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


[Na$^+$]_i = intracellular Na$^+$ concentration (mmol/l)

[Na$^+$]_e = extracellular Na$^+$ concentration (mmol/l)

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

[Na$^+$]_OT = total Na$^+$ concentration in oedematous tissue (mmol/l)

[K$^+$]_i = intracellular K$^+$ concentration (mmol/l)

[K$^+$]_e = extracellular K$^+$ concentration (mmol/l)

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

[K$^+$]_OT = total 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

ECV% = extracellular volume fraction (%) = 100 · $V_e/V_T$

OE% = percentage of oedema added to a tissue
Model for expected total concentration of Na\textsuperscript{+} and K\textsuperscript{+} in a tissue

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

Na\textsuperscript{+} total moles = Na\textsuperscript{+} extracellular moles + Na\textsuperscript{+} intracellular moles

Therefore:

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

or

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

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

Assuming a convenient reference volume of tissue containing 1 L of total (intracellular + extracellular) water solution, absolute Na\textsuperscript{+} tissue content (moles) numerically coincides (\approx) with [Na\textsuperscript{+}].

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\textsuperscript{+} tissue content (moles) \approx [K\textsuperscript{+}].

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

Model for expected total concentration of Na\textsuperscript{+} and K\textsuperscript{+} 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\textsuperscript{+} content in the oedematous tissue is:

Na\textsuperscript{+} total moles \textit{ot} = (Na\textsuperscript{+} extracellular moles + Na\textsuperscript{+} intracellular moles)\textsubscript{T} + Na\textsuperscript{+} moles in oedema

= (Na\textsuperscript{+} total moles)\textsubscript{T} + Na\textsuperscript{+} moles in oedema

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\textsuperscript{+} concentration in the oedematous tissue is:

\[[\text{Na}^+]_\textit{OT} = \text{Na}^+ \text{ total moles }_\textit{OT} / \text{ total Volume}\]

= Na\textsuperscript{+} total moles \textit{ot} / (Volume \textsubscript{T} + Volume \textsubscript{oedema})

= Na\textsuperscript{+} total moles \textit{ot} / (1L + 1L \cdot \text{OE}/100)

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

Similarly, for potassium:

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

\[[K^+]_\textit{OT} = [K^+]_e \cdot \text{ECV}/100 + [K^+]_i \cdot (1\text{-ECV})/100 + [K^+]_e \cdot \text{OE}/100) / (1L + 1L \cdot \text{OE}/100)\]
[Na\(^+\)]\(_{\text{OT}}\) and [K\(^+\)]\(_{\text{OT}}\) equations were used to generate the model for expected total concentration of Na\(^+\) and K\(^+\) in an oedematous tissue, after addition of 5% oedema (Figure, left panel, closed symbols).

**Changes in Na\(^+\), K\(^+\) and water**

Percentage changes (Δ%) for absolute Na\(^+\) content and concentration were defined, respectively, as:

\[
\Delta\% \text{ absolute Na}^+ \text{ content} = \frac{\text{Na}^+ \text{ total moles}_{\text{OT}} - \text{Na}^+ \text{ total moles}_T}{\text{Na}^+ \text{ total moles}_T} \times 100
\]

\[
\Delta\% \text{ Na}^+ \text{ concentration} = \frac{[\text{Na}^+]_{\text{OT}} - [\text{Na}^+]_T}{[\text{Na}^+]_T} \times 100
\]

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

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

**Biological assumptions**

This mathematical model is obviously affected in absolute, but not relative, terms by changes in the baseline assumptions, i.e. [Na\(^+\)]\(_{\text{i}}\), [Na\(^+\)]\(_{e}\), [K\(^+\)]\(_{\text{i}}\), and [K\(^+\)]\(_{e}\): 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:

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

**Supplemental references**