News in sodium balance

A. Tissue sodium in healthy and hypertensive patients
B. Sodium sensing in the interstitium and relationship to hypertension.

Jens Titze

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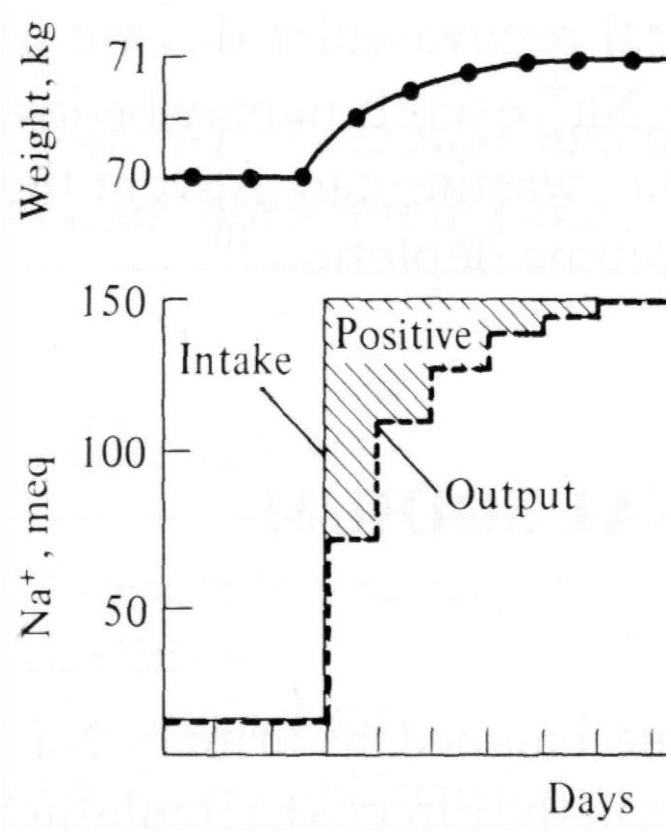
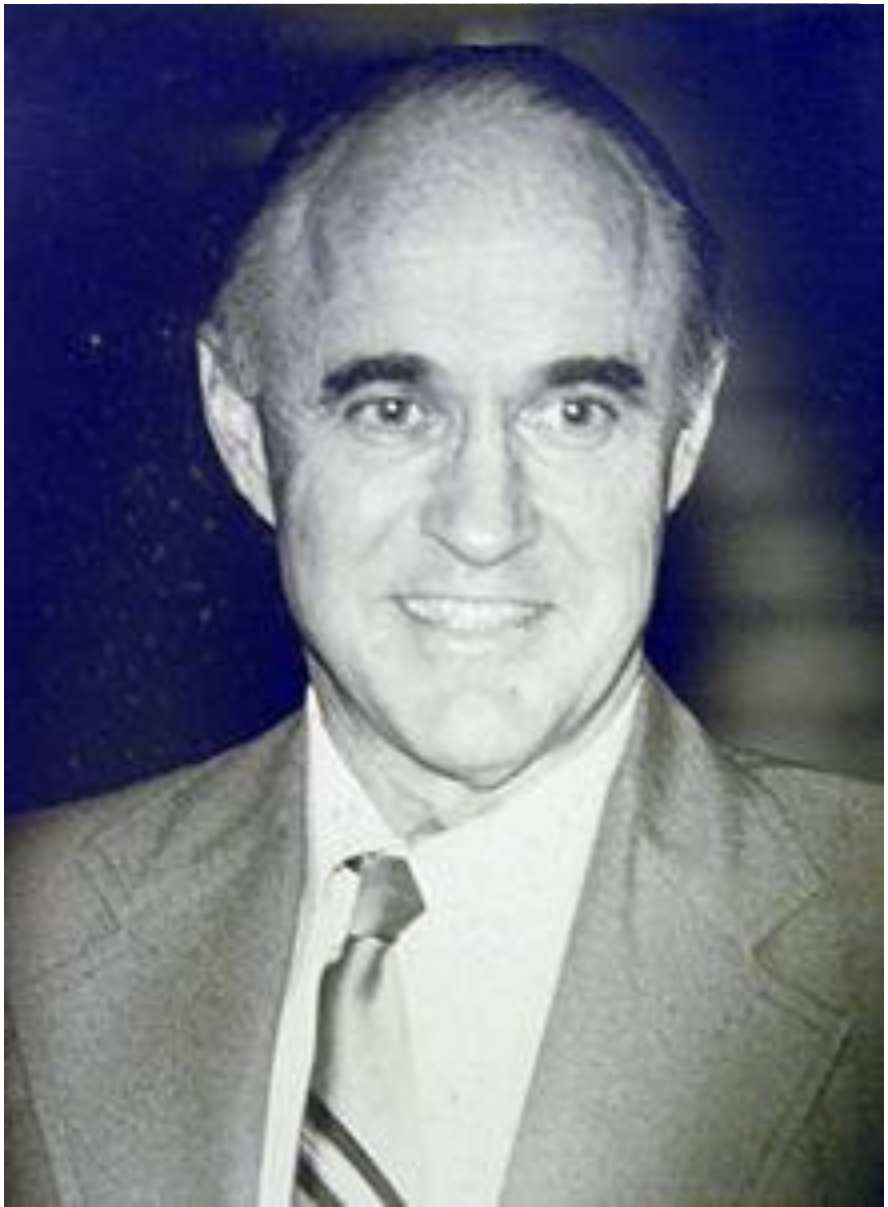
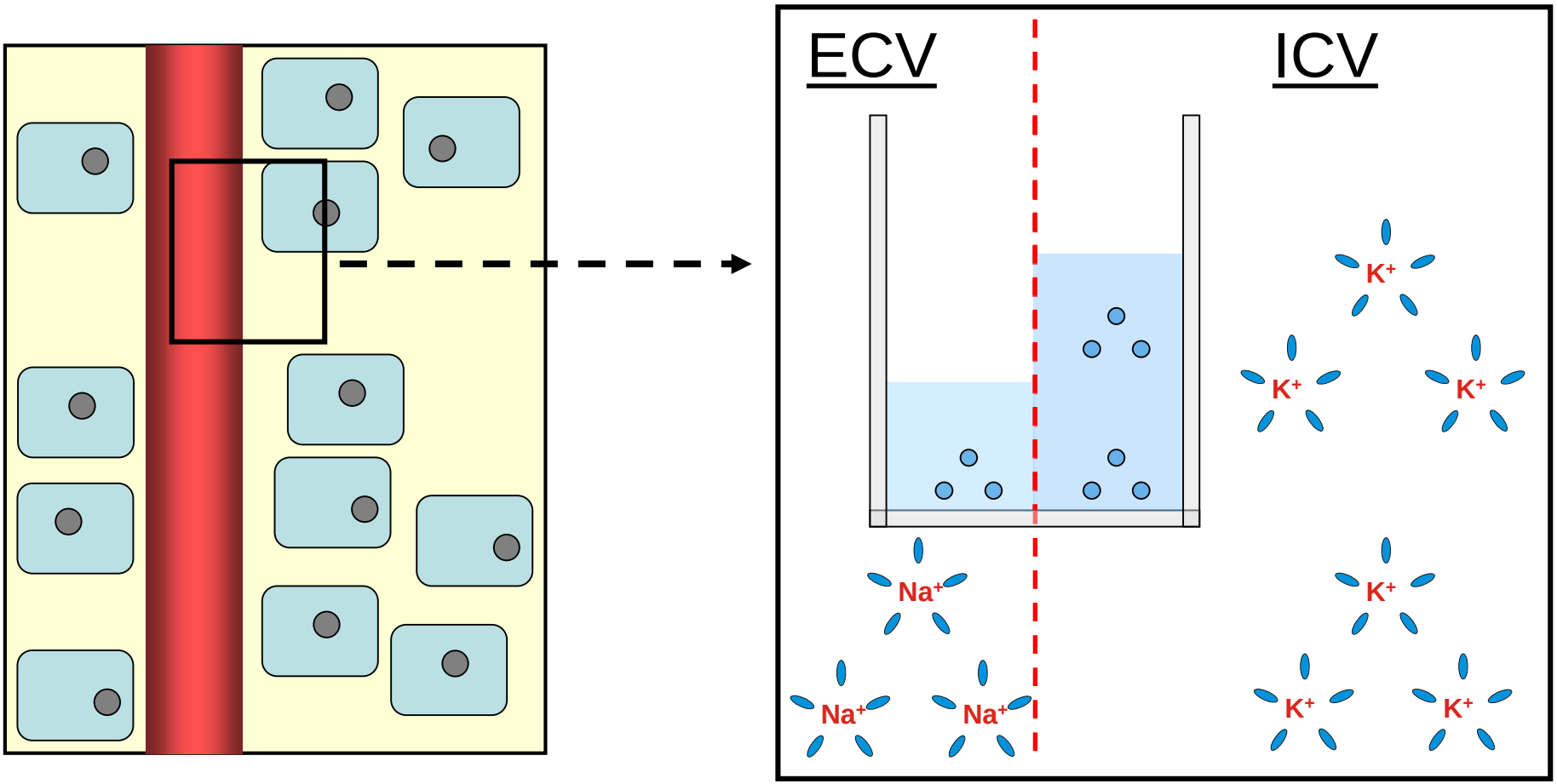
Sodium balance





Isotonicity of the internal environment: the two-compartment model



Na^+ and maintenance of internal environment composition

Intake:

Thirst

9 g NaCl

Na^+

Na^+

Excretion:

Skin

Kidney

9 g NaCl

ADH

RAAS ↓

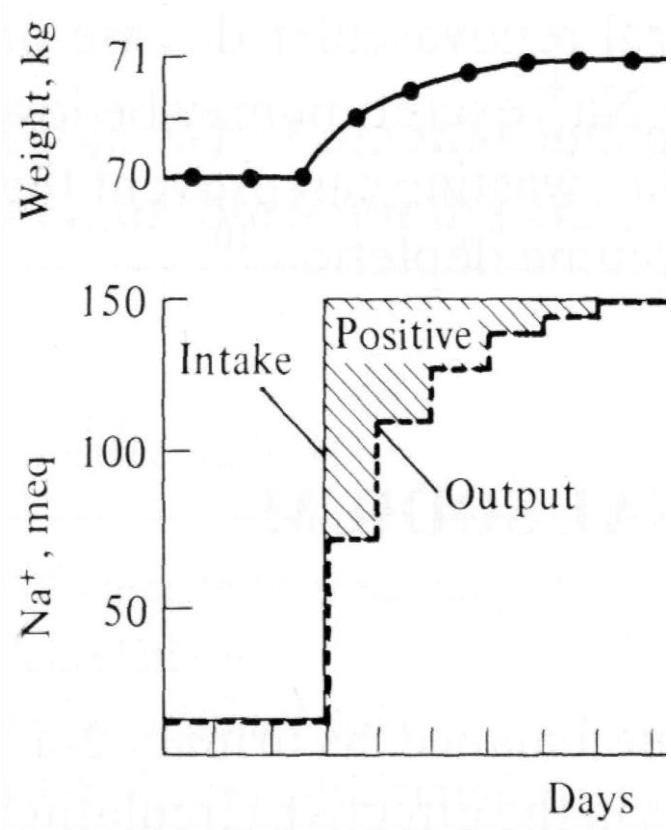
Nerves

ECV	ICV
Na^+	K^+
Na^+	K^+
Na^+	K^+

≈ 140 mmol/L
(≈ 9 g NaCl/L)

≈ 140 mmol/L

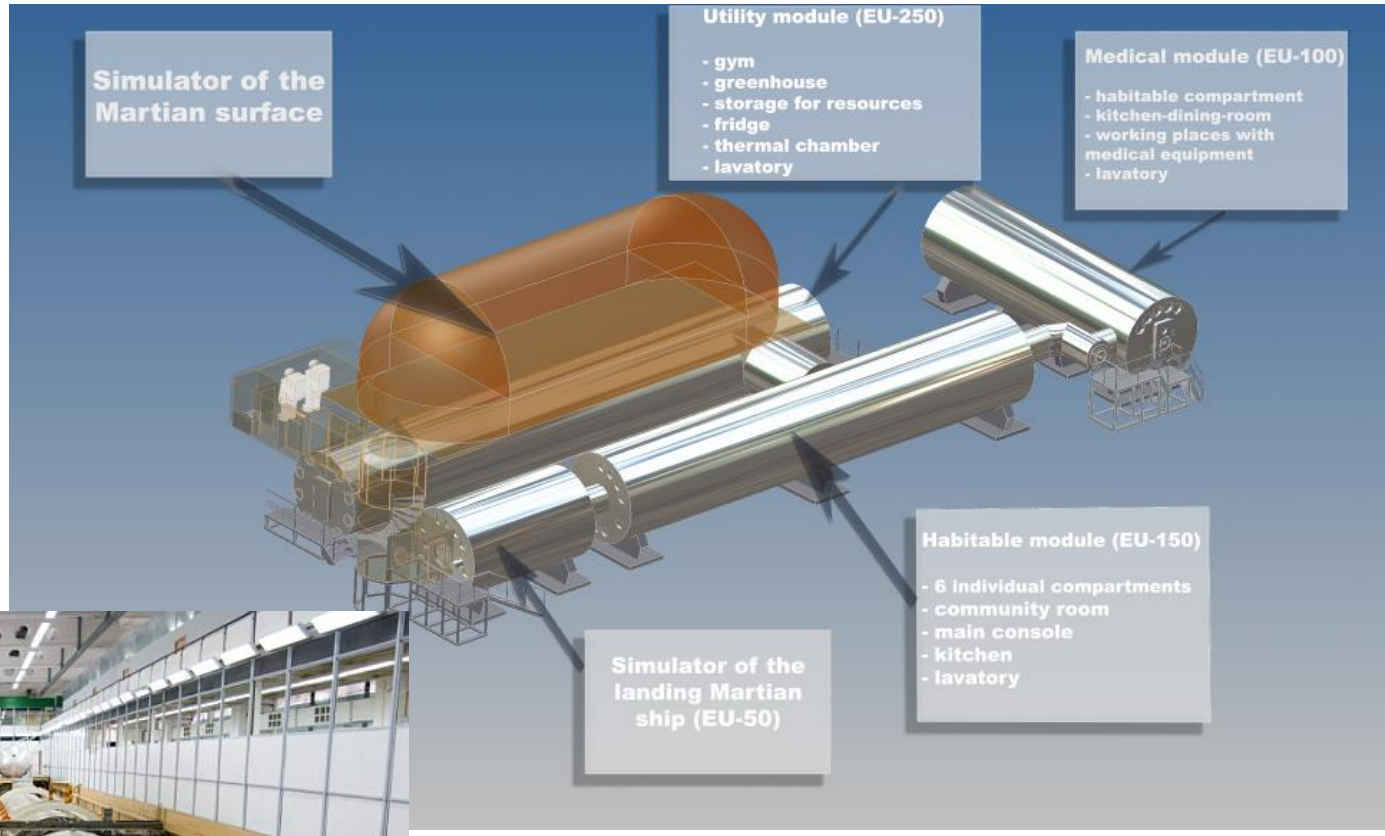
Sodium balance



What is the reverse experiment?

The Mars500 Project

The metabolic ward.

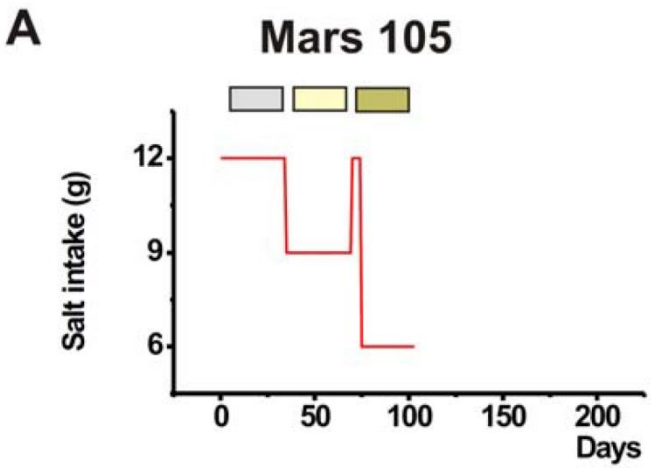


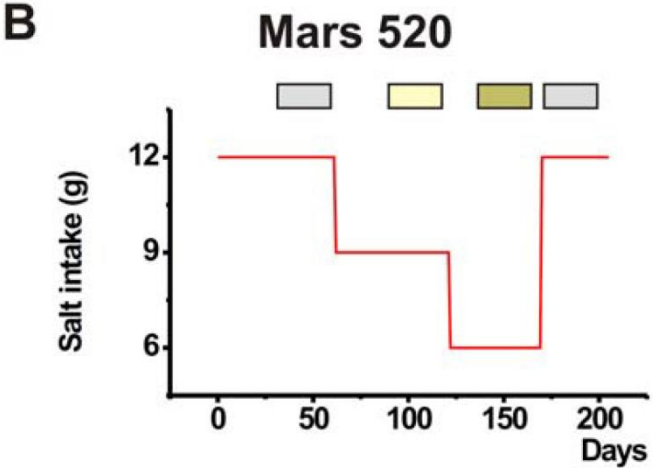
- Temp. 18-25°C
- Humidity: 40-75%
- Air Pressure: 660 - 880 mmHg
- PCO_2 < 8 mmHg
- PO_2: 140-200 mmHg

