



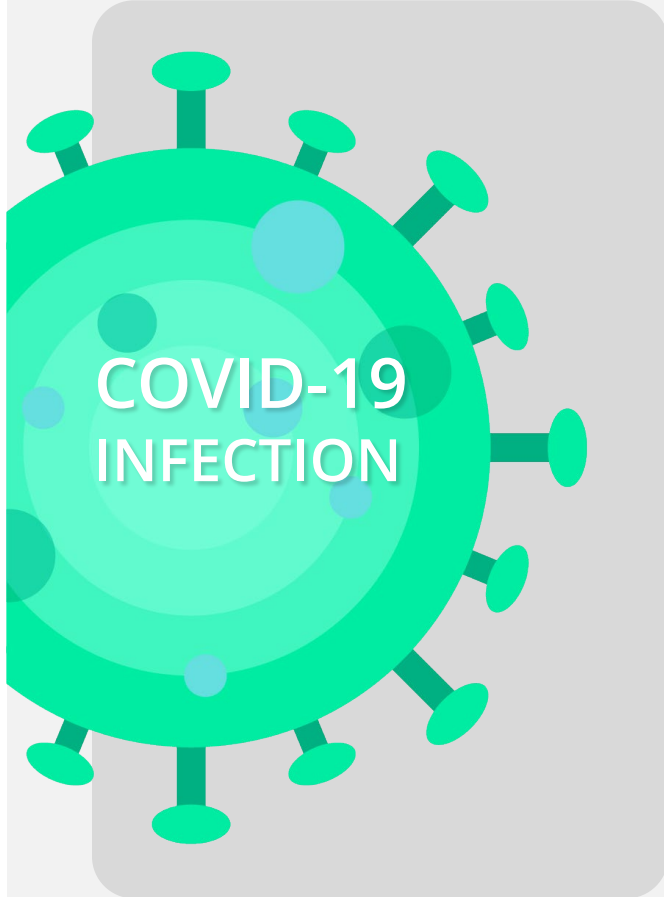
# A UNIFYING PATHOPHYSIOLOGICAL CONCEPT FOR ME/CFS AND A DERIVED THERAPEUTIC STRATEGY

ANALYSIS BASED ON OBJECTIVE FINDINGS;  
CARDINAL SYMPTOMS AND RECOGNITIONS  
FROM COVID-19

Klaus Wirth



# THE CORONA INFECTION CAUSES A SEVERE VASCULAR AND PERFUSION DISTURBANCE



## RISK FACTORS

**Long COVID**

Severe & complex  
**MICROVASCULAR  
DISORDER<sup>1</sup>**

## PATHOMECHANISMS

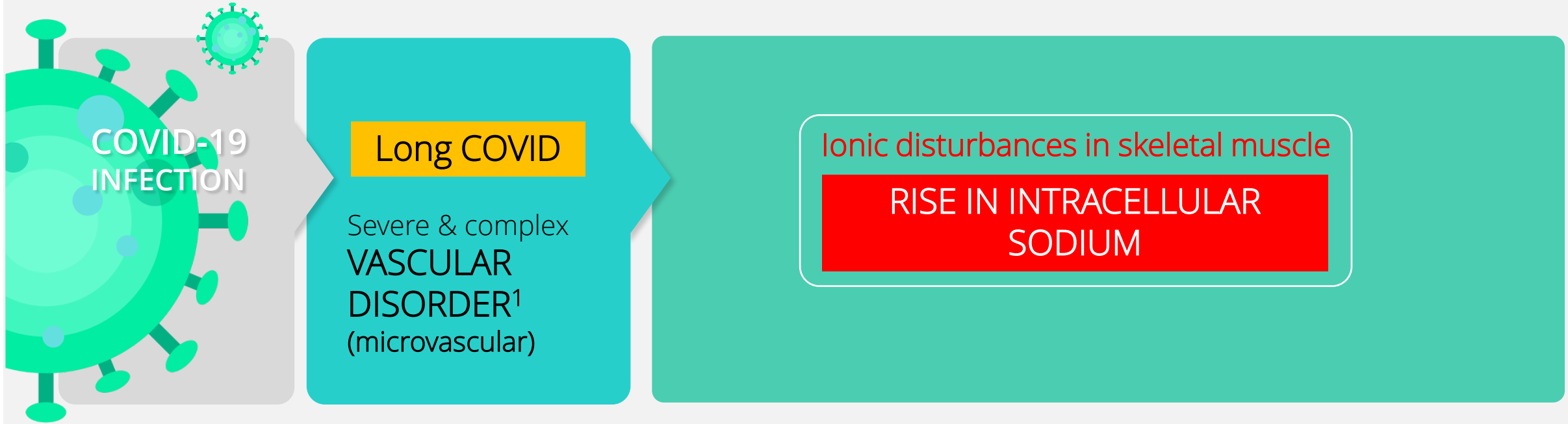
- Microthrombi
- Oversized blood cells
- Inflammatory, prothrombotic capillary wall changes
- Autoantibodies
- Cardiovascular disorders (precapillary)
- Autonomic dysfunction
- Endothelial dysfunction
- High sympathetic nervous system activity

