

# **Much Ado About N...atrium:**

## **Modelling Tissue Sodium As A Highly Sensitive Marker Of Subclinical And Localised Oedema**

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### **SUPPLEMENTAL MATERIAL**

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## Abbreviations

$[\text{Na}^+]_i$  = intracellular  $\text{Na}^+$  concentration (mmo/l)

$[\text{Na}^+]_e$  = extracellular  $\text{Na}^+$  concentration (mmol/l)

$[\text{Na}^+]_T$  = total  $\text{Na}^+$  concentration in tissue (mmol/l)

$[\text{Na}^+]_{OT}$  = total  $\text{Na}^+$  concentration in oedematous tissue (mmol/l)

$[\text{K}^+]_i$  = intracellular  $\text{K}^+$  concentration (mmol/l)

$[\text{K}^+]_e$  = extracellular  $\text{K}^+$  concentration (mmol/l)

$[\text{K}^+]_T$  = total  $\text{K}^+$  concentration in a tissue (mmol/l)

$[\text{K}^+]_{OT}$  = total  $\text{Na}^+$  concentration in oedematous tissue (mmol/l)

$V_i$  = volume of intracellular water solution in tissue

$V_e$  = volume of extracellular water solution in tissue

$V_T$  = volume of total (extracellular + intracellular) water solution in tissue

$\text{ECV}\%$  = extracellular volume fraction (%) =  $100 \cdot V_e/V_T$

$\text{OE}\%$  = percentage of oedema added to a tissue

### Model for expected total concentration of Na<sup>+</sup> and K<sup>+</sup> in a tissue

For any tissue, considered as a sum of two different water solutions:

Na<sup>+</sup> total moles = Na<sup>+</sup> extracellular moles + Na<sup>+</sup> intracellular moles

Therefore:

$$[\text{Na}^+]_T \cdot V_T = [\text{Na}^+]_e \cdot V_e + [\text{Na}^+]_i \cdot V_i$$

or

$$\begin{aligned} [\text{Na}^+]_T &= [\text{Na}^+]_e \cdot V_e/V_T + [\text{Na}^+]_i \cdot V_i/V_T \\ &= [\text{Na}^+]_e \cdot \text{ECV\%/100} + [\text{Na}^+]_i \cdot (1-\text{ECV\%})/100 \end{aligned}$$

Assuming a convenient reference volume of tissue containing 1 L of total (intracellular + extracellular) water solution, absolute Na<sup>+</sup> tissue content (moles) numerically coincides (≈) with [Na<sup>+</sup>]<sub>T</sub>.

Similarly, for potassium:

$$[\text{K}^+]_T = [\text{K}^+]_e \cdot \text{ECV\%/100} + [\text{K}^+]_i \cdot (1-\text{ECV\%})/100$$

For a similar reference volume of tissue as above, absolute K<sup>+</sup> tissue content (moles) ≈ [K<sup>+</sup>]<sub>T</sub>

The last two equations were used to generate the model for expected total concentration of Na<sup>+</sup> and K<sup>+</sup> for any tissue with 15% < ECV% < 85% in its “baseline” conditions (Figure, left panel, open symbols).

### Model for expected total concentration of Na<sup>+</sup> and K<sup>+</sup> in an oedematous tissue

We simulated the effect of adding a fixed and biologically plausible moiety of oedema to tissues by adding 1%, 2.5% and 5% (OE%) of a solution equal in composition to the extracellular. The above percentages were defined as v/v in relation to the “baseline” volume of the water solution in the tissue, which equals 1 L in the aforementioned convenient reference tissue.

As per first equation above, absolute Na<sup>+</sup> content in the oedematous tissue is:

$$\begin{aligned} \text{Na}^+ \text{ total moles}_{OT} &= (\text{Na}^+ \text{ extracellular moles} + \text{Na}^+ \text{ intracellular moles})_T + \text{Na}^+ \text{ moles in oedema} \\ &= (\text{Na}^+ \text{ total moles})_T + \text{Na}^+ \text{ moles in oedema} \end{aligned}$$

For the reference tissue, it numerically corresponds to

$$\approx [\text{Na}^+]_e \cdot \text{ECV\%/100} + [\text{Na}^+]_i \cdot (1-\text{ECV\%})/100 + [\text{Na}^+]_e \cdot \text{OE\%/100}$$