A little help from our friends

Acknowledgements

Doing the reverse experiment: the Mars500 project





Urinary Na^+ recovery: 95% 95%

Source: esa.com

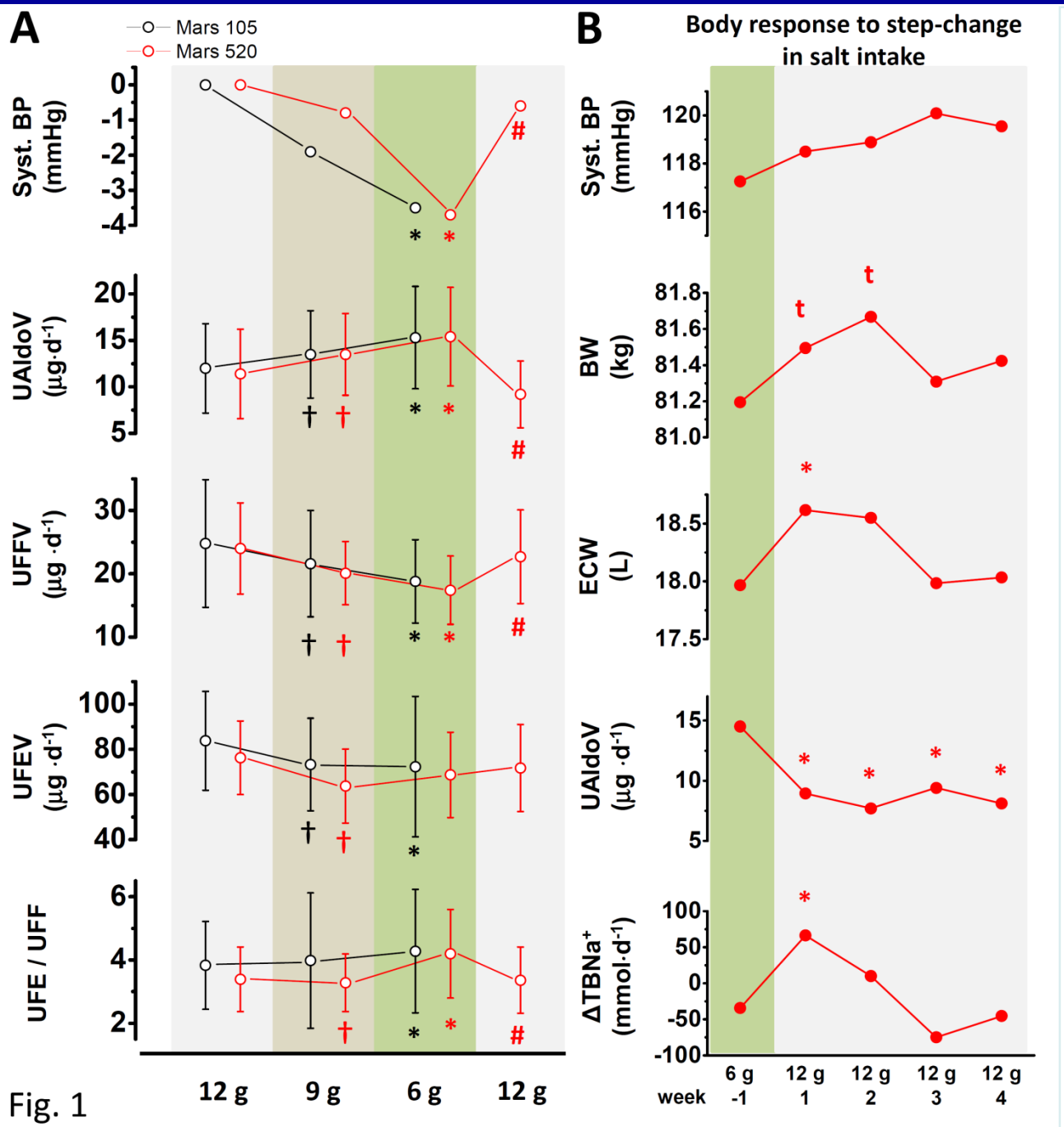
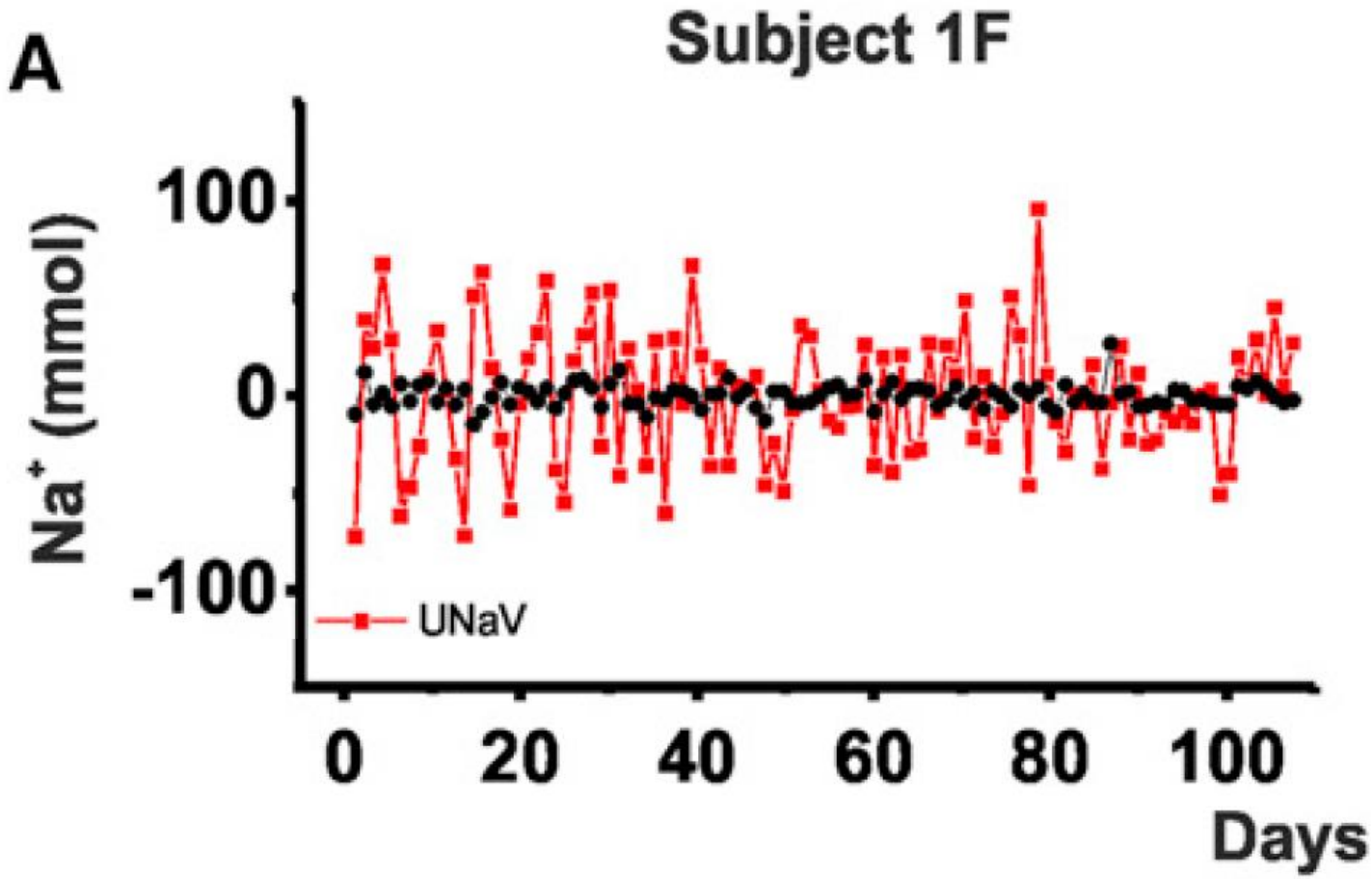


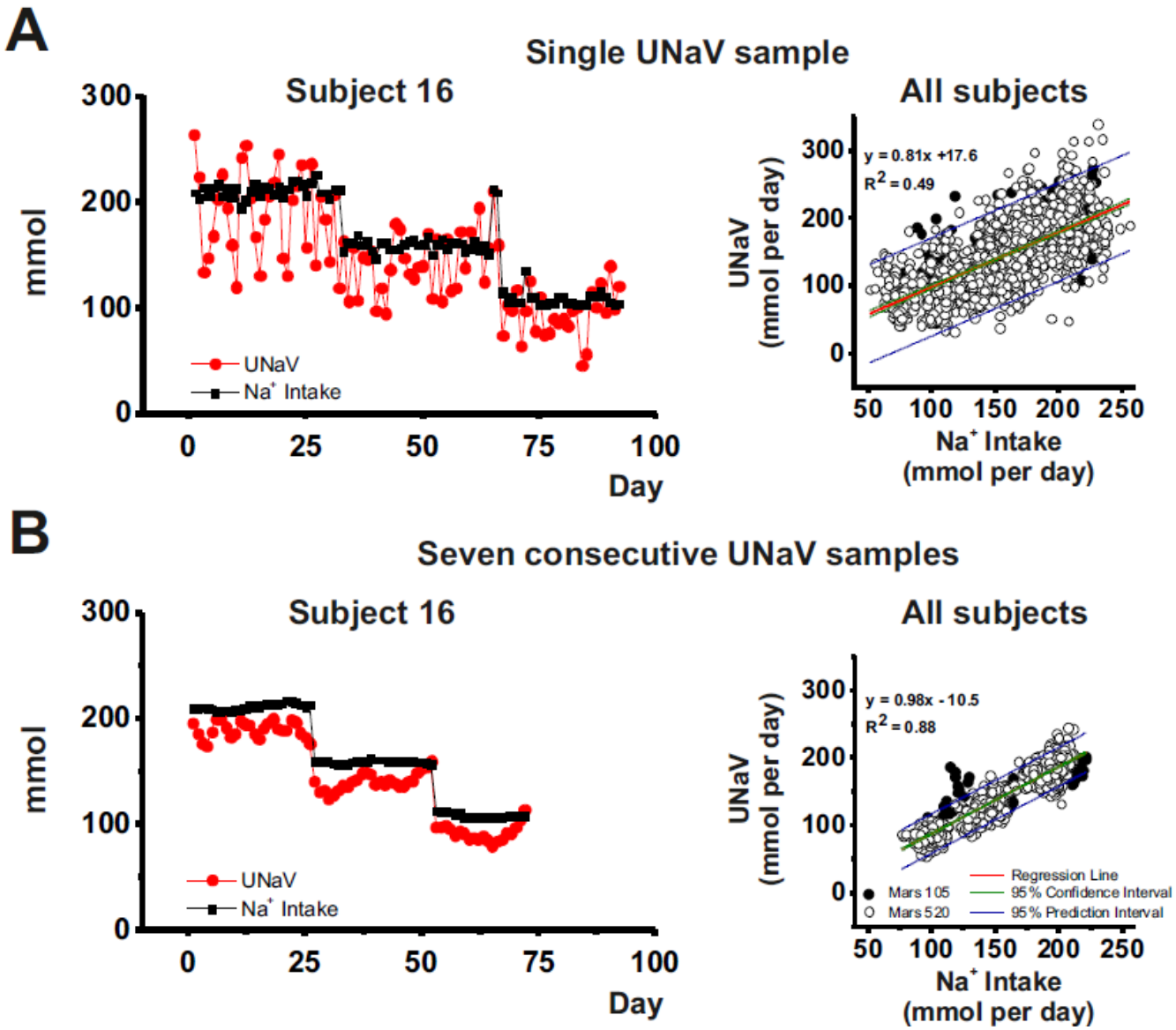
Fig. 1

Great!
Let‘s go home!



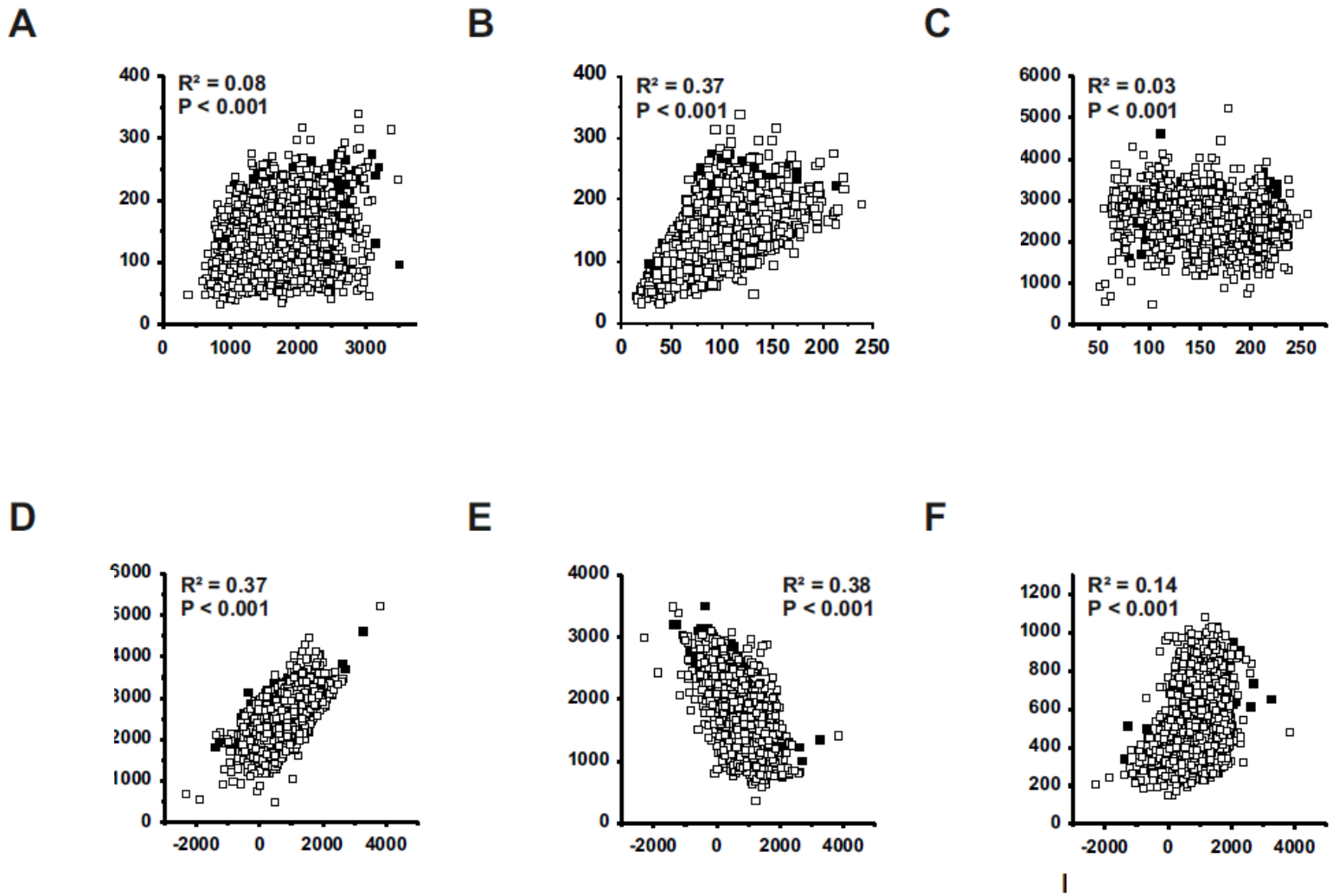
Cell Metabolism 17: 125-131, 2013

The Mars500 Project: Value of an accurately UNaV sample



Unpublished

The Mars500 Project: Does salt intake determine fluid intake?



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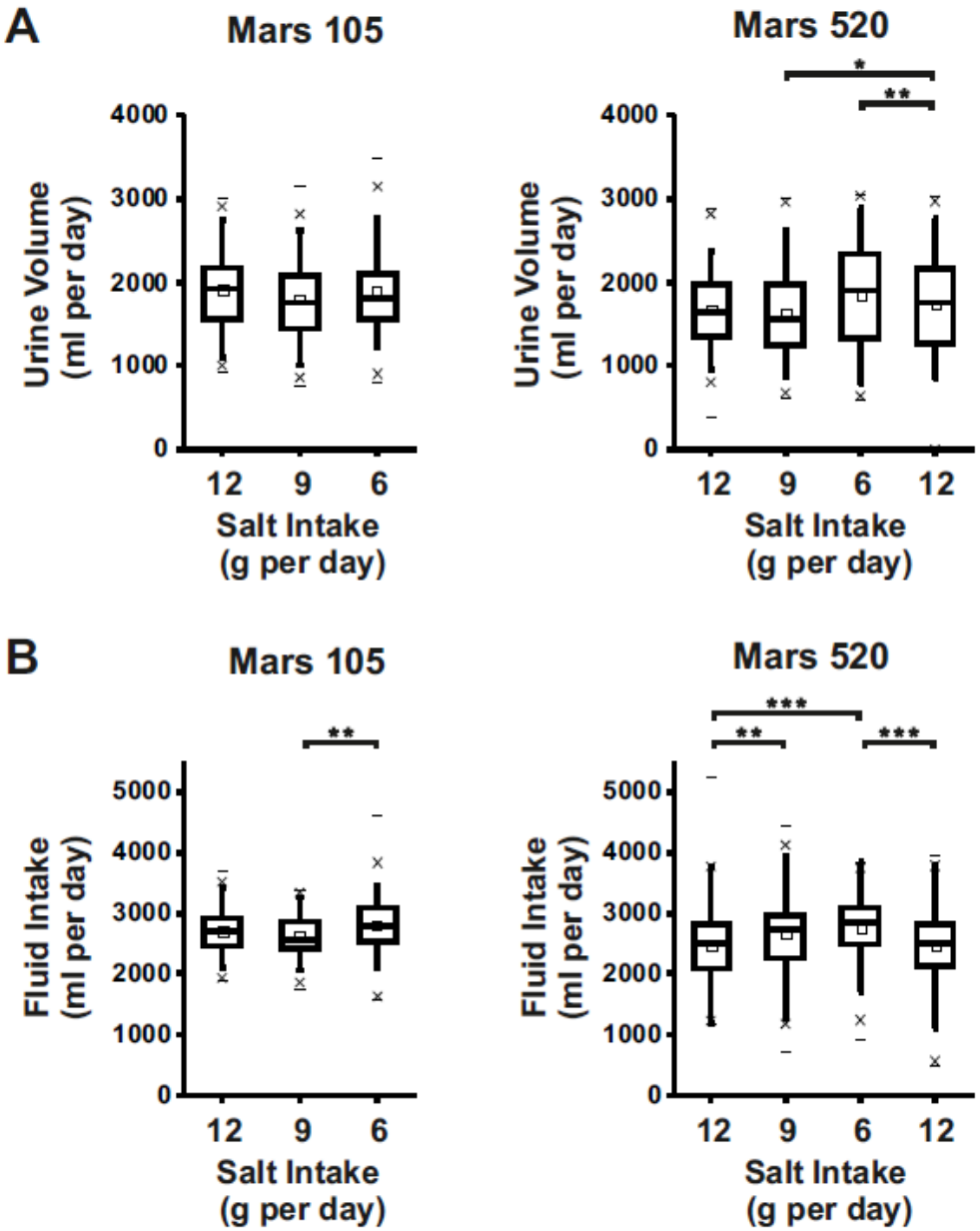

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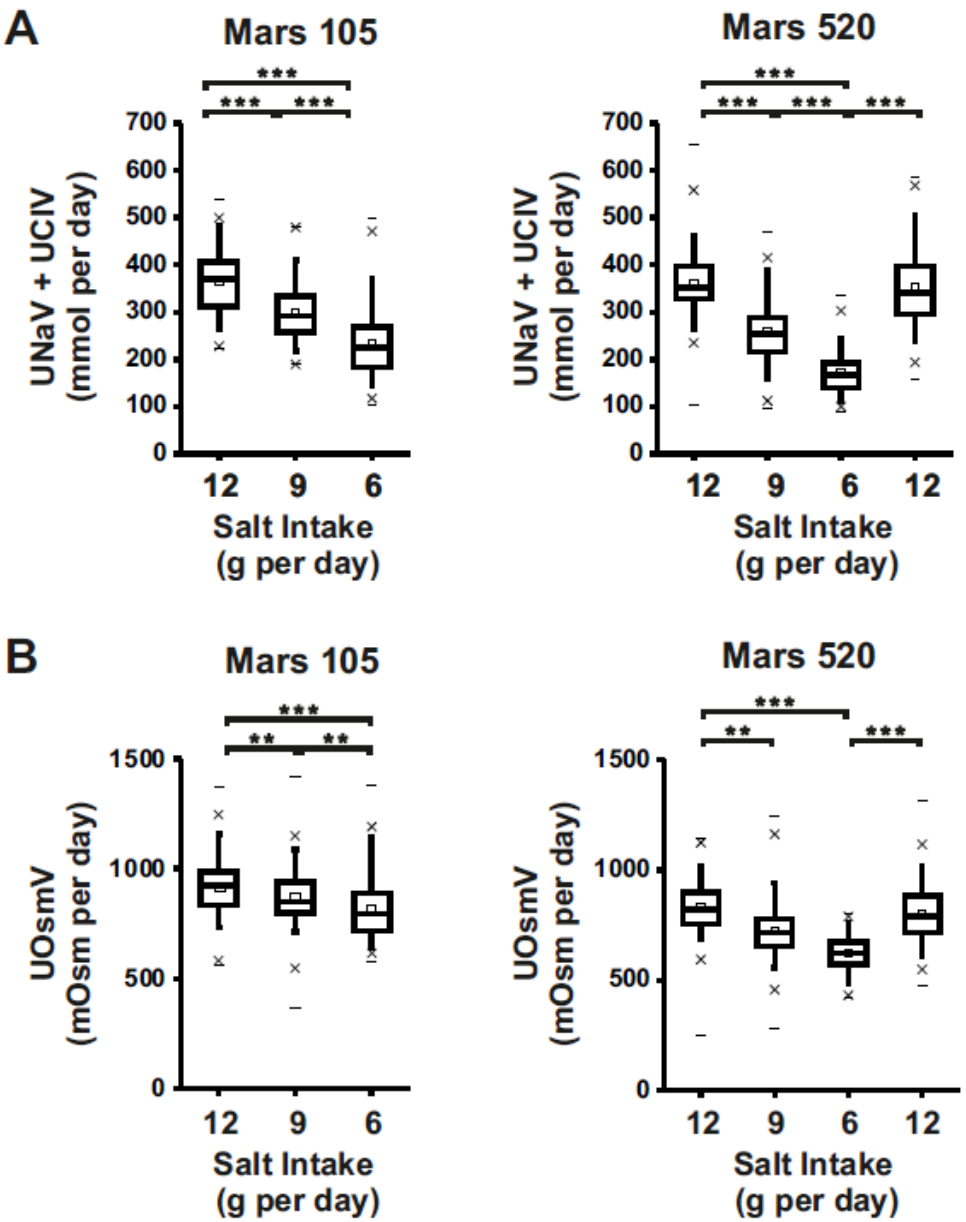
The Mars500 Project: Dietary salt leads to urinary Na^+ concentration.