Physical and mental efforts require a strong rise in blood flow

➡ **Exercise intolerance**

<sup>1</sup>Kruger et al.; 2025 Semin Thromb Hemost; Summarized in Löhn and Wirth, 2024 Medicina

# DISTURBED PERFUSION IN POST-COVID-SYNDROME LEADS TO AN INCREASE IN INTRACELLULAR SODIUM IN THE SKELETAL MUSCLE CELLS DURING MUSCLE WORK

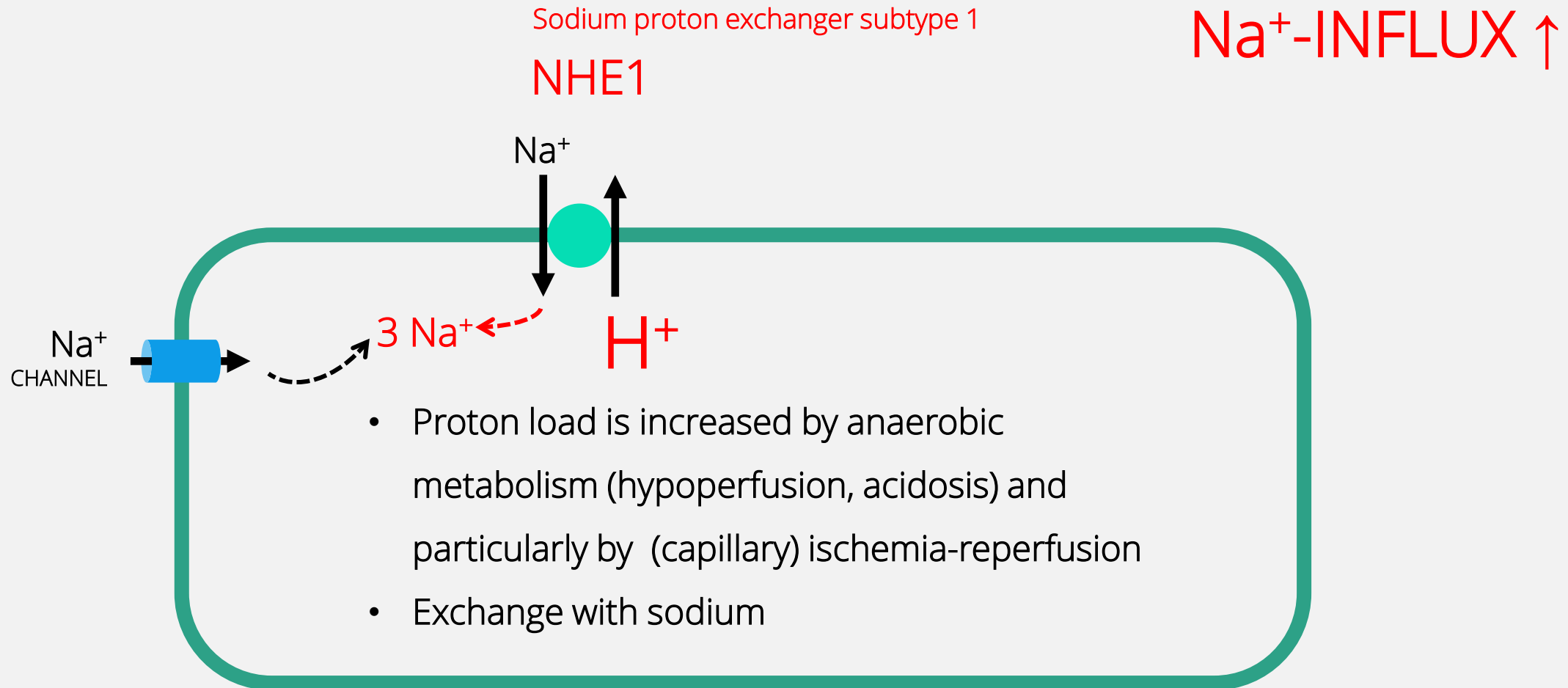


**Na<sup>+</sup>-INFLUX ↑**

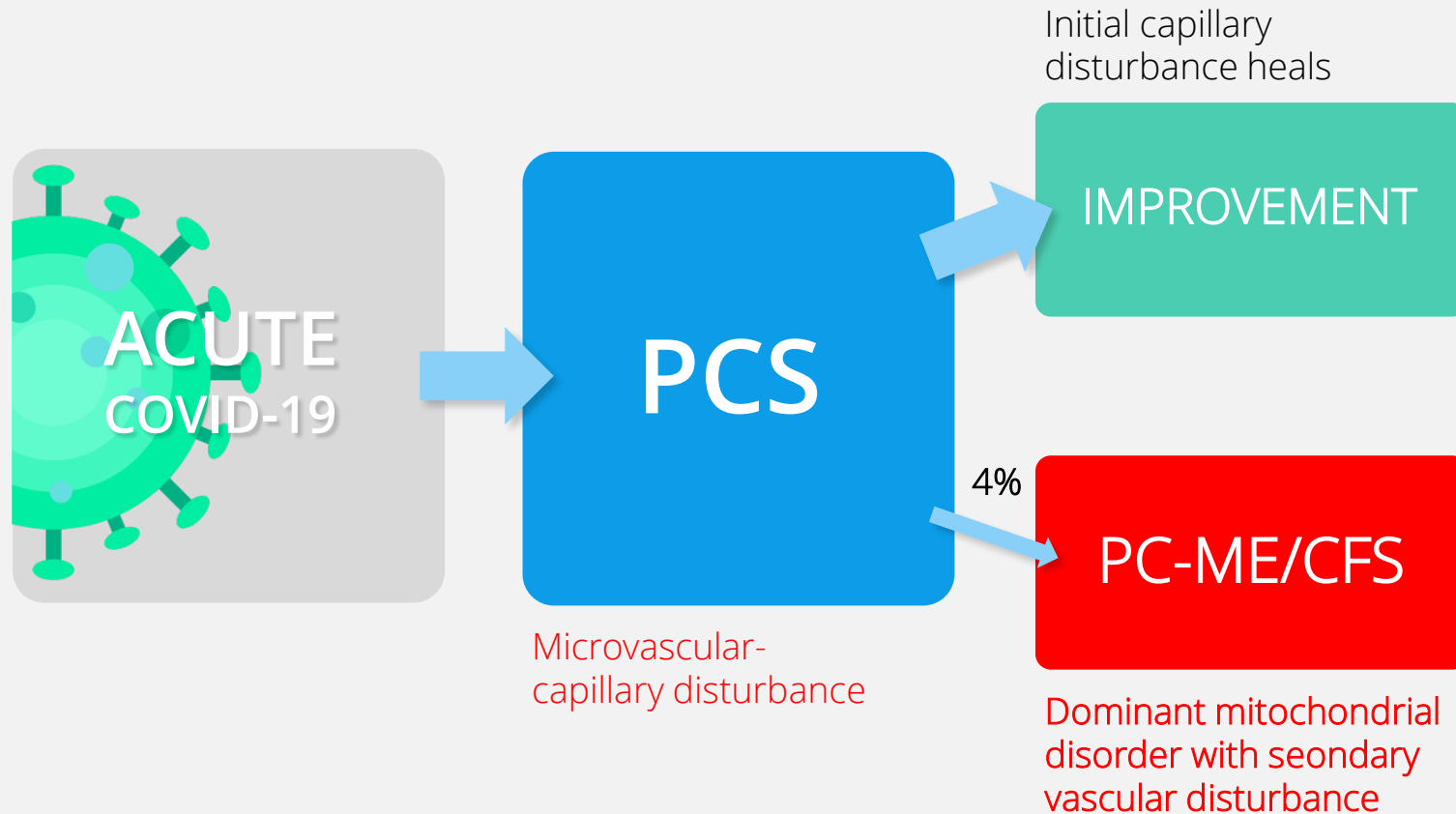
<sup>1</sup>Kruger et al.; 2025 Semin Thromb Hemost; Summarized in Löhn and Wirth, 2024 Medicina

# PERFUSION DISTURBANCE INCREASES INTRACELLULAR PROTON CONCENTRATION IN MUSCLES (ACIDOSIS): EXCHANGE WITH SODIUM RAISES INTRACELLULAR SODIUM

Protons cannot freely diffuse through the cell membrane but are transported



# MOST PCS-PATIENTS SHOW IMPROVEMENT OVER TIME. WHY DOES A FRACTION OF PATIENTS DEVELOP ME/CFS? THE ROLE OF RISK FACTORS?

