically inactive $Na^+$ storage). Broadly speaking, several mechanisms account for excess $Na^+$ storage: negative $K^+$ balance offsets positive $Na^+$ balance such that total cation balance is unchanged; positive total cation balance ($Na^+ + K^+$) with negative balance for effective osmoles other than $Na^+$ or $K^+$ salts such that total body effective osmoles remain constant; positive cation balance with osmotically active $Na^+$ associating with interstitial glycosaminoglycans, thereby increasing total body tonicity relative to plasma; or positive cation balance with osmotically inactive $Na^+$ associating with bone mineral matrix or possibly intracellular proteins (Figure 8).

Although measuring $K^+$ balance is straightforward, defin-
ing other mechanisms for excess Na\(^+\) storage is difficult. Over the last half century, investigators have debated whether the movement of Na\(^+\) ions into or out of a storage compartment is necessary to account for positive sodium balance with high sodium diet and edematous states and negative sodium balance in volume depletion or hypotonicity. Many studies neglect K\(^+\) balance, which can often offset a positive Na\(^+\) balance.\(^{139–143}\) Even after accounting for K\(^+\) balance, most short term metabolic balance studies (3 to 5 days) and long term (1 to 3 months) radioisotopic studies generally find reasonable correlation between cation and water balance and plasma tonicity,\(^{144–149}\) whereas intermediate balance studies (7 to 14 days) often suggest Na\(^+\) storage.\(^{150–152}\) Whether these differences reflect biologic phenomena or technical differences remains unclear.\(^{150,153–155}\)

Excess Na\(^+\) storage occurs with high sodium diet (>300 mEq/d). Some excess Na\(^+\) exchanges with intracellular K\(^+\) primarily from skeletal and vascular smooth muscle; thus, total cation balance in this case is unchanged.\(^{147,156}\) Excess Na\(^+\) storage in skin exceeds negative K\(^+\) balance and has recently garnered attention, although the hypothesis dates back over 30 years in the Russian literature.\(^{150,157,158}\) Animal studies demonstrate increased Na\(^+\) concentration in skin (20 to 40 mEq/L tissue water), which translates to about 1 to 2 mEq/kg excess Na\(^+\) storage, assuming that skin water is at most 5% of body weight.\(^{27,156,159}\) Excess Na\(^+\) may accumulate intracellularly in exchange for non-K\(^+\) osmotropes or alternatively associate with interstitial glycosaminoglycans (Figure 8). Radiotracer Na\(^+\) dynamics in isolated skin from animals on high sodium diets suggest an increase in the rapidly exchanging extracellular Na\(^+\) pool rather than the more slowly exchanging intracellular Na\(^+\) pool. Within the rapidly exchanging pool, a compartment outside the insul in space accounts for the majority of the increased Na\(^+\) content, suggesting a stERICally inaccessible site such as interstitial glycosaminoglycans.\(^{157}\) Indeed, negatively charged, sulfated glycosaminoglycan content rises in skin with dietary Na\(^+\) loading.\(^{159–161}\) Na\(^+\) loading transiently increases interstitial fluid and possibly Na\(^+\) concentration, which are known stimulators of interstitial cell matrix production, particularly sulfated GAGs.\(^{162–165}\)

Na\(^+\) associated with negatively charged purified glycosaminoglycans in cartilage exhibits an osmotic coefficient similar to normal saline; thus, skin GAG-associated Na\(^+\) is most likely osmotically active.\(^{86,166}\) Assuming that 20 to 40 mEq/L Na\(^+\) is stored in association with skin interstitial GAGs, \(\Pi_{GAG}\) would rise about 100 to 200 mmHg or approximately 5 to 10 mOsm/kg to achieve the required negative charge density (see supplemental material). Typical transcapillary Starling forces tend to be orders of magnitude smaller in comparison with 100 to 200 mmHg. Dermal swelling pressures can reach up to 100 to 150 mmHg in situations where \(P_{collagen}\) is reduced, suggesting that \(\Pi_{GAG}\) is normally quite high but counteracted by \(P_{collagen}\).\(^{111,167}\) Thus, \(\Pi_{GAG}\) can rise significantly but requires similar increases in \(P_{collagen}\) to prevent high filtration rates and interstitial edema caused by low \(P_i\) (\(P_i \propto P_{collagen} - \Pi_{GAG}\)). Hydrostatic pressure (\(P_{collagen}\)) counterbalances osmotic pressure (\(\Pi_{GAG}\)) to eliminate water movement and maintain a small tonicity gradient between dermal interstitium and plasma. Dermal fibroblasts like their chondrocyte counterparts probably accommodate interstitial hypertonicity with osmolyte accumulation to maintain cell volume.\(^{168,169}\)

When the mechanism of excess Na\(^+\) storage across tissues is broadly surveyed, a hypothetical framework comes into view. Relativeley cellular tissues such as muscle exchange Na\(^+\) for K\(^+\) or other intracellular osmotropes as their high cell mass relative to interstitial space provide a large osmole depot for transcellular exchange. Conversely, relatively acellular connective tissues have minimal intracellular osmoles at their disposal and alternatively depend on osmotically active storage with interstitial glycosaminoglycans or osmotically inactive storage with mineral matrix.