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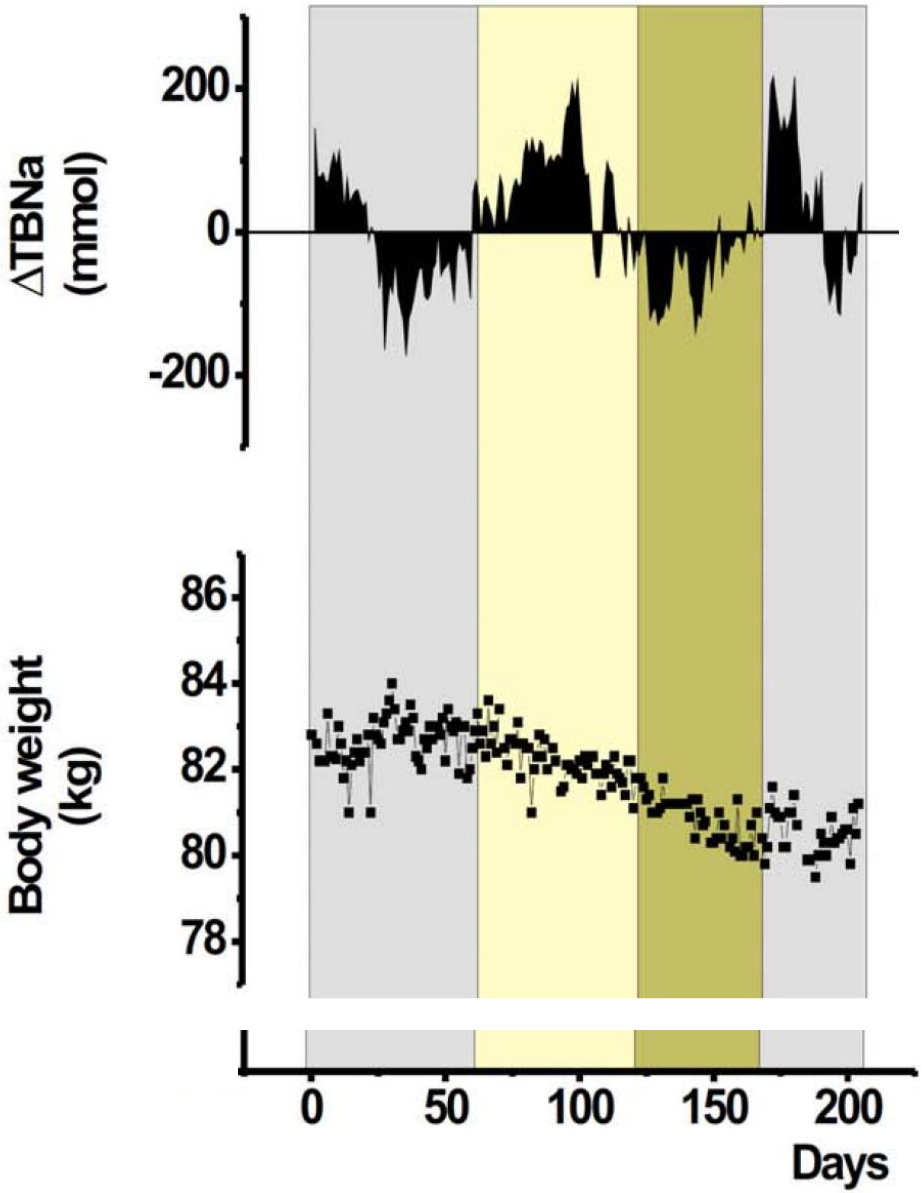


Where is the salt?

Cell Metabolism 17: 125-131, 2013

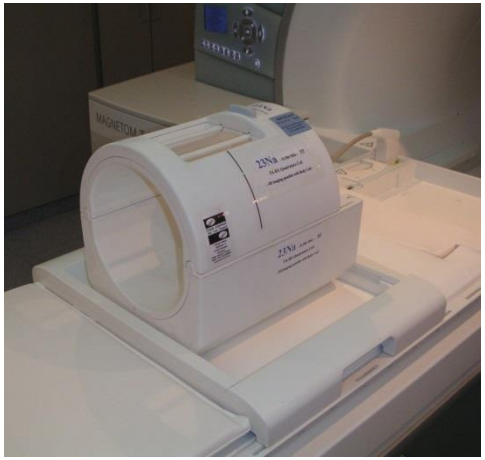
1. Why do we want to see the sodium?

a) Because serum electrolytes do not tell us much about tissue electrolyte composition.

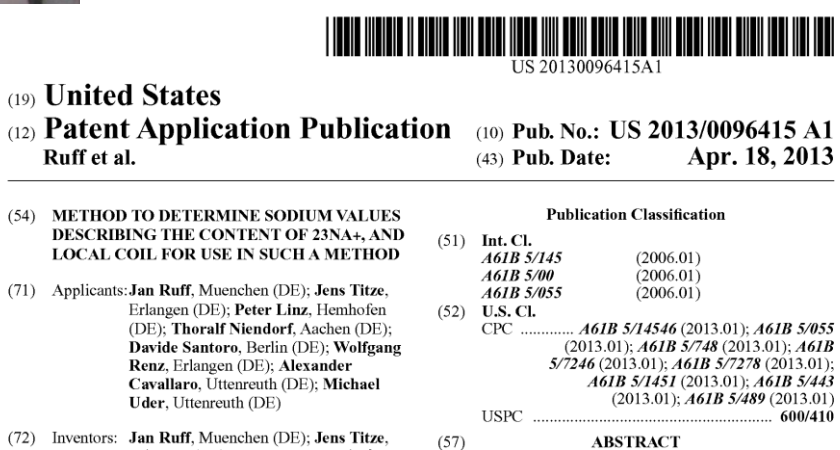
b) Because immune cells seem to regulate interstitial electrolyte homeostasis, and because interstitial electrolytes may boost immune responses.

c) Because tissue Na^+ accumulation may be hidden disease entity.

^{23}Na MRI for detection of hidden Na^+ storage in humans



TE = 2…3 ms



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(19) **United States**

(12) **Patent Application Publication**
Ruff et al.

(10) **Pub. No.: US 2013/0096415 A1**
(43) **Pub. Date: Apr. 18, 2013**

(54) **METHOD TO DETERMINE SODIUM VALUES DESCRIBING THE CONTENT OF 23NA+, AND LOCAL COIL FOR USE IN SUCH A METHOD**

(71) Applicants: **Jan Ruff**, Muenchen (DE); **Jens Titze**, Erlangen (DE); **Peter Linz**, Hemhofen (DE); **Thoralf Niendorf**, Aachen (DE); **Davide Santoro**, Berlin (DE); **Wolfgang Renz**, Erlangen (DE); **Alexander Cavallaro**, Uttenreuth (DE); **Michael Uder**, Uttenreuth (DE)

(72) Inventors: **Jan Ruff**, Muenchen (DE); **Jens Titze**,

Publication Classification

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A61B 5/055 (2006.01)

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CPC ***A61B 5/14546*** (2013.01); ***A61B 5/055*** (2013.01); ***A61B 5/748*** (2013.01); ***A61B 5/7246*** (2013.01); ***A61B 5/7278*** (2013.01); ***A61B 5/1451*** (2013.01); ***A61B 5/443*** (2013.01); ***A61B 5/489*** (2013.01)
USPC **600/410**

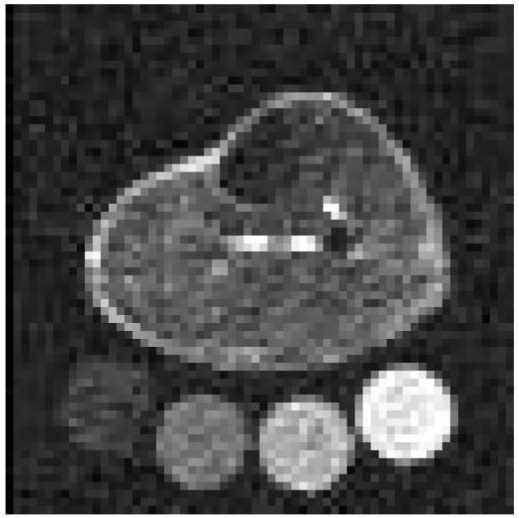
(57) **ABSTRACT**

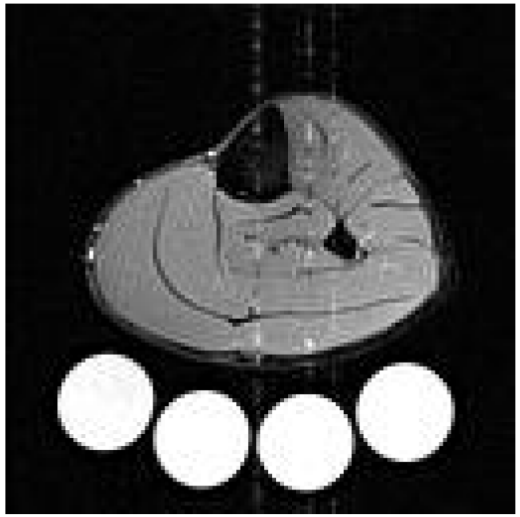
Sodium storage and its coincidence with hypertension.

Hypertension, 2013

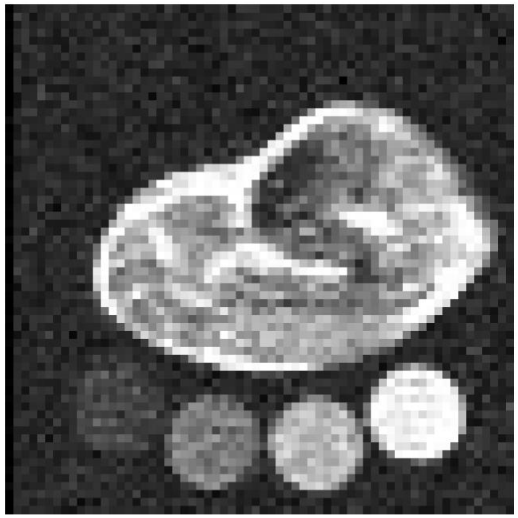
23Na MRI of tissue Na^+ content

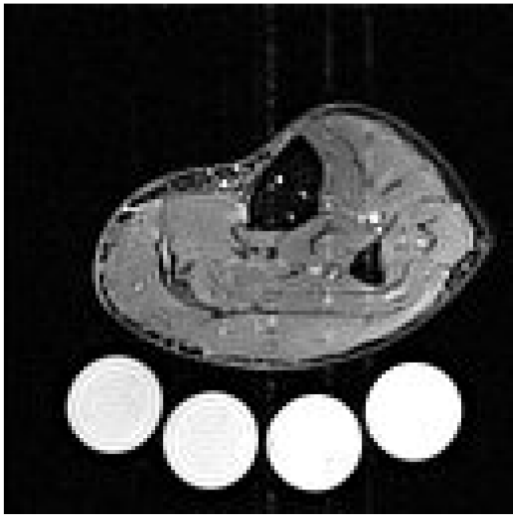
Man, 24 y, healthy





Man, 85 y, hypertension





Hypertension, 2013

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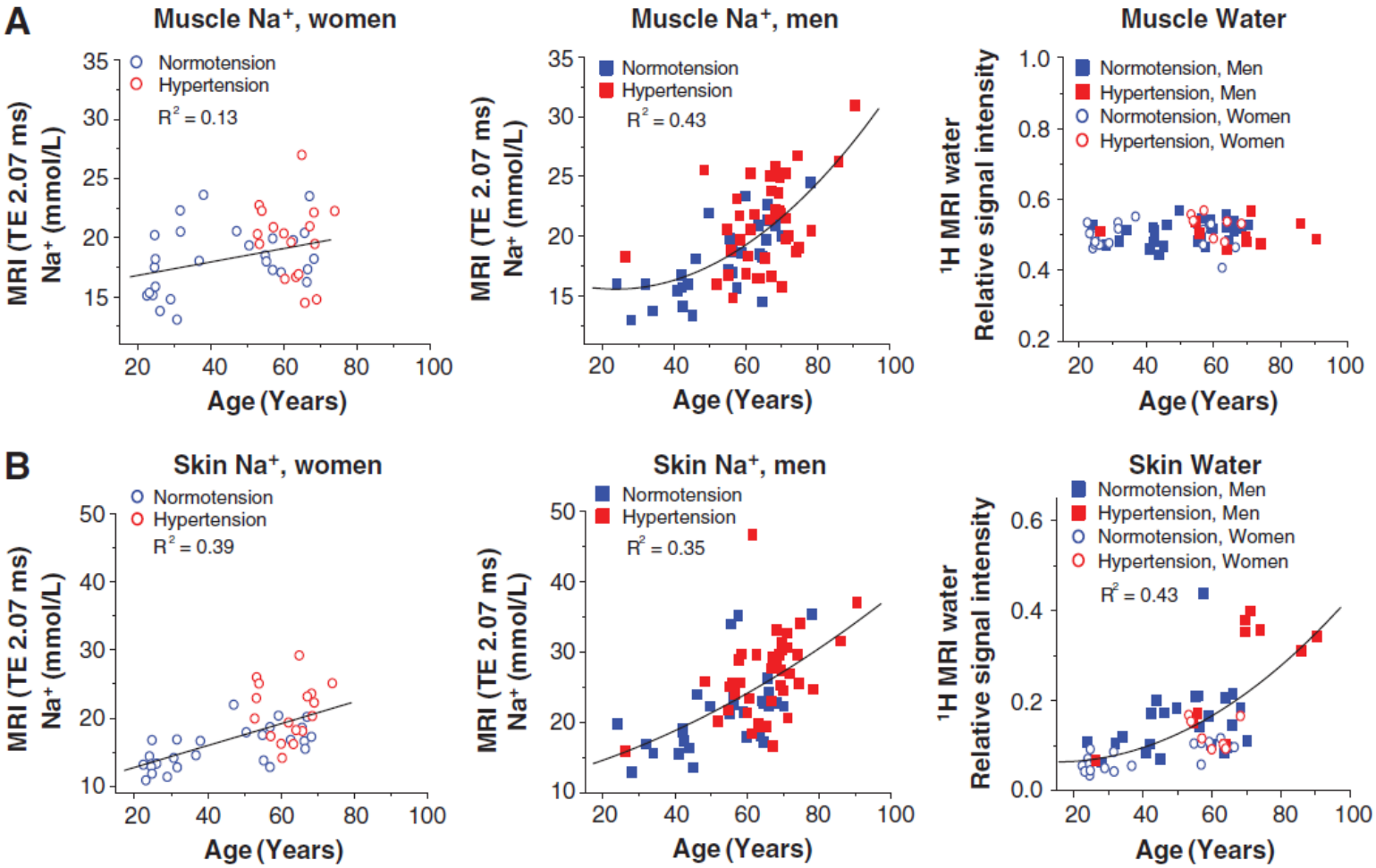

Hypertension, 2013

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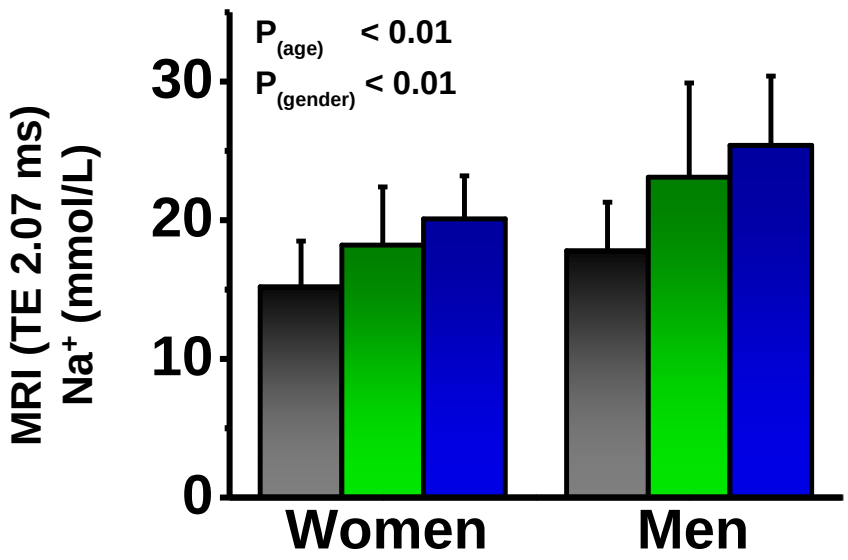
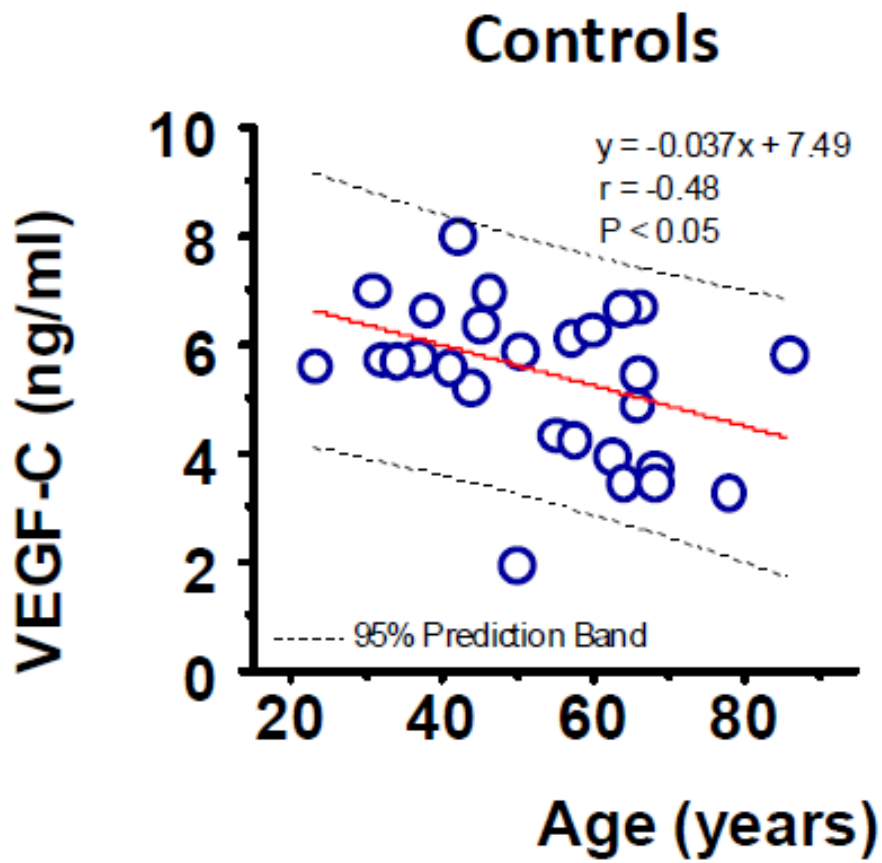
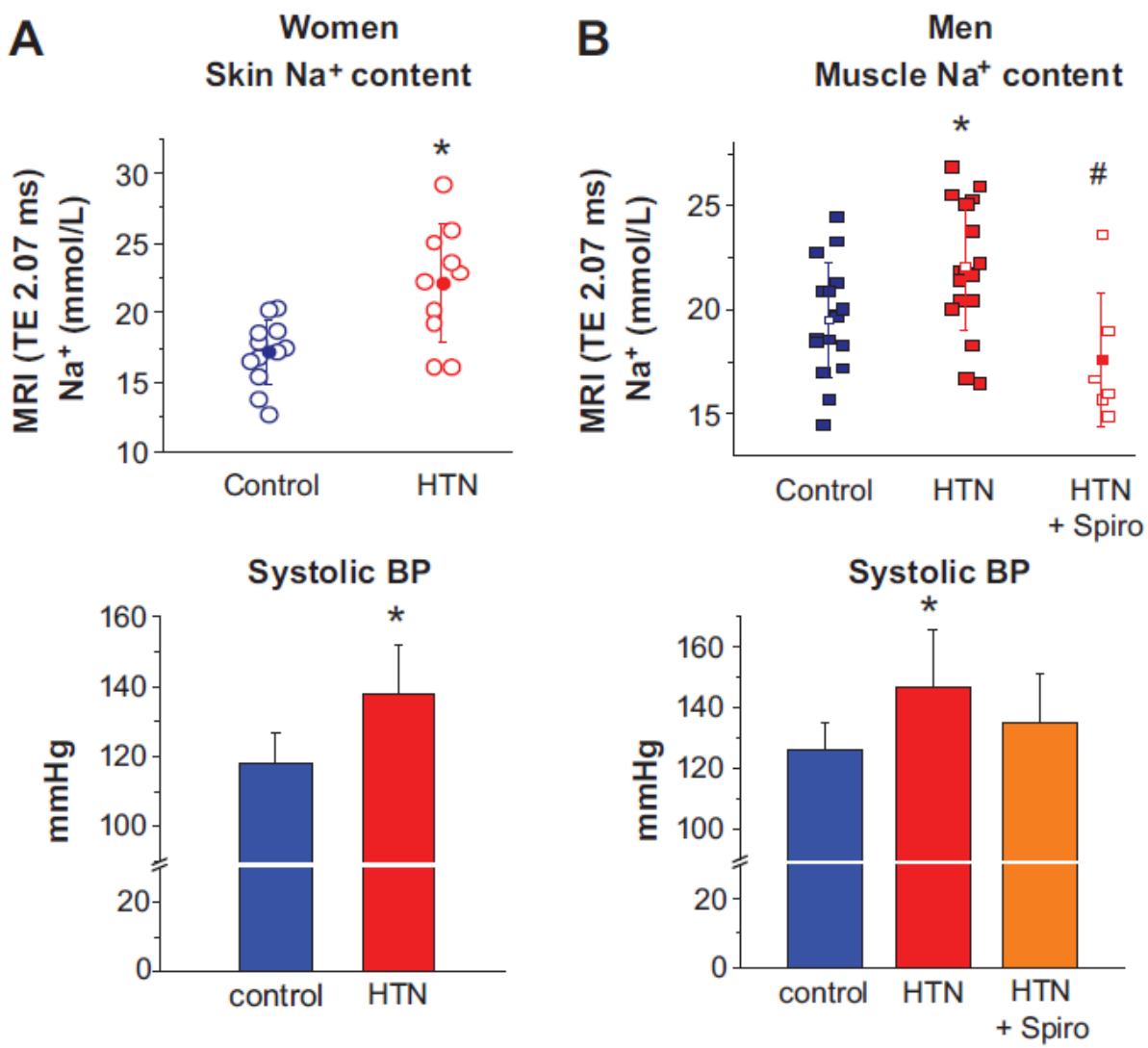