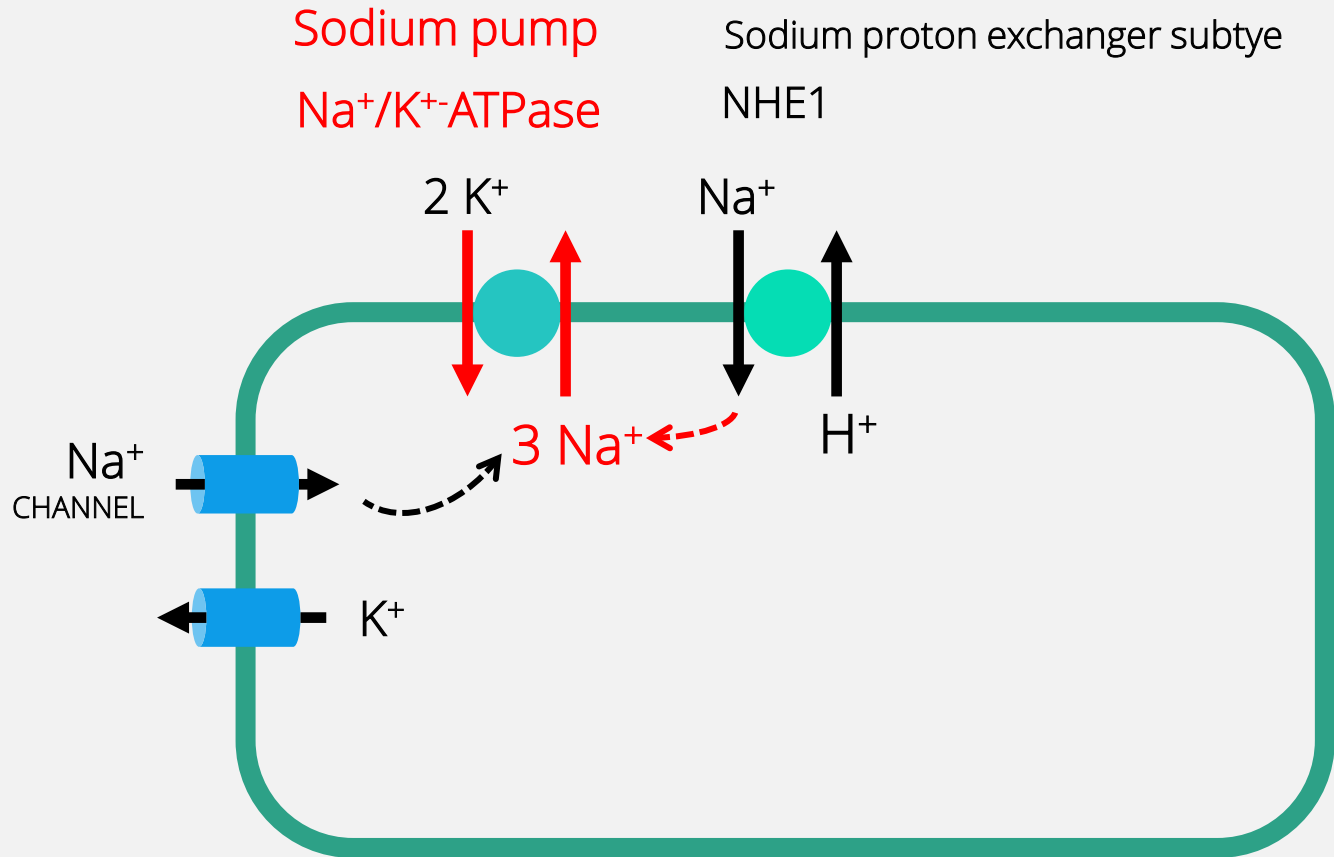


## RISK FACTORS FOR ME/CFS

- Autoantibodies
- Small fiber neuropathy
- TRPM3 dysfunction
- Collagenoses
- Ehlers-Danlos syndromes
- Orthostatic dysfunction
- Variants of vascular and mitochondrial genes
- Mast cell activation
- Etc.