Na<sup>+</sup> concentration in the oedematous tissue is:

$$\begin{aligned} [\text{Na}^+]_{OT} &= \text{Na}^+ \text{ total moles}_{OT} / \text{total Volume} \\ &= \text{Na}^+ \text{ total moles}_{OT} / (\text{Volume}_T + \text{Volume}_{\text{oedema}}) \\ &= \text{Na}^+ \text{ total moles}_{OT} / (1\text{L} + 1\text{L} \cdot \text{OE\%/100}) \\ &\approx \{[\text{Na}^+]_e \cdot \text{ECV\%/100} + [\text{Na}^+]_i \cdot (1-\text{ECV\%})/100 + [\text{Na}^+]_e \cdot \text{OE\%/100}\} / (1\text{L} + 1\text{L} \cdot \text{OE\%/100}) \end{aligned}$$

Similarly, for potassium:

$$\text{K}^+ \text{ total moles}_{OT} \approx [\text{K}^+]_e \cdot \text{ECV\%/100} + [\text{K}^+]_i \cdot (1-\text{ECV\%})/100 + [\text{K}^+]_e \cdot \text{OE\%/100}$$

$$[\text{K}^+]_{OT} \approx \{[\text{K}^+]_e \cdot \text{ECV\%/100} + [\text{K}^+]_i \cdot (1-\text{ECV\%})/100 + [\text{K}^+]_e \cdot \text{OE\%/100}\} / (1\text{L} + 1\text{L} \cdot \text{OE\%/100})$$

$[\text{Na}^+]_{\text{OT}}$  and  $[\text{K}^+]_{\text{OT}}$  equations were used to generate the model for expected total concentration of  $\text{Na}^+$  and  $\text{K}^+$  in an oedematous tissue, after addition of 5% oedema (Figure, left panel, closed symbols).

### Changes in $\text{Na}^+$ , $\text{K}^+$ and water

Percentage changes ( $\Delta\%$ ) for absolute  $\text{Na}^+$  content and concentration were defined, respectively, as:

$$\Delta\% \text{ absolute } \text{Na}^+ \text{ content} = (\text{Na}^+ \text{ total moles}_{\text{OT}} - \text{Na}^+ \text{ total moles}_{\text{T}}) \cdot 100 / \text{Na}^+ \text{ total moles}_{\text{T}}$$

$$\Delta\% \text{ Na}^+ \text{ concentration} = ([\text{Na}^+]_{\text{OT}} - [\text{Na}^+]_{\text{T}}) \cdot 100 / [\text{Na}^+]_{\text{T}}$$

Percentage changes ( $\Delta\%$ ) for absolute  $\text{K}^+$  content and concentration were similarly calculated but not plotted because not informative: they showed a stable decrease, numerically close to  $-\text{OE}\%$ , non-significantly affected by  $\text{ECV}\%$  (*data not shown*).

Percentage changes ( $\Delta\%$ ) for water content was assumed as equal to  $\text{OE}\%$ , which in fact corresponds to the v/v  $\Delta\%$  of the solution, rather than solvent. Of note, this approximation would at most over-estimate the  $\Delta\%$  for water compared to  $\Delta\%$  for  $\text{Na}^+$  and  $\text{K}^+$ .

### Biological assumptions

This mathematical model is obviously affected in absolute, but not relative, terms by changes in the baseline assumptions, i.e.  $[\text{Na}^+]_{\text{i}}$ ,  $[\text{Na}^+]_{\text{e}}$ ,  $[\text{K}^+]_{\text{i}}$  and  $[\text{K}^+]_{\text{e}}$ : all these concentrations are subject to multiple and tight regulations (particularly for the intracellular site), which can act differently in different individuals and/or conditions. Nevertheless, despite minimal shifts along the vertical axes, curves behave consistently across multiple intra-extra cellular simulated conditions (*data not shown*), thus strengthening the robustness of the model.

For the purpose of this paper, the figure was generated assuming:

$[\text{Na}^+]_{\text{e}} = 144 \text{ mmol/l}$  and  $[\text{K}^+]_{\text{e}} = 4.64 \text{ mmol/l}$  (as reported in an experimental setting, for comparability (1); normal values for humans: 135-145 and 3.5-5.5, respectively(2)).  $[\text{Na}^+]_{\text{i}}$  and  $[\text{K}^+]_{\text{i}}$  were assumed as 10 and 140 mmol, respectively, as classically reported (2).

### Supplemental references

1. Titze J, Bauer K, Schafflhuber M, Dietsch P, Lang R, Schwind KH, Luft FC, Eckardt KU, Hilgers KF. Internal sodium balance in DOCA-salt rats: a body composition study. *American journal of physiology Renal physiology*. 2005;289:F793-802.
2. Herring NPDJ. Levick's Introduction to Cardiovascular Physiology. Sixth ed: CRC Press Book; 2018 April 10, 2018.