DuoSet ELISA Development Kit
R&D Systems
Sandwich Elisa

Can we mobilize?



Hypertension, 2013

Epidermis with blood capillary loop and an initial lymph vessel (Magnification)

BK = Blood capillary
IL = Initial lymph vessel
CP = Corium papilla

Initial lymph vessel
Phase of opening

E = Endothelial cells
AF = Anchor filaments
IF = Inflow of interstitial fluid
L = Outflow direction of lymph

Lymph capillary network

Lymph vessels (green)

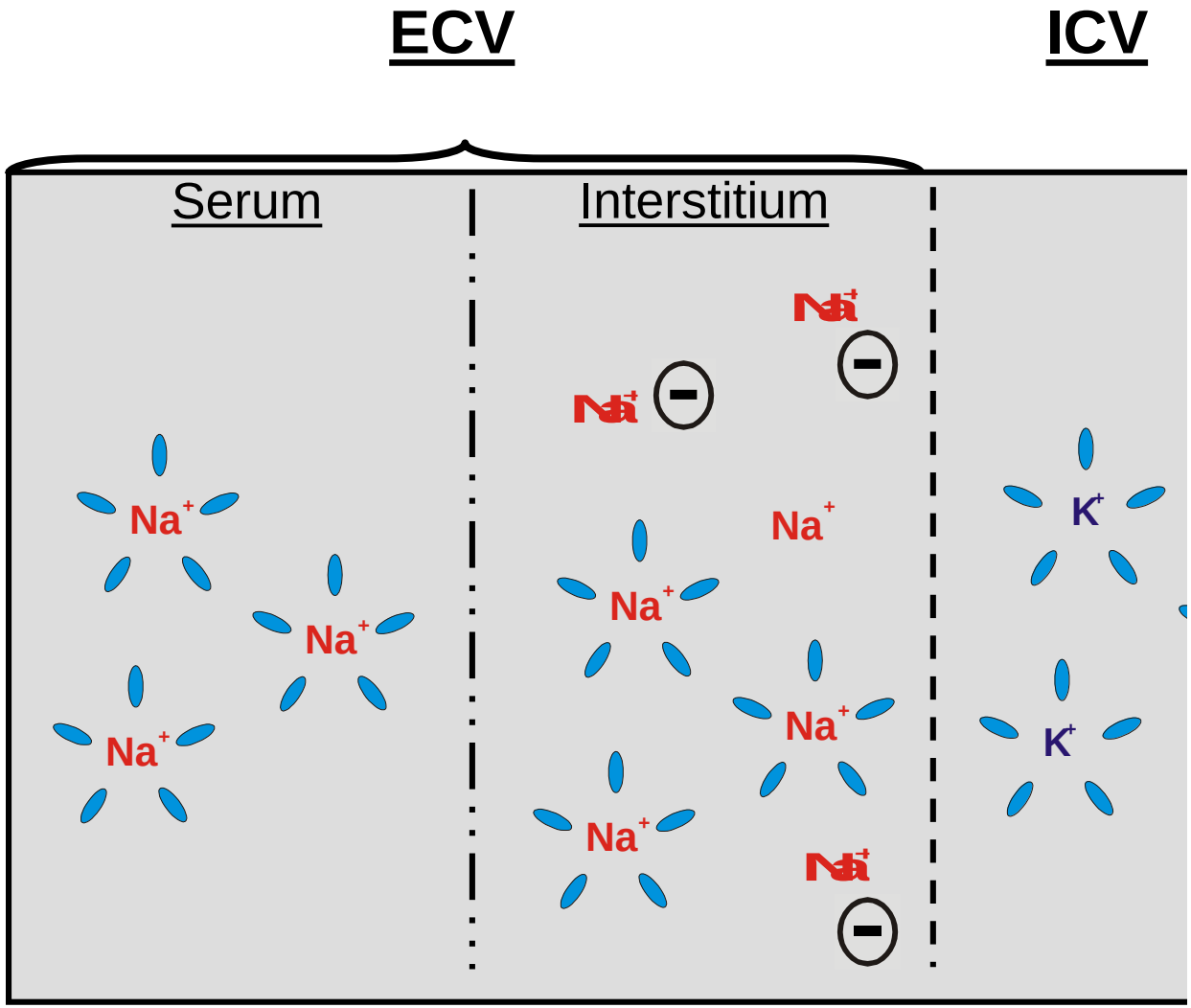
1 Lymph capillary (initial lymph vessel)
2 Precollector
3 Lymph collector (lymphatic ducts)
4 Deep lymph vessels
5 Lymphangion
6 Lymphatic trunk
7 Confluence (Junction) of the lymphatic trunks in the veins
8 Afferent lymph vessel
9 Efferent lymph vessel

Blood Vessels (veins = blue, arteries = red)

10 Superficial vein
11 Superficial artery
12 Deep veins
13 Deep artery
14 Blood vessels of the musculature
15 Blood vessels of the lymph node

Lymph capillary network

Na^+ storage in the interstitium: the three-compartment model



1. *Am J Kidney Dis*, **2002** 40(3): 508-16.

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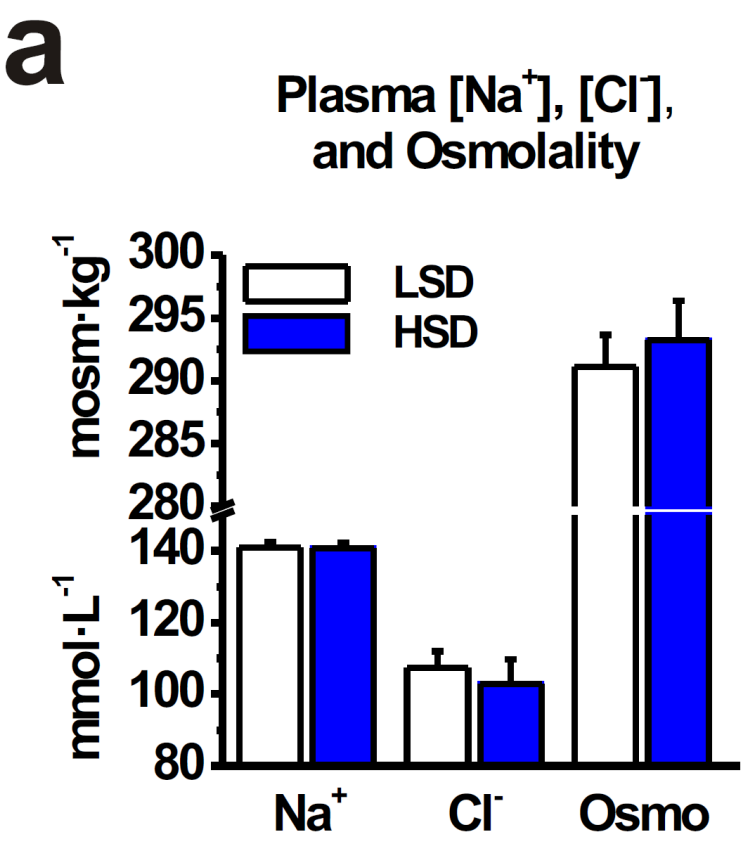
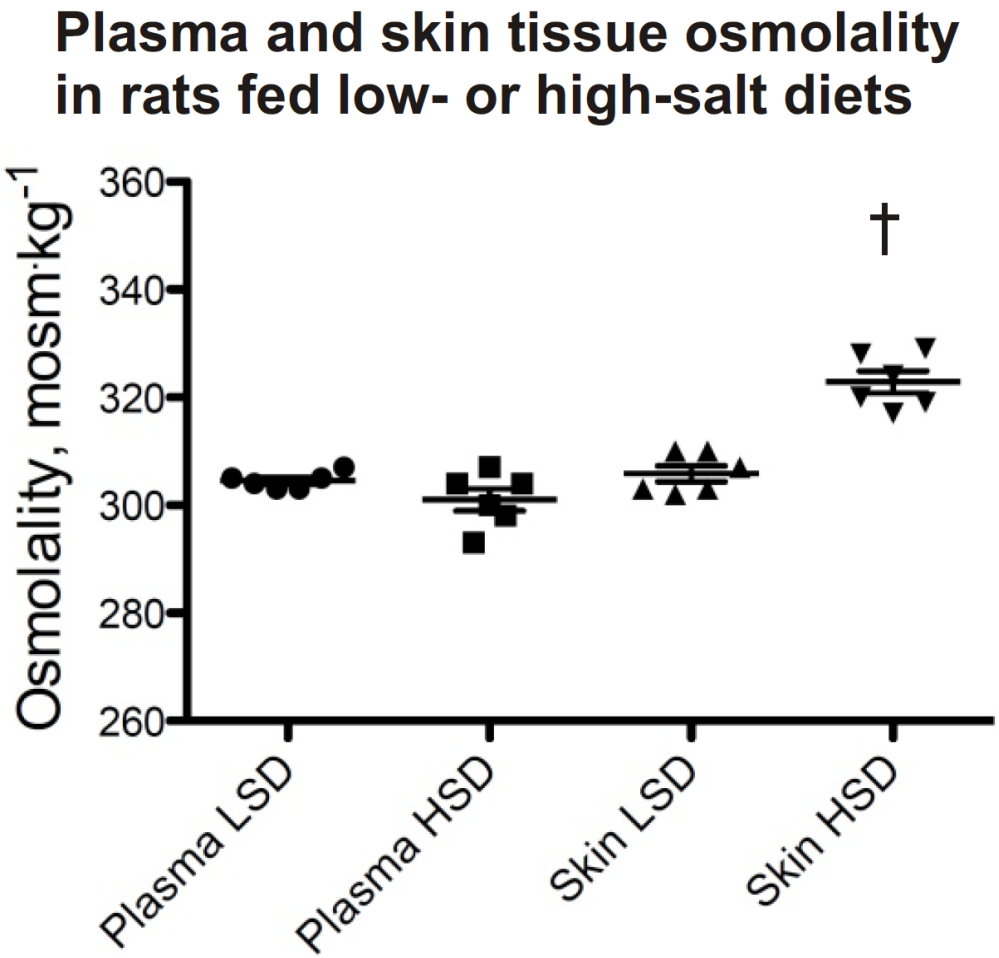
8. *Nat Med*, **2009** 15 (5): 545-552.

9. *Hypertension*, **2010** 55: 755-761.

Is the skin interstitium hypertonic compared to plasma?