Mitochondrial dysfunction develops due to risk factors in patients with ME/CFS

# PHYSIOLOGICAL ROLE OF THE $\text{Na}^+/\text{K}^+$ -ATPASE IN SKELETAL MUSCLE



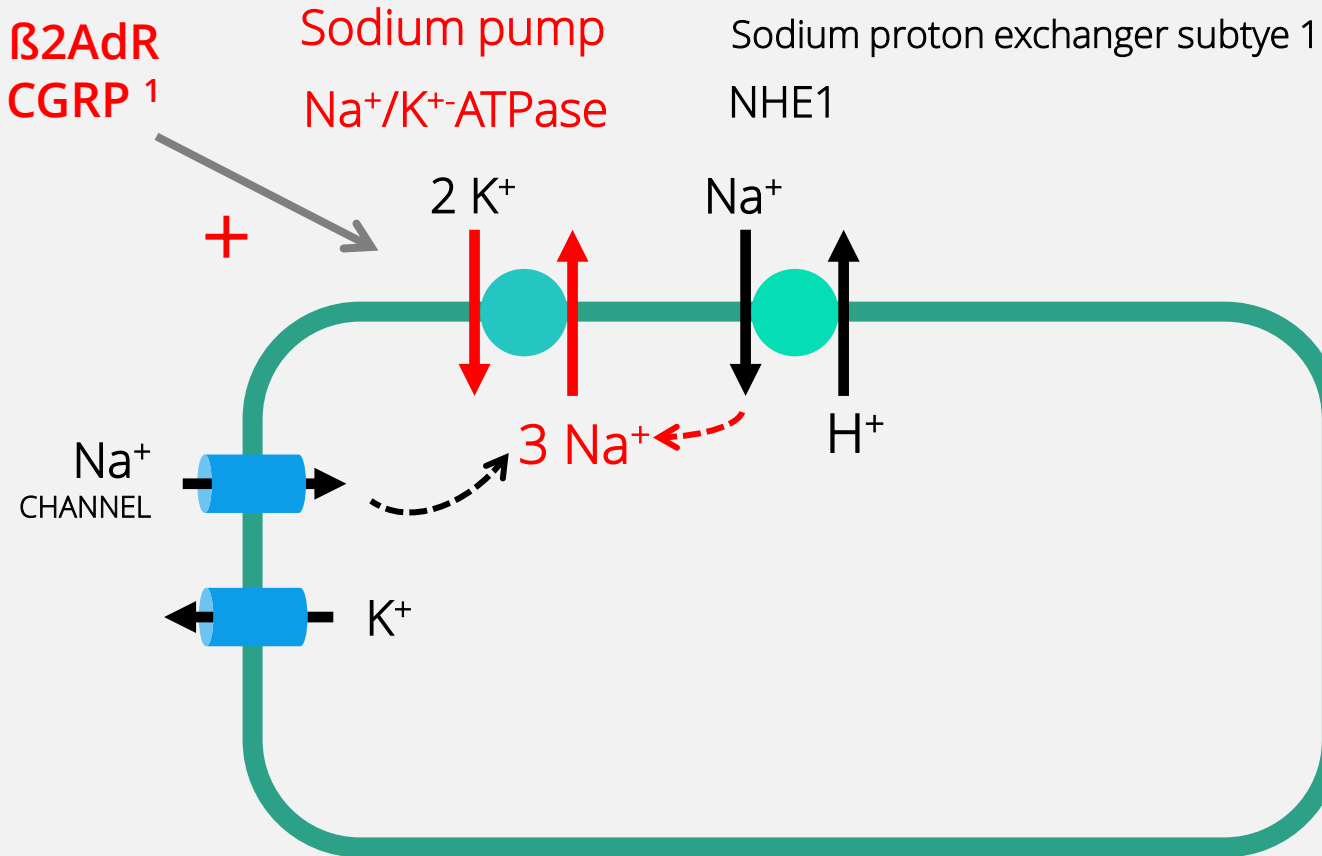
Apart from exporting sodium, the main function of  $\text{Na}^+/\text{K}^+$ -ATPase is