The Na\(^+\) counter-anion may also modify Na\(^+\) storage. When subjects consume large amounts of Na\(^+\) either as Cl\(^-\) or bicarbonate (or equivalents such as citrate or ascorbate) salts, hypertension and plasma volume expansion ensues only with NaCl intake despite equivalent positive sodium balance and weight gain with sodium bicarbonate. Furthermore, NaCl consumption results in hypercalciuria, whereas sodium bicarbonate does not change urinary calcium excretion.\(^{170–173}\) Taken together, water distribution tends to be extravascular and does not affect calcium homeostasis when the Na\(^+\) counter-anion is bicarbonate. Na\(^+\) with a base equivalent may possess a larger pool of intracellular and bone storage mechanisms. Intrapcellular proteins can simply titrate bicarbonate with protons with the resulting protein anionic side chain acting as a counter-ion for excess Na\(^+\) in a potentially osmotically inactive form. For NaCl to store Na\(^+\) in association with intracellular proteins, Na\(^+\) would have to displace protein side chain H\(^+\) or exchange with predominantly protein bound Ca\(^{2+}\). The former is unlikely because cells function poorly with intracellular acidosis, whereas the latter necessitates Ca\(^{2+}\) excretion. The low solubility of calcium bicarbonate probably precludes intracellular Na\(^+\)/Ca\(^{2+}\) exchange with sodium bicarbonate but promotes bone surface crystal integration of sodium bicarbonate \textit{in toto}. Conversely, NaCl requires Na\(^+\)/Ca\(^{2+}\) exchange at the bone matrix interface again leading to hypercalciuria.\(^{174–176}\) Thus, negative Ca\(^{2+}\) balance potentially limits Na\(^+\) storage in the setting of high NaCl intake, but not with bicarbonate salts. Although purely speculative, these hypotheses provide fertile ground for future investigation.

Alterations in intracellular, skin, and bone Na\(^+\) storage may critically regulate blood volume homeostasis and participate in the pathogenesis of salt-sensitive hypertension. These storage mechanisms may buffer the blood volume against transient or sustained sodium loads. Animals and patients with reduced Na\(^+\) storage capacity are prone to blood volume expansion and hypertension.\(^{158,177,178}\) Alternatively, these storage mechanisms activate deleterious neurohormonal and/or inflammatory signaling pathways.\(^{159}\) Although this work points to an exciting paradigm shift in blood volume regulation, whether
these mechanisms contribute to pathology broadly or in a narrow subset of patients remains unknown. Because United States dietary Na\textsuperscript{+} intake is 150 to 200 mEq/d ± 100 mEq/d (2 SD)\textsuperscript{179–181} and storage mechanisms regulating Na\textsuperscript{+} homeostasis require dietary intakes exceeding 300 mEq/d,\textsuperscript{140,150} only about 5% of essential hypertension in American patients may involve alterations in Na\textsuperscript{+} storage.

Conclusions
Understanding body fluid dynamics is critical to the practice of medicine. Phenomenal work accomplished during the last century has lulled us into relying on aging textbook dogma or believing there is little left to discover. However, re-examination of foundational literature suggests some teachings stray from original data. The division of TBW into ICF and ECF is frequently taught as an arbitrary distribution rather than a product of cell volume homeostasis and the relative partitioning of body fat, protein, Na\textsuperscript{+}, and K\textsuperscript{+}. New investigations also suggest novel paradigms involving the dynamic nature of the interstitium that critically regulate ECF homeostasis. Although diet and the kidneys arbitrate blood volume homeostasis in the long run, the interstitium plays a larger role in short term blood and interstitial volume adjustments. Short term Na\textsuperscript{+} storage and interstitial volume homeostasis may be relevant to transient or nonequilibrium phenomena such as BP dipping, flash pulmonary edema, rapid blood loss, burns, and sepsis, to name a few. Future investigation will hopefully unify the molecular and structural biology of interstitial cell-matrix interactions with classic Starling physiology to identify new therapeutic targets for hemodynamic derangements.

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