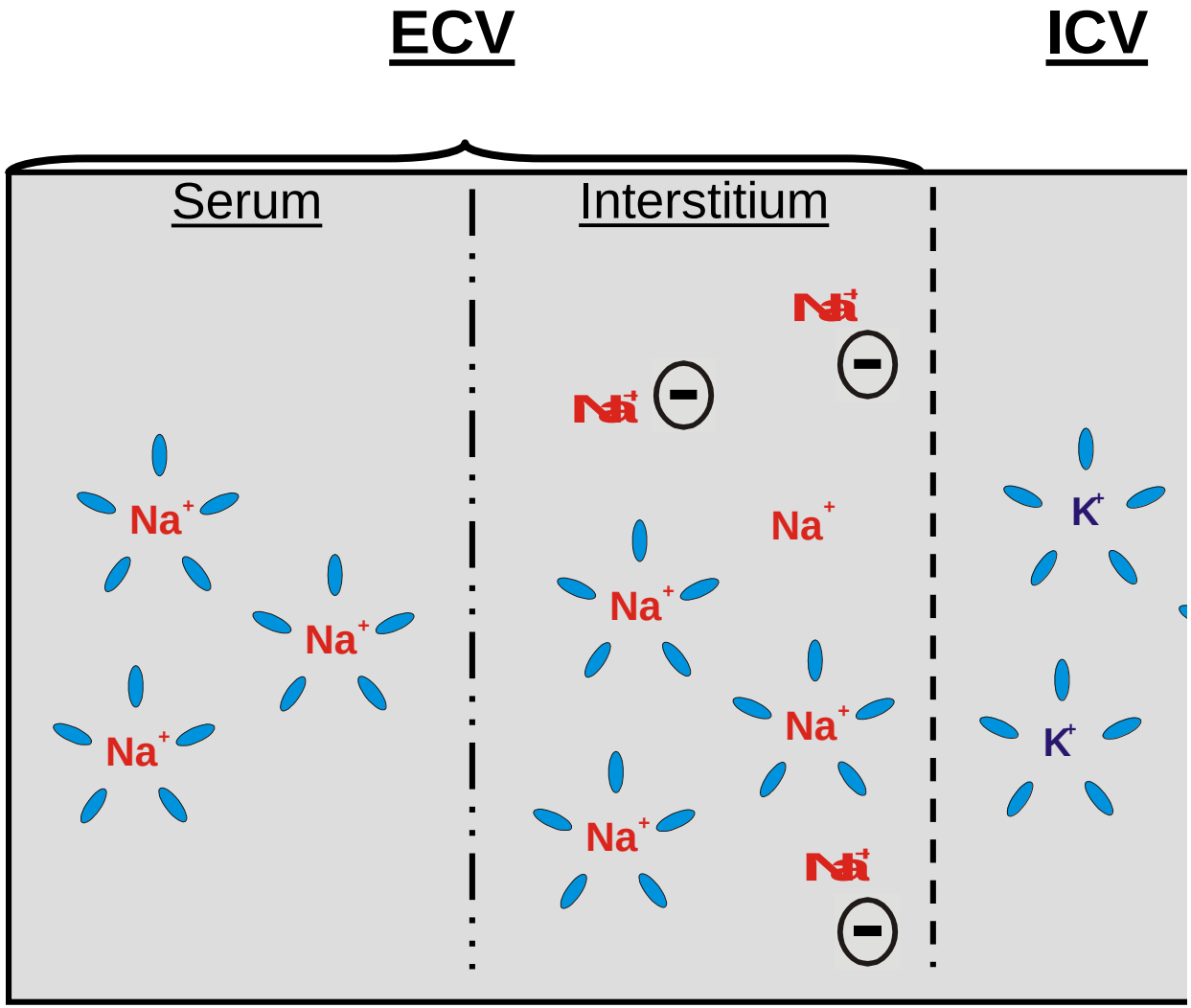
Chemical analysis





JCI, 2013; 123: 2803-2815

Na^+ storage in the interstitium: the three-compartment model



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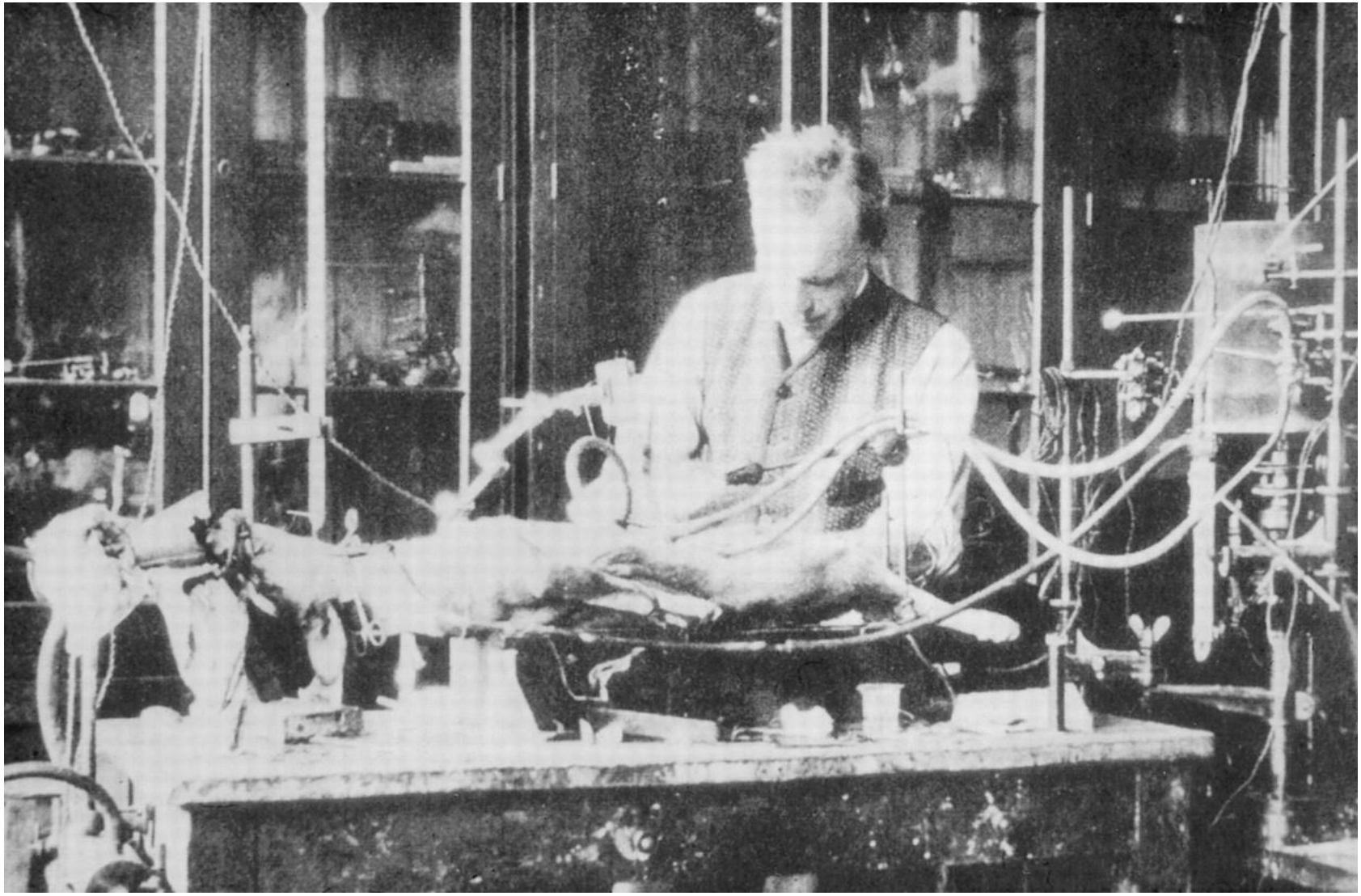
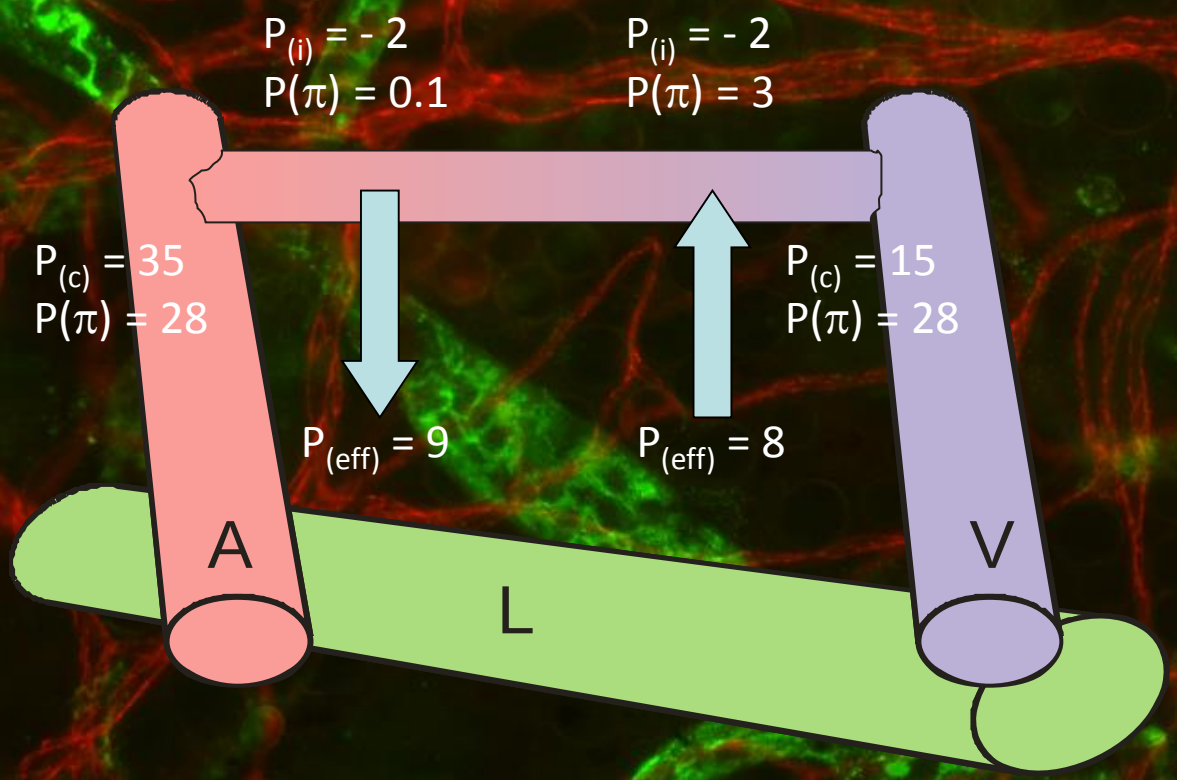
Ernest Henry Starling (1866 –1927)

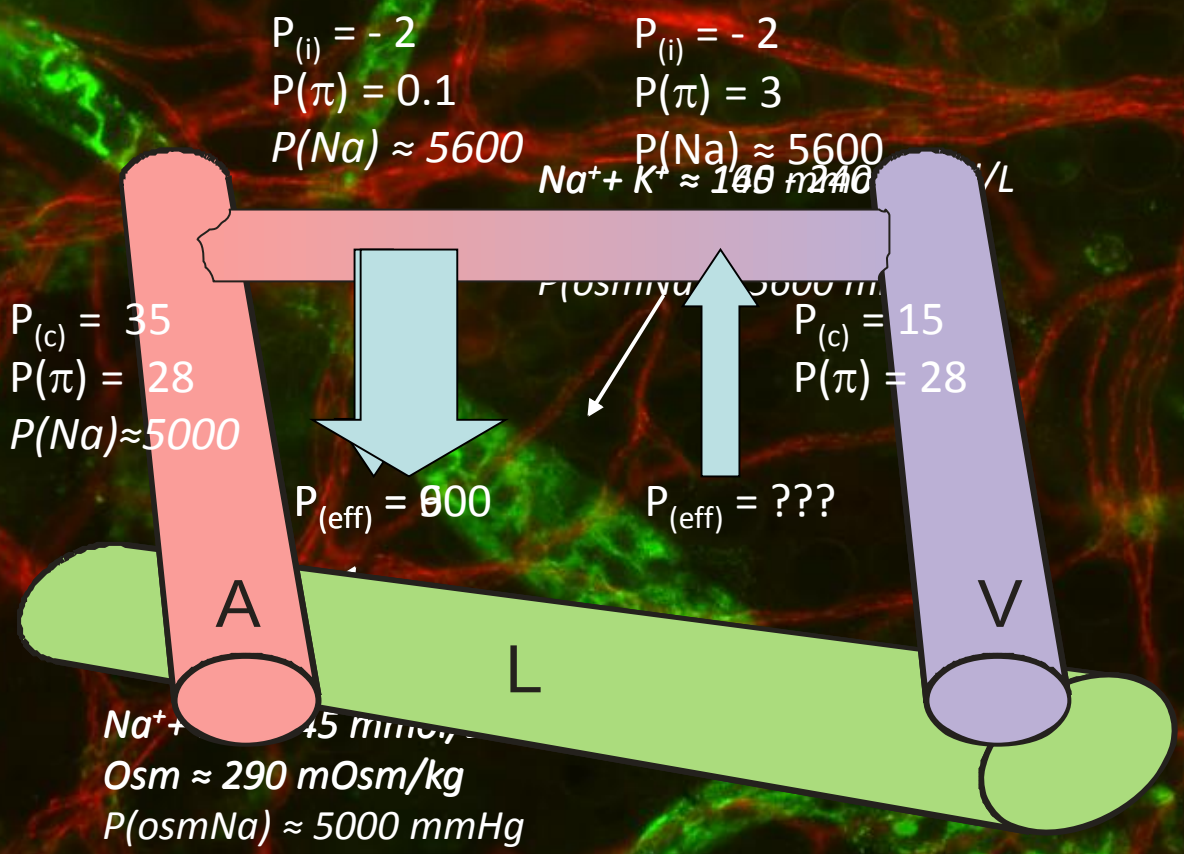


How is microcirulation organized?

Traditional view (Starling, J Physiol, 19, 312-326, 1896)



How is microcirulation organized - why not questioning Starling's equation?



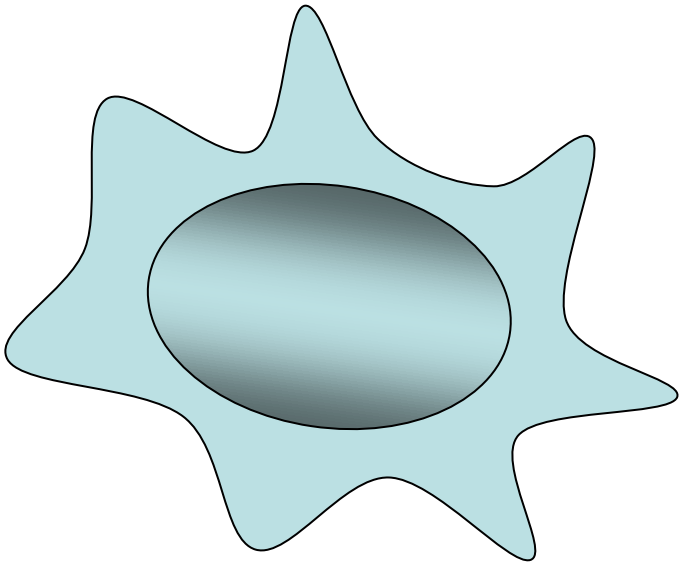
2. How can we see the sodium?

a) By chemical analysis (19th and 20th century).

b) Invasively by EDX-SEM microscopy.

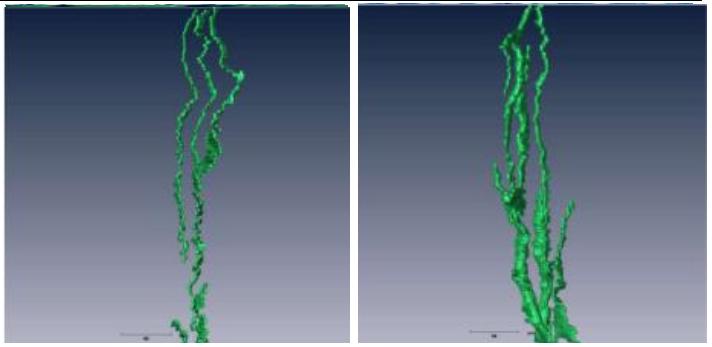
c) Non-invasively by 23NaMRI (21th century).

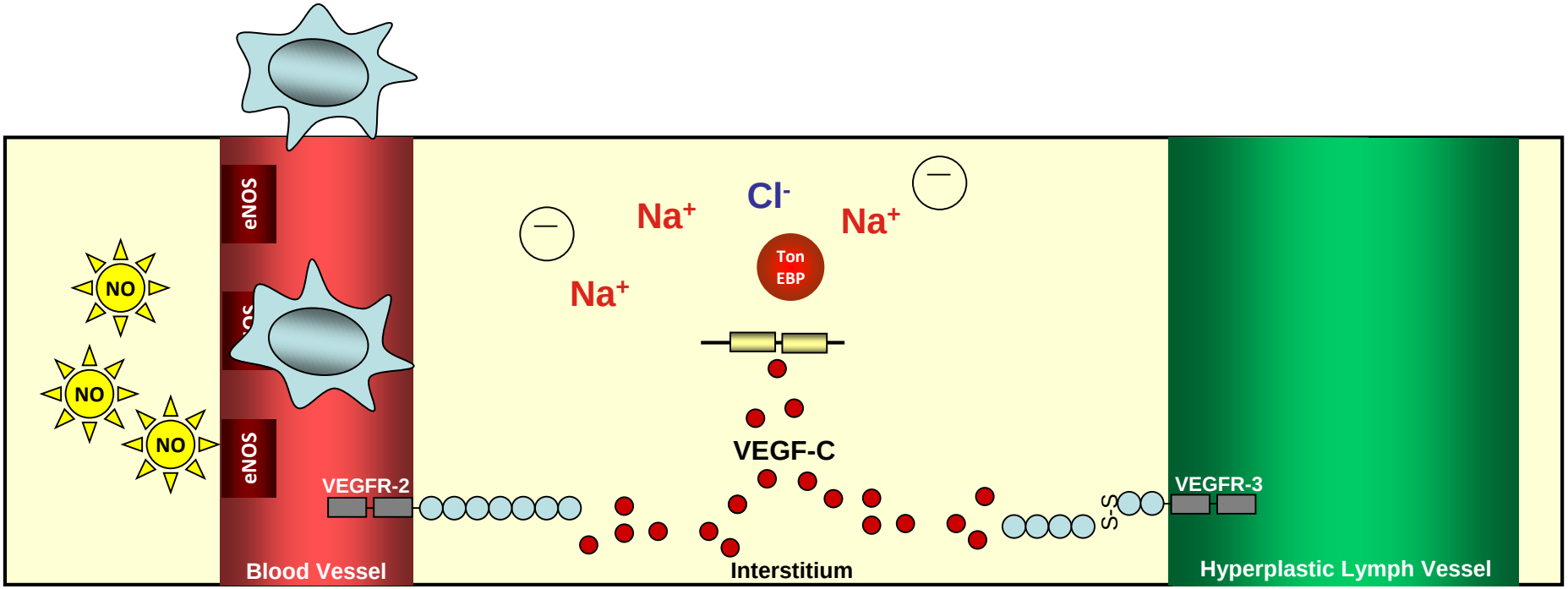
Sodium sensing in interstitium and Relationship to hypertension



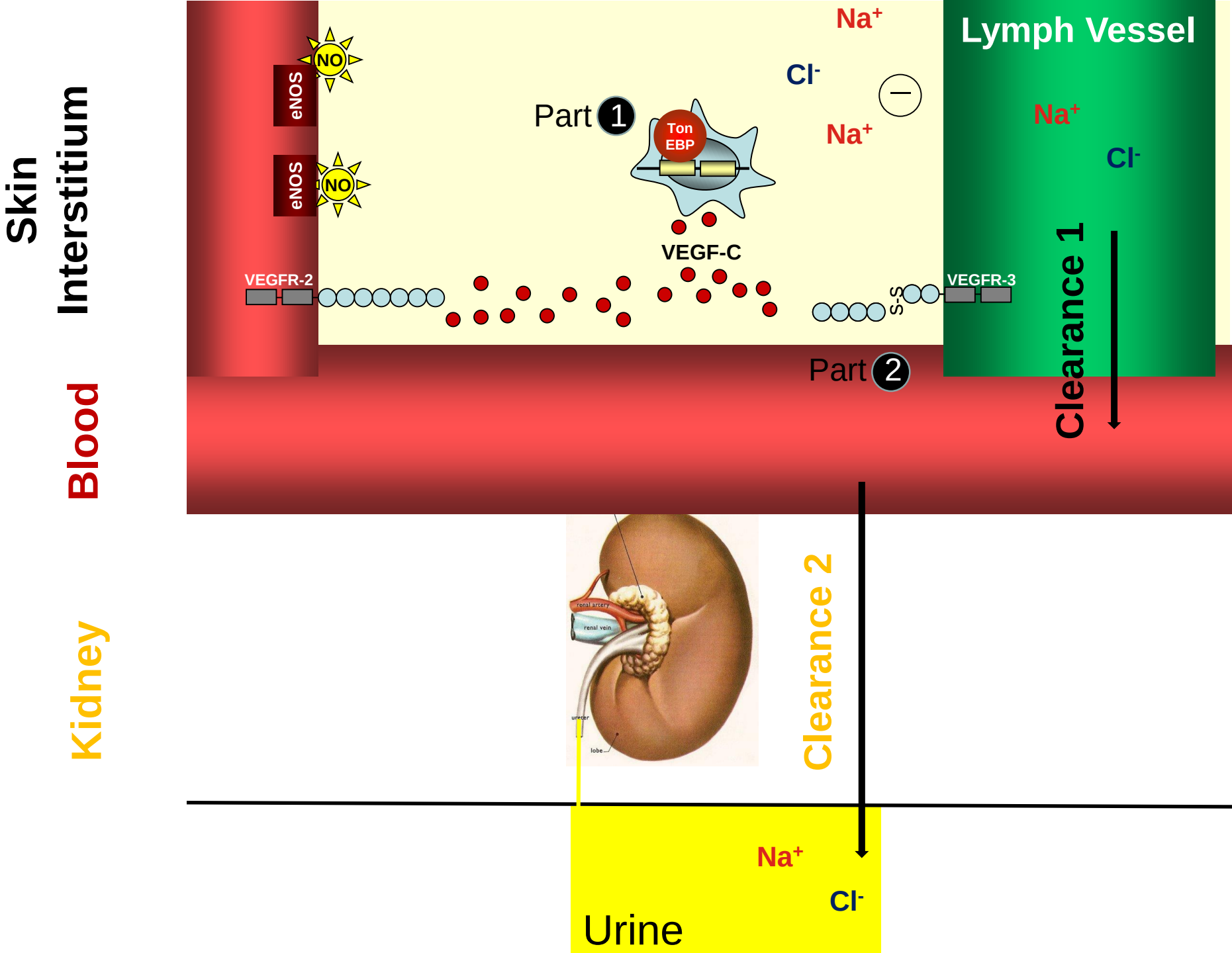
	LSD	HSD
Blood: [$Na^+ + K^+$]	143 ± 2 mM	145 ± 2 mM
Skin: [$Na^+ + K^+$]	177 ± 8 mM	191 ± 7 * mM

Agnes Schröder





Nature Medicine, 2009

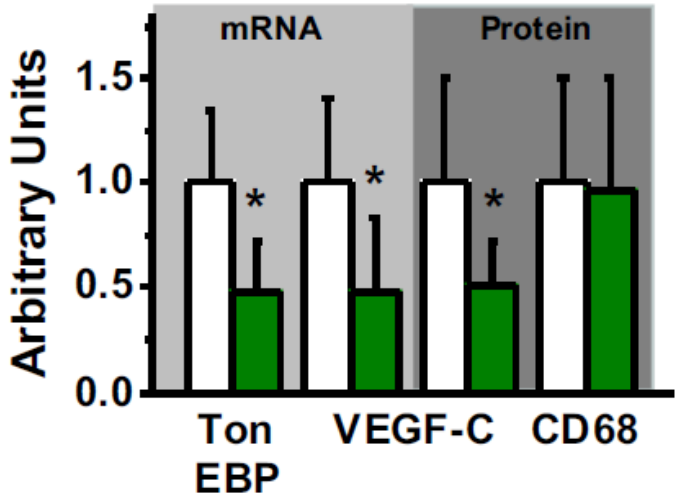

Skin
Interstitium
Blood
Kidney
Lymph Vessel
eNOS
NO
eNOS
NO
Part 1
Ton EBP
VEGF-C
Na+
Cl-
Na+
Na+
Cl-
VEGFR-2
S-S
VEGFR-3
Part 2
Clearance 1
Clearance 2
renal artery
renal vein
ureter
lobe
Na+
Cl-
Urine

Questions:

1. *MPS: regulators of electrolytes and blood pressure?*
2. *Lymphatic regulation of blood pressure?*
3. *Is blood pressure regulated in the skin?*

Macrophages regulate skin electrolyte homeostasis and blood pressure

A



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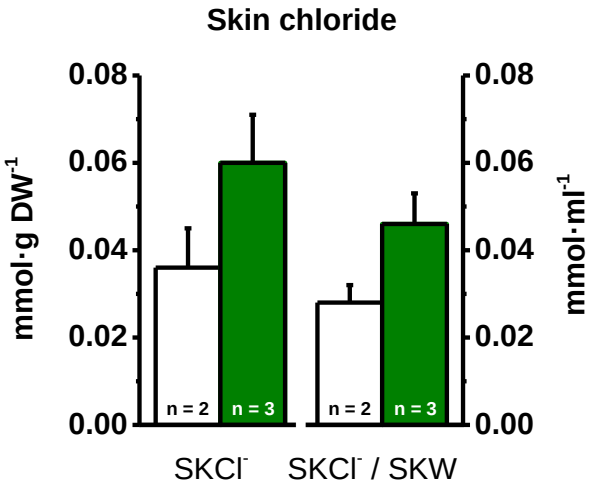

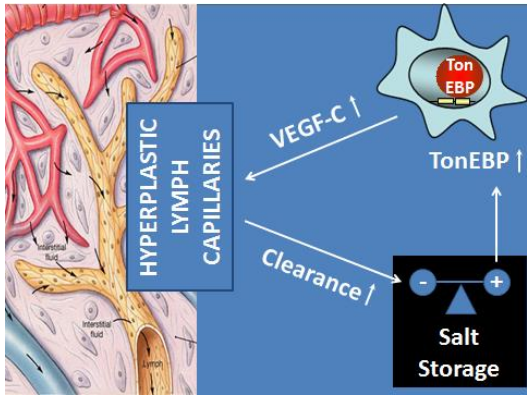

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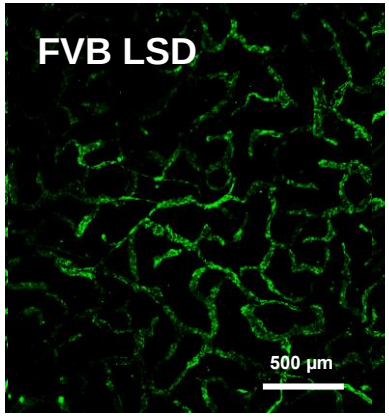

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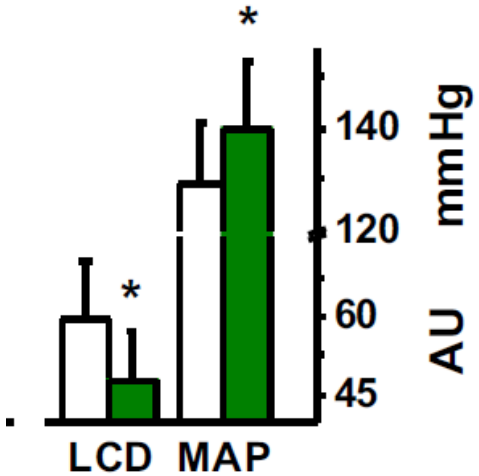


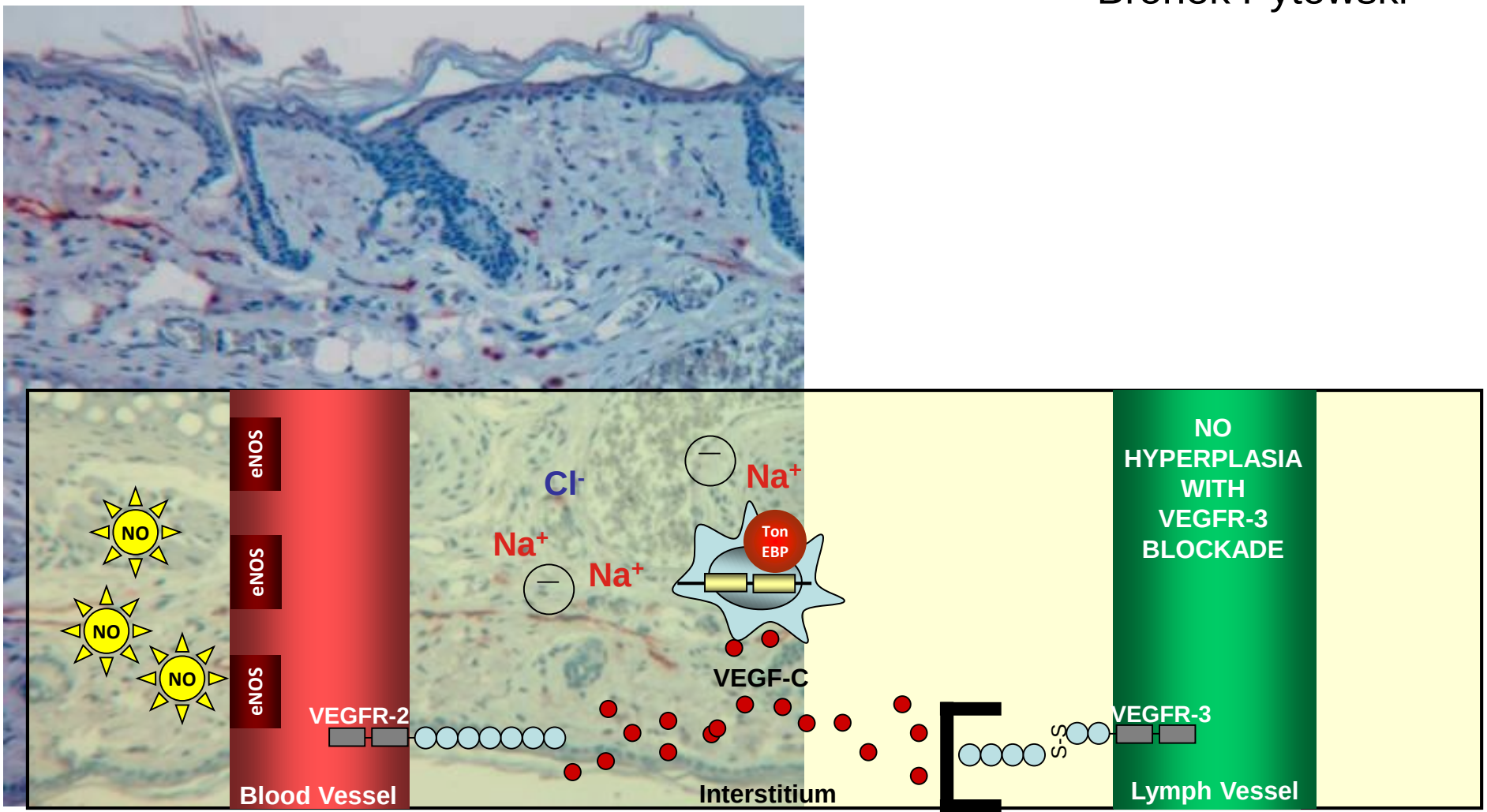
JCI, 2013; 123: 2803-2815

Questions:

1. *Is the skin microenvironment hypertonic?*
2. *Are lymph capillaries important for blood pressure?*
3. *Is skin VEGF-C important for blood pressure control?*

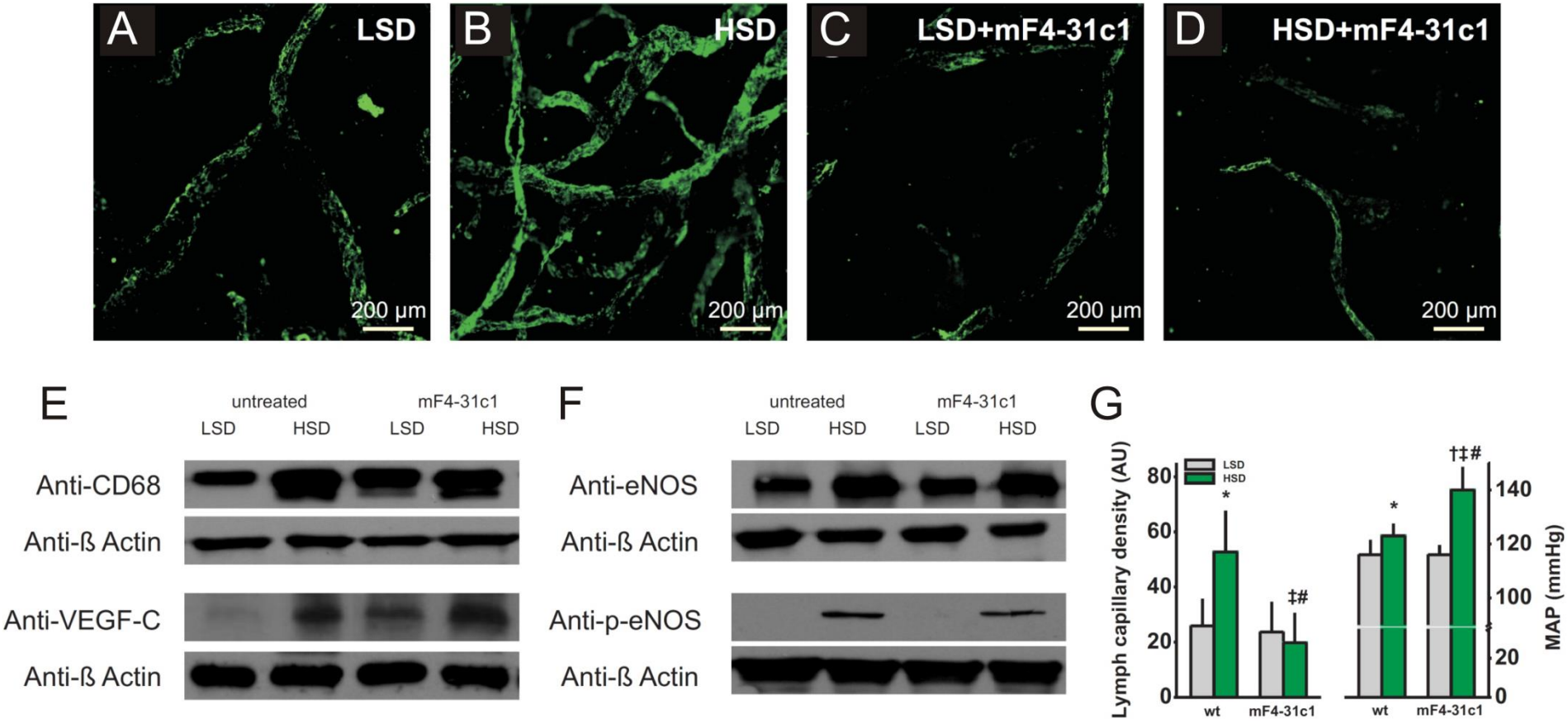
Lymphatic regulation of blood pressure?

Agnes Schröder
Bronek Pytowski



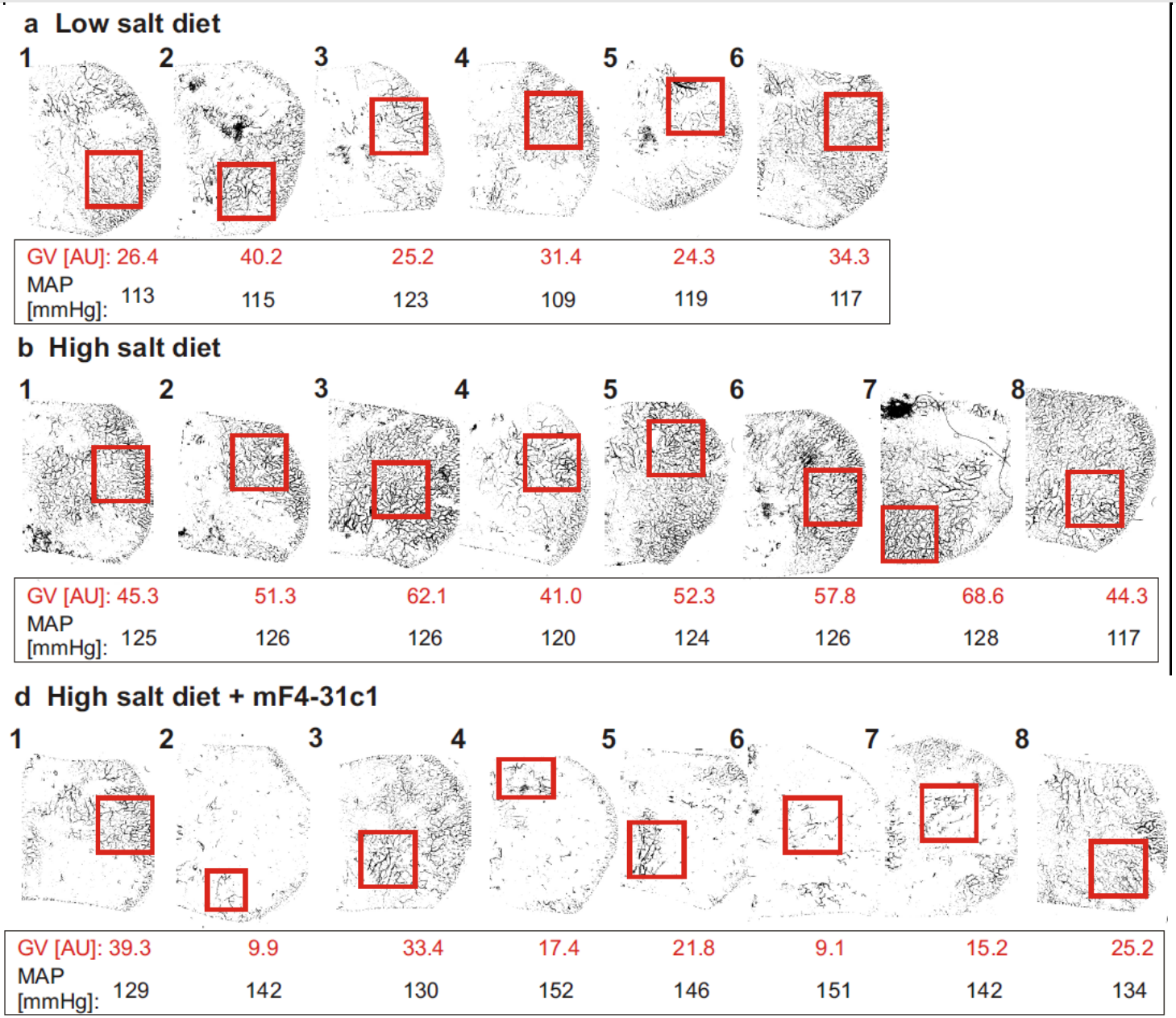
Lymphatic regulation of blood pressure?

Experiments with mF4-31c1



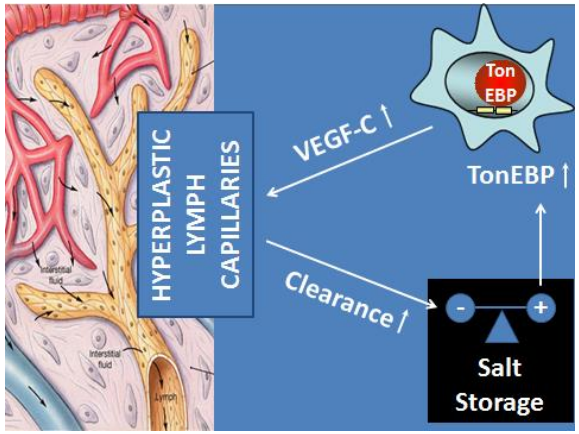
JCI, 2013; 123: 2803-2815

Lymphatic regulation of blood pressure

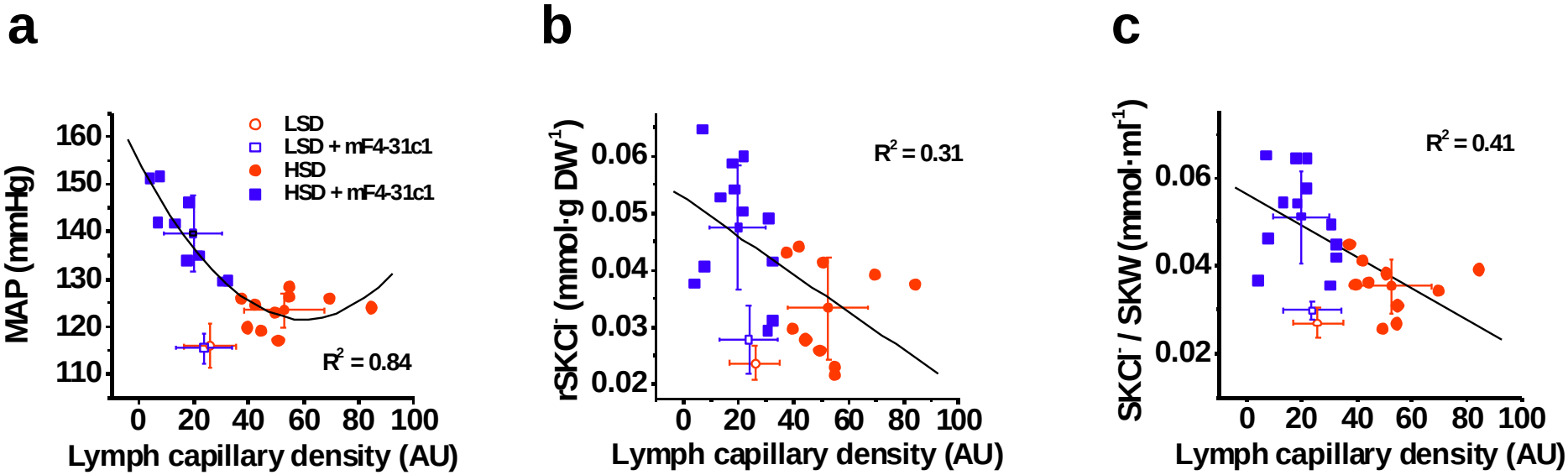


JCI, 2013; 123:

Lymphatic regulation of blood pressure



Experiments with mF4-31c1



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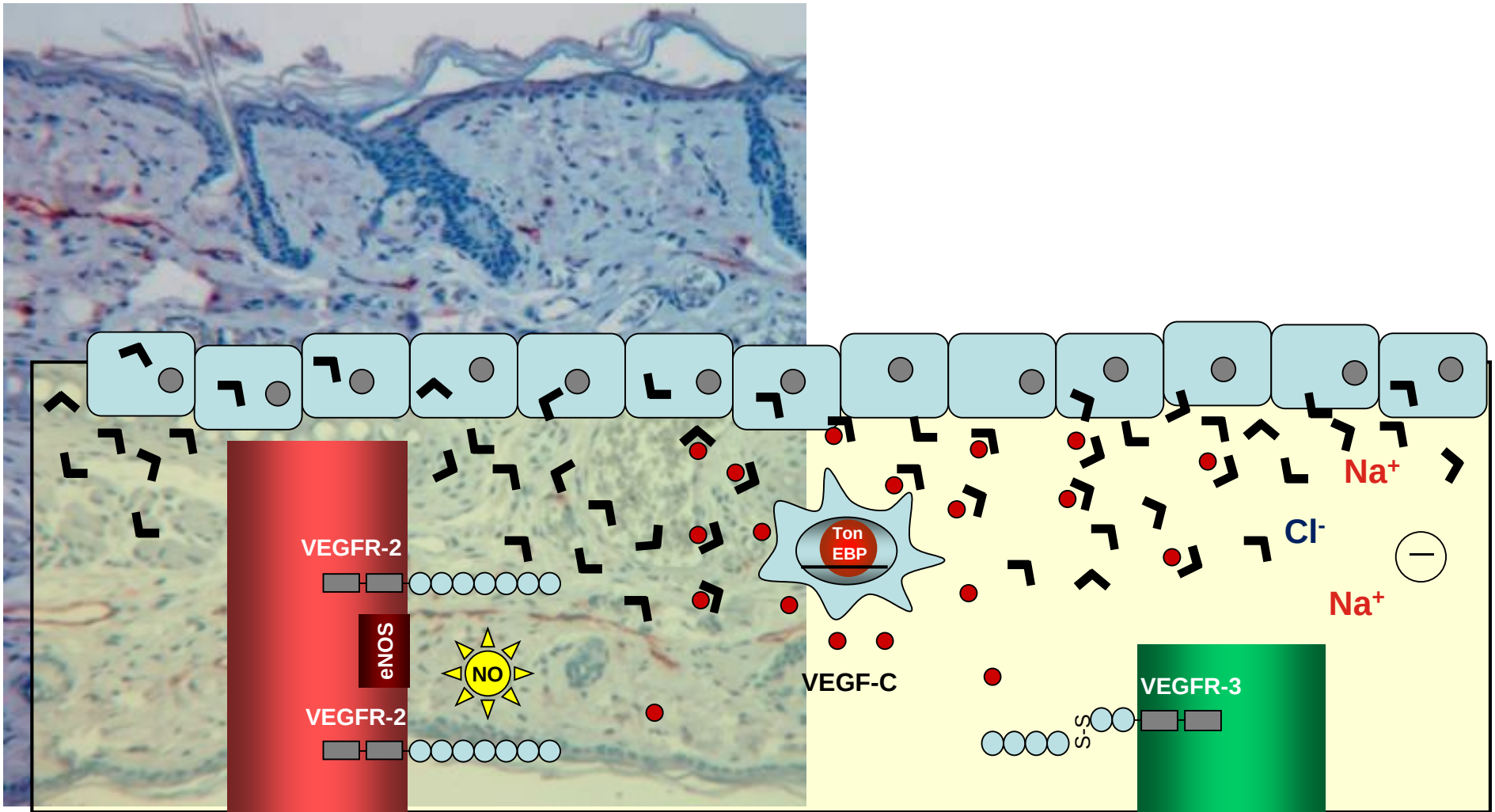
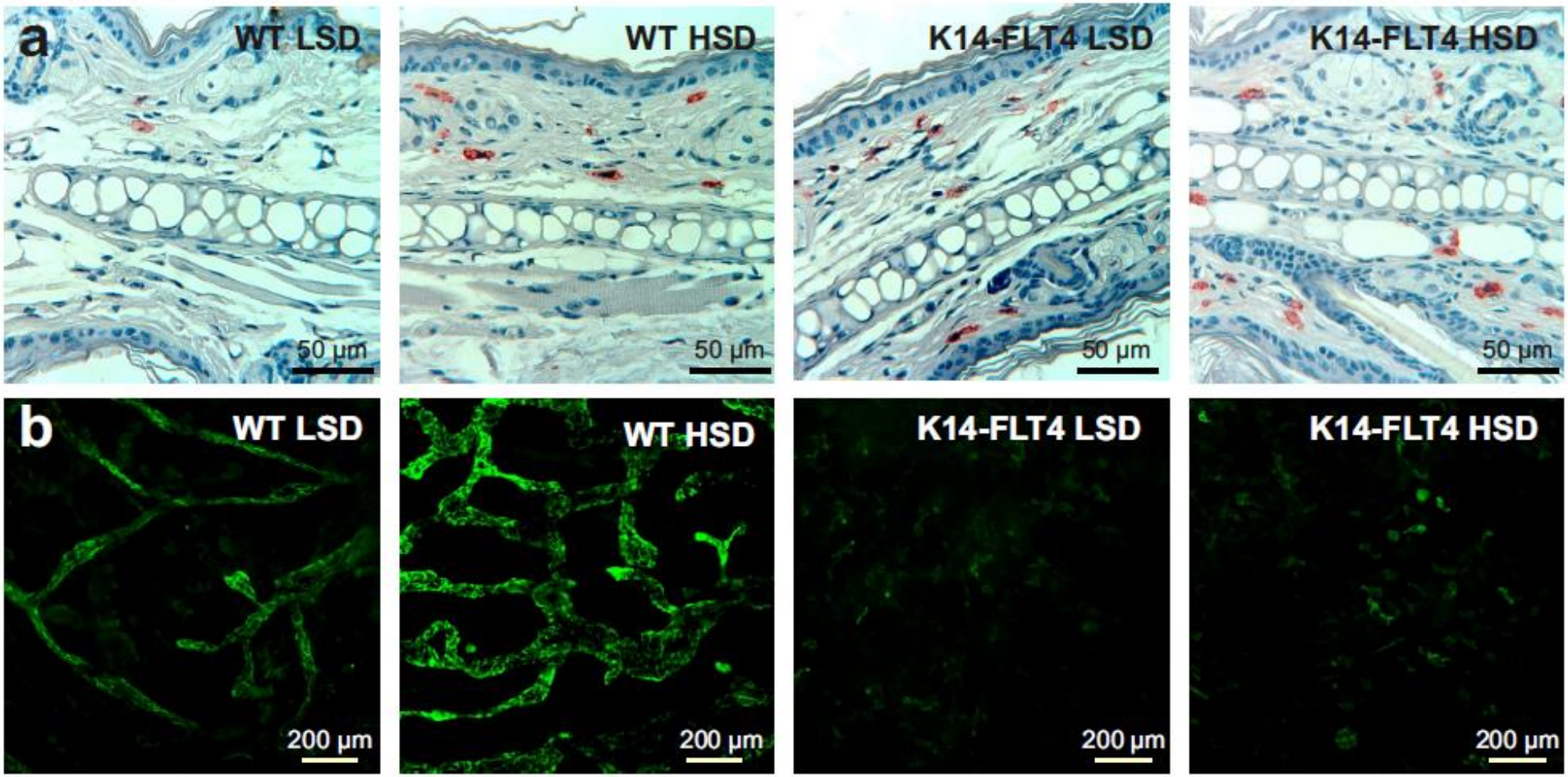
1. *Is the skin microenvironment hypertonic?*
2. *Are lymph capillaries important for blood pressure?*
3. *Is skin VEGF-C important for blood pressure control?*

Skin VEGF-C and blood pressure

Agnes Schröder
Kari Alitalo



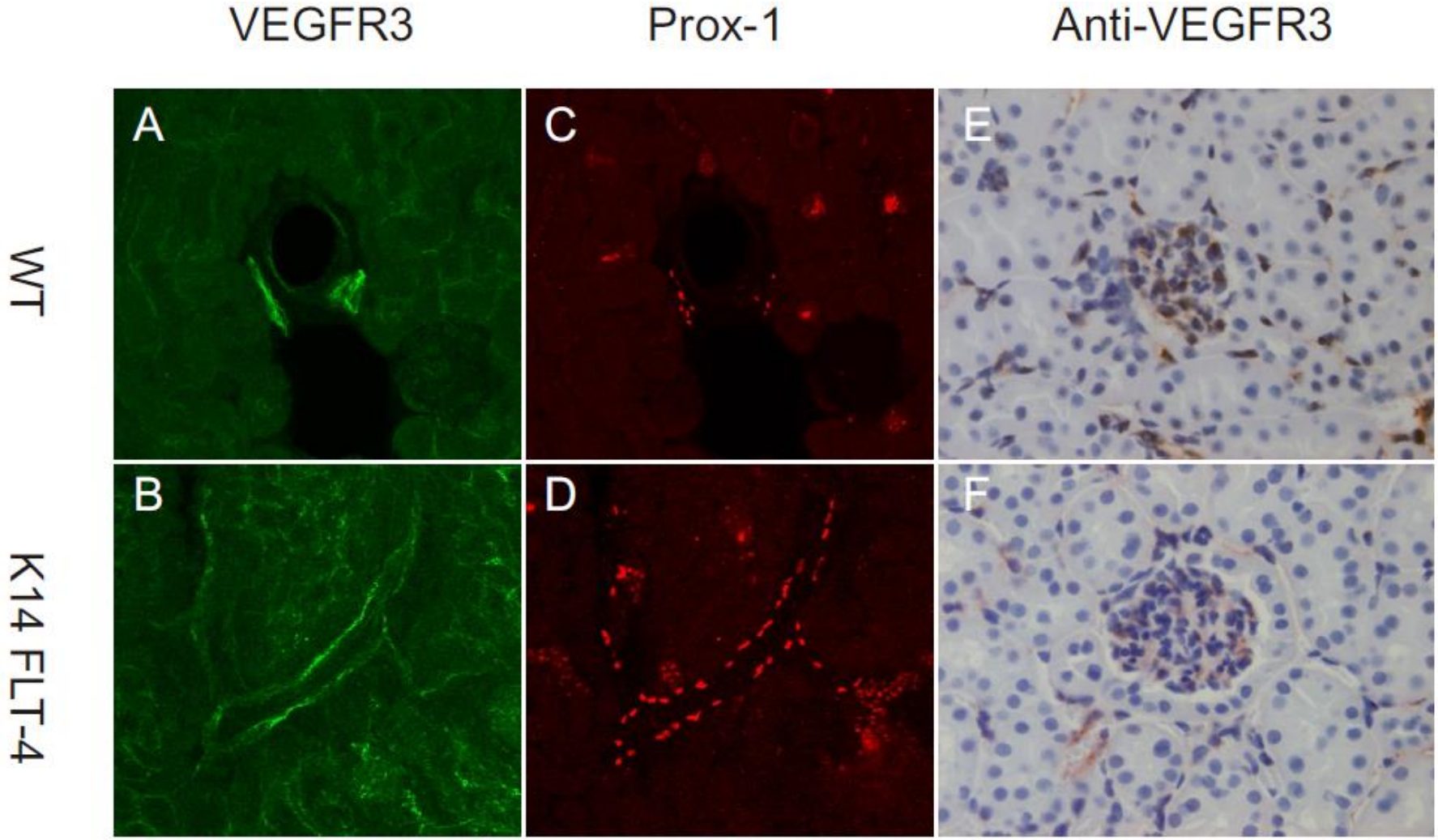
Skin VEGF-C and blood pressure



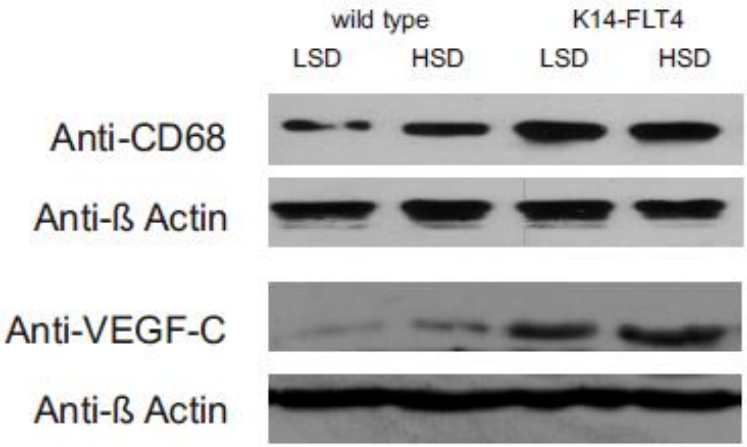
JCI, 2013; 123: 2803-2815

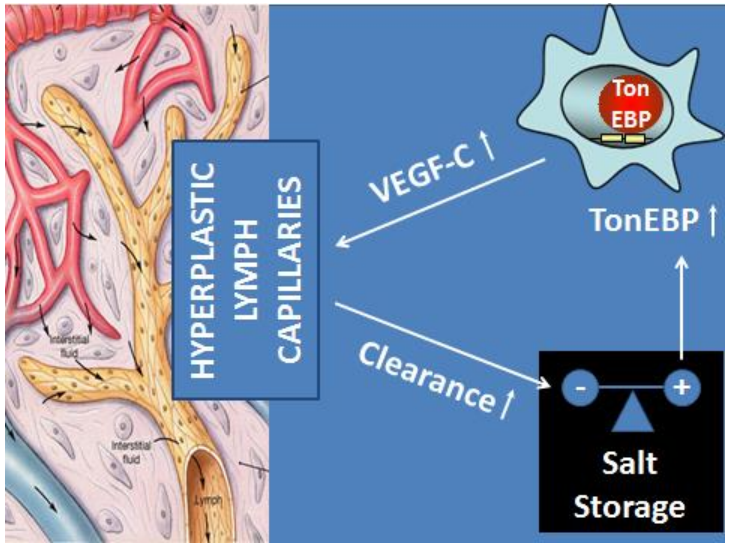
Skin VEGF-C and blood pressure

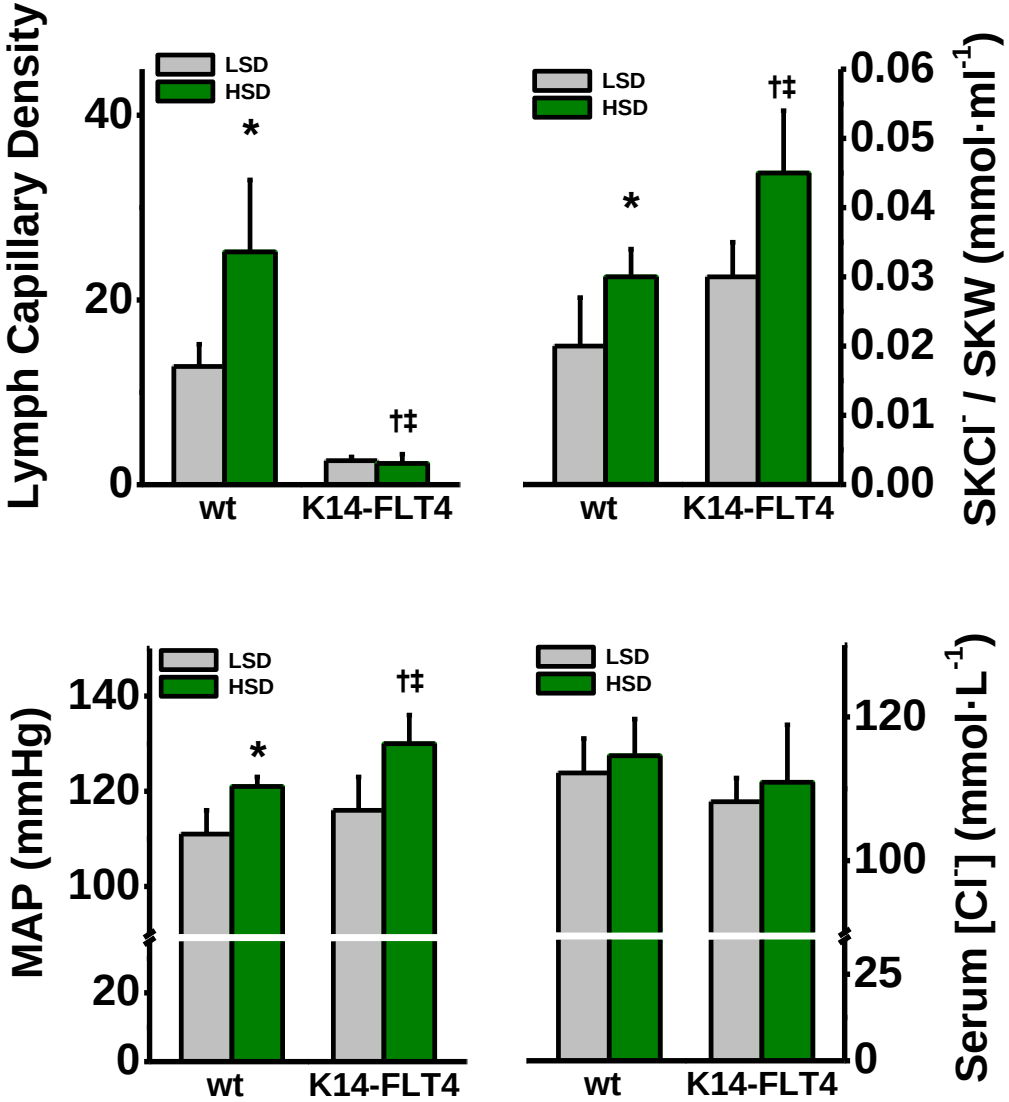
Does not seem to be a kidney problem.



Skin VEGF-C and blood pressure





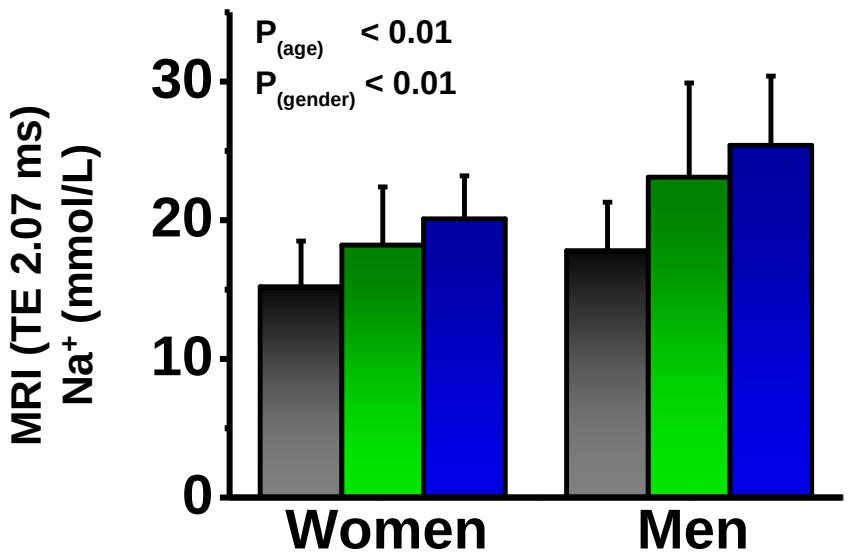


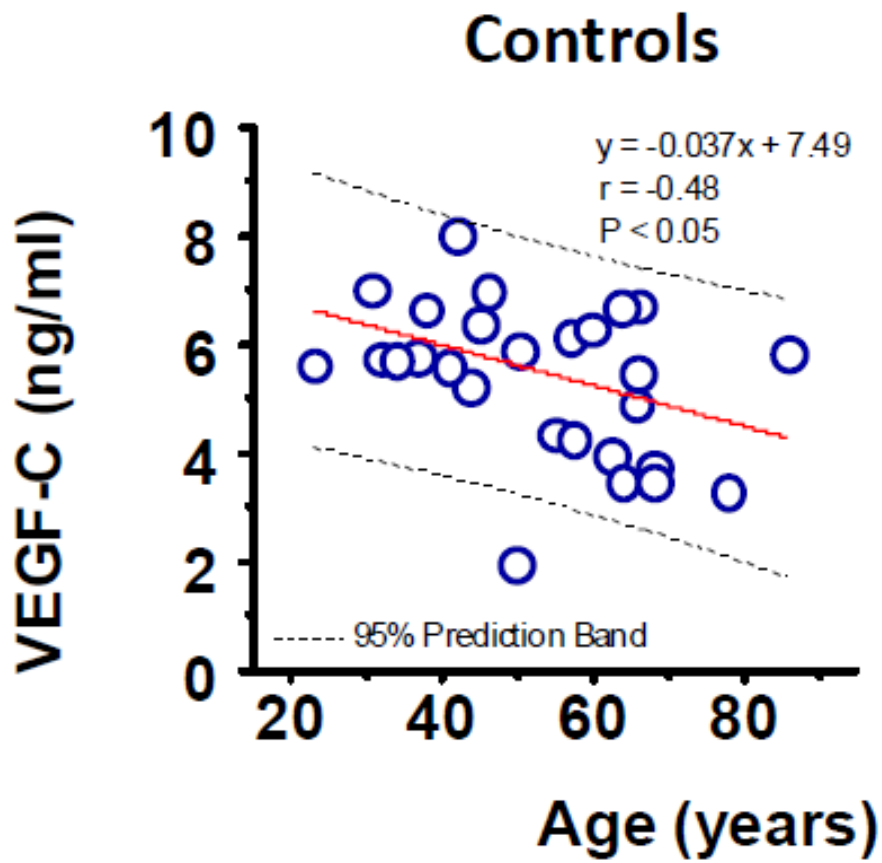
JCI, 2013; 123: 2803-2815


„Model“
research
Asleep at the
switch?
„Patient“
research

ESRD patients

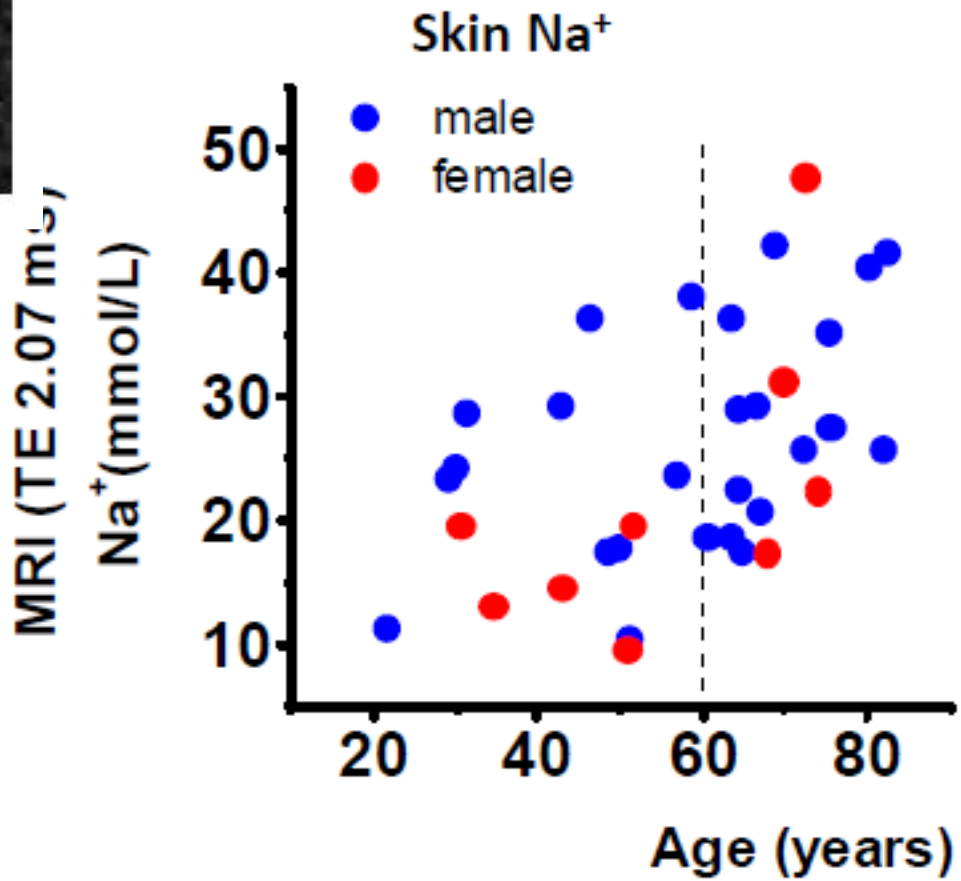
Sodium storage and its coincidence with hypertension.



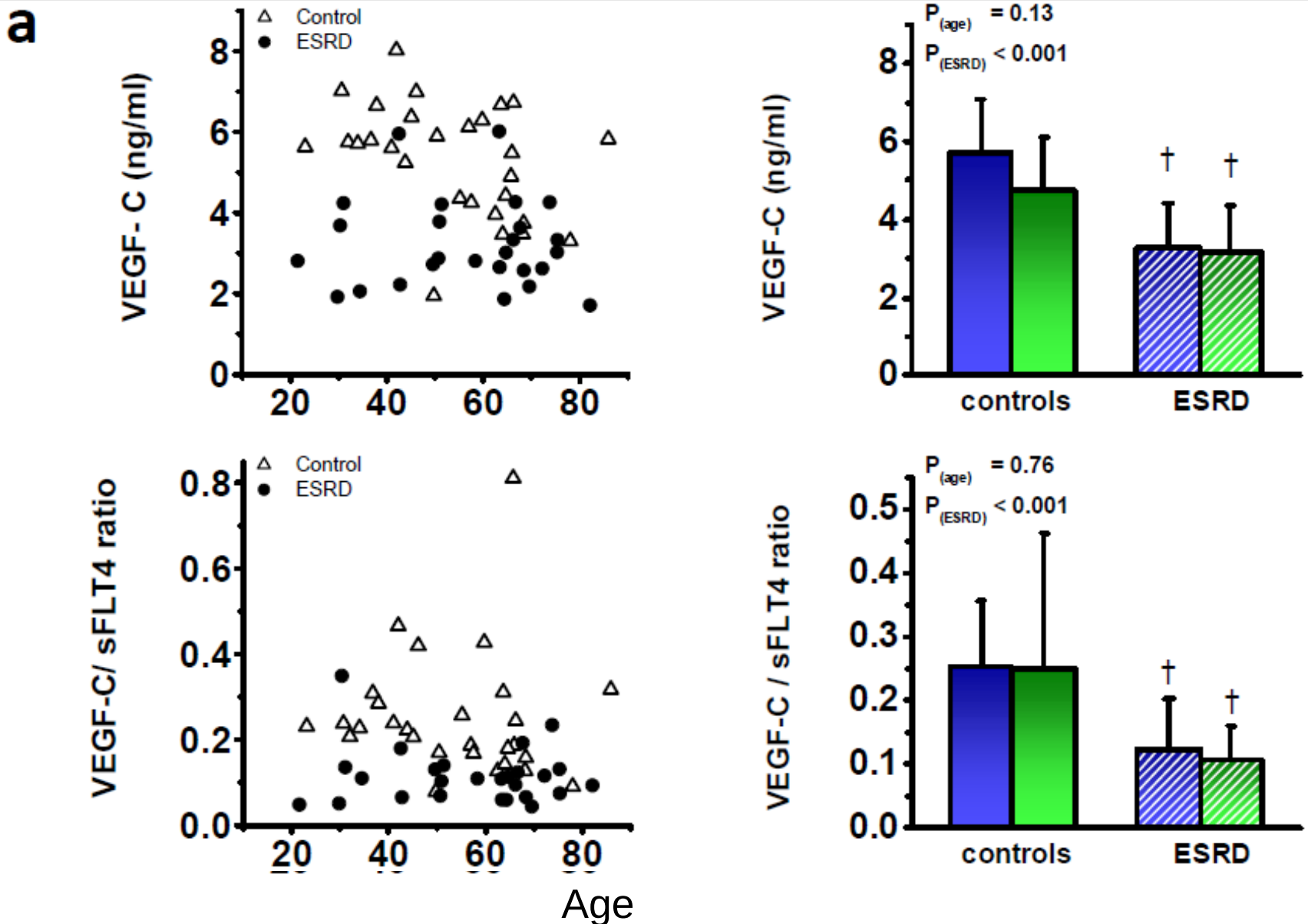


DuoSet ELISA Development Kit
R&D Systems
Sandwich Elisa

ESRD patients

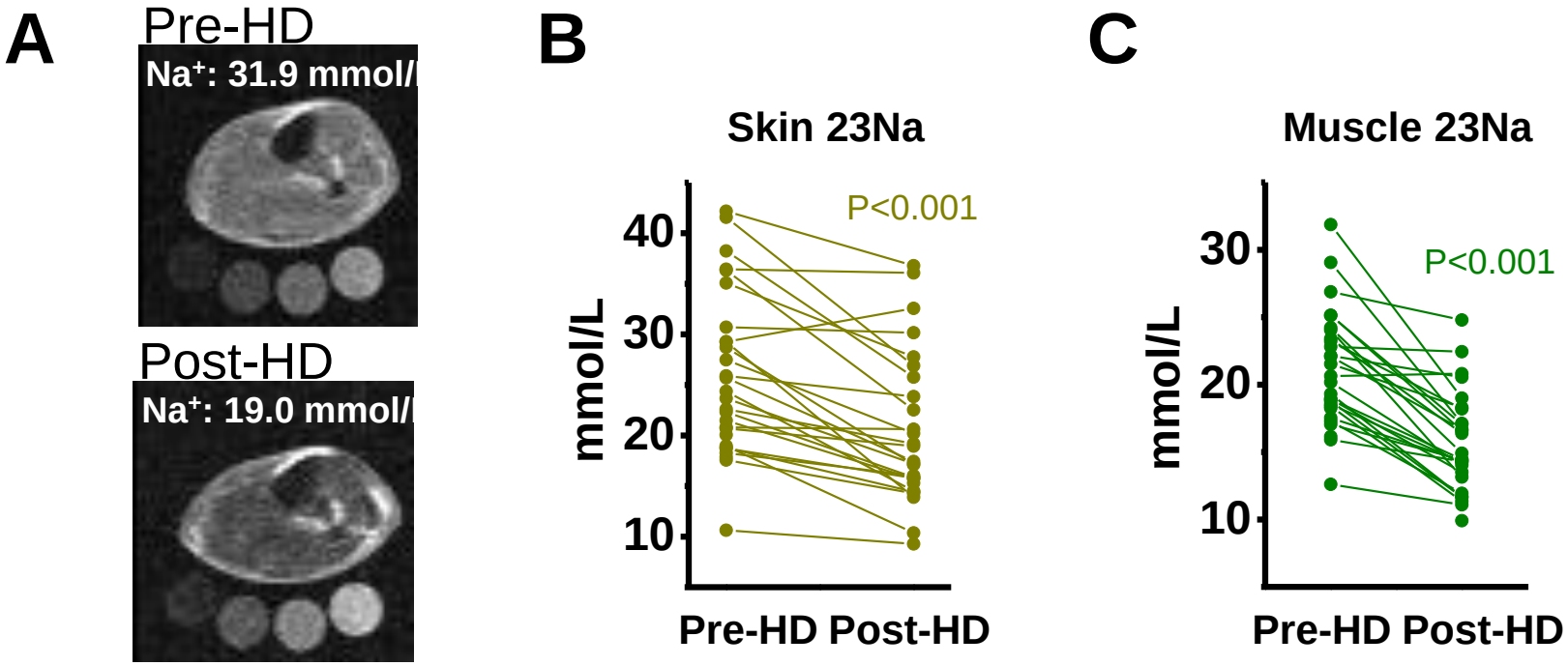


ESRD patients



Skin
Interstitium
Blood
Kidney
Lymph Vessel
eNOS
eNOS
NO
NO
Na+
Cl-
Na+
Ton
EBP
VEGF-C
VEGFR-2
S-S
VEGFR-3
Na+
Cl-
Clearance 1
Dirty
Dialysate
Out
renal artery
renal vein
ureter
lobe
Clearance 2

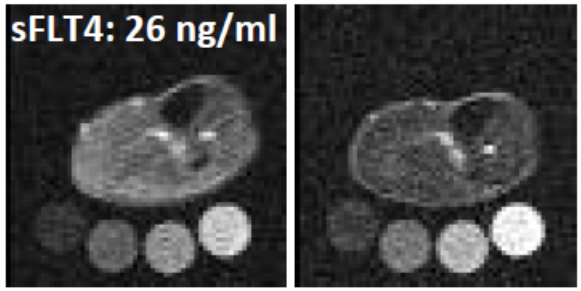
Sodium removal in ESRD patients



ESRD patients

Man, 64 y, high Na^+ removal

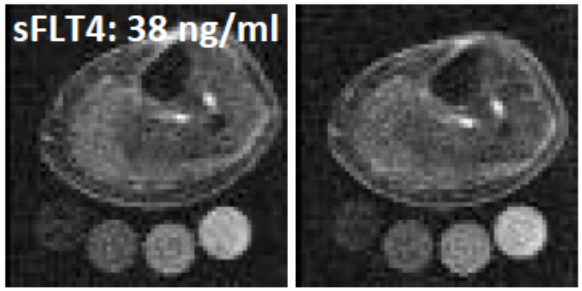
Pre-HD | Post-HD



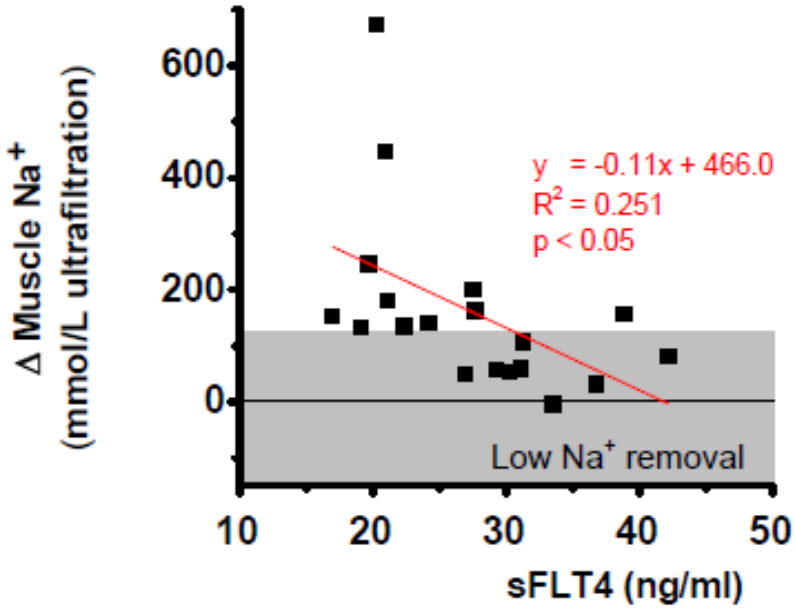
Muscle Na^+: 24.0 mmol/L | 13.1 mmol/L

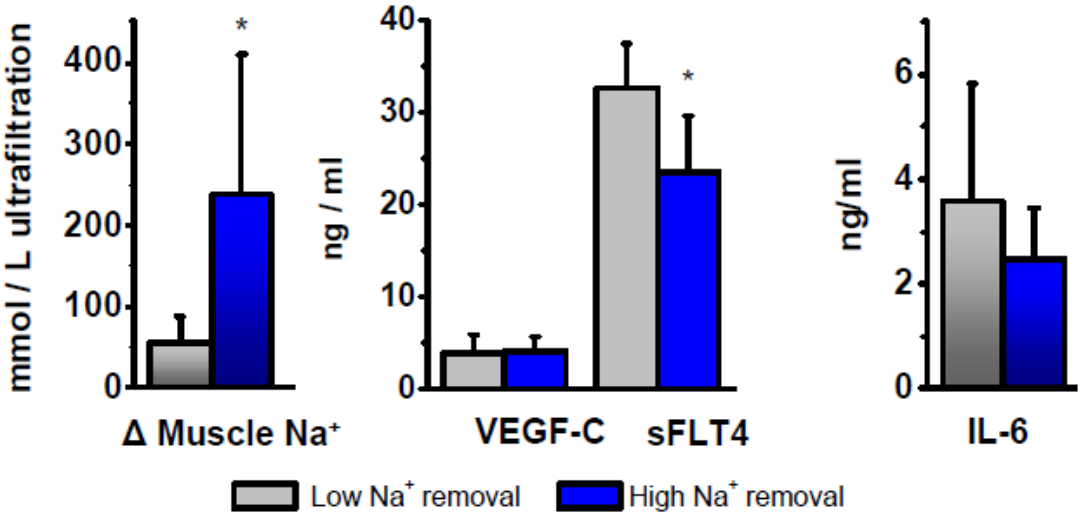
Man, 77 y, low Na^+ removal

Pre-HD | Post-HD



22.1 mmol/L | 20.6 mmol/L





Electrolyte homeostasis:
Immunology beyond innate and adaptive stereotypes

Summary

1. Isotonicity versus hypertonicity.
2. Clearance.
3. What is immune function?

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Christoph Kopp, MD

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Ulrike Goller (technician)

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Kai-Uwe Eckardt

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Funded by:

IZKF (TP B13, Junior Research Group 2)

DFG (Ti-345/2, Lymphatics)

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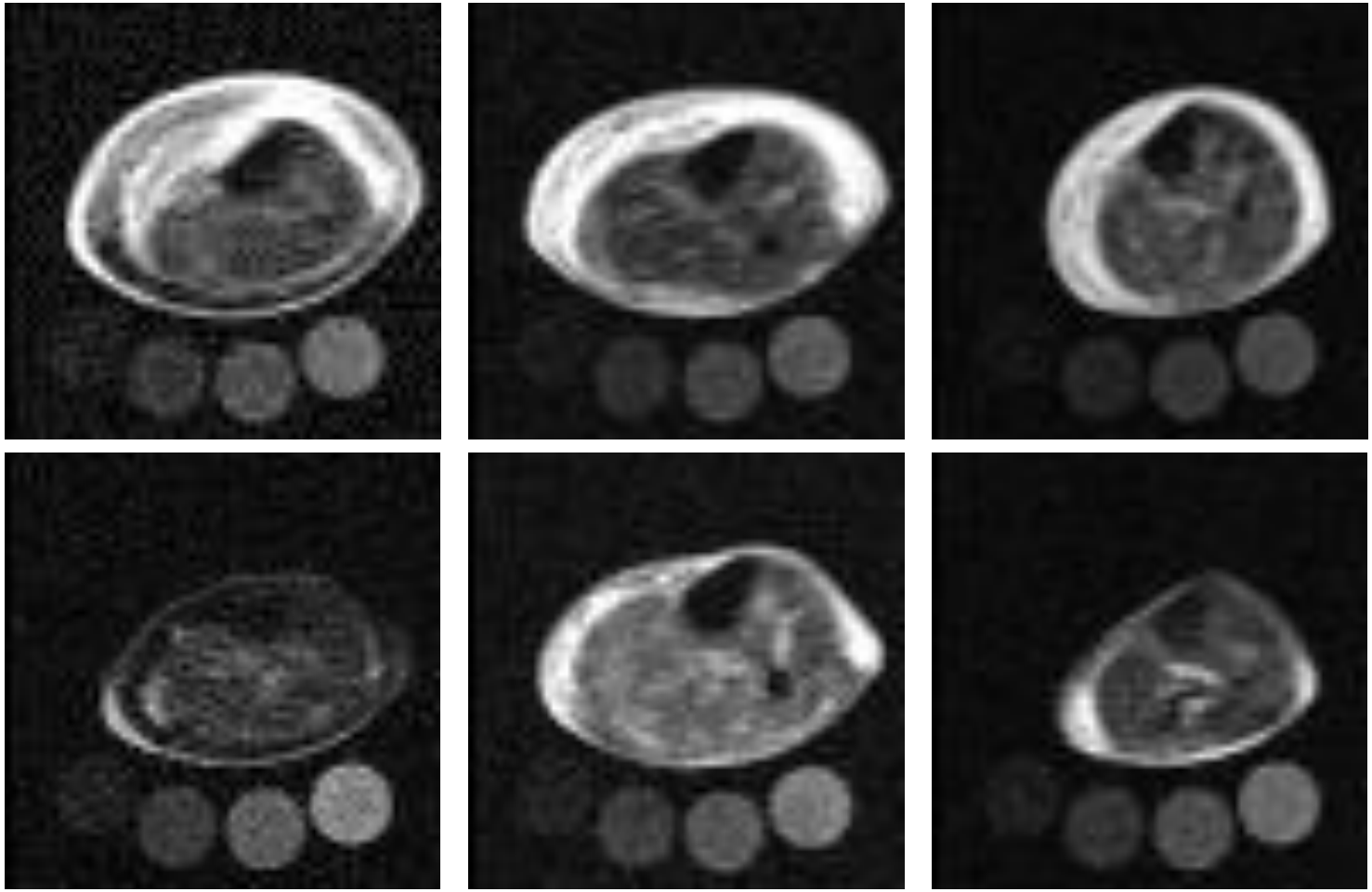
Results:
Sodium during Therapy

Before Therapy (69.5 kg) (103 kg) (73.5 kg)



After Therapy (65.7 kg) (100 kg) (70.4 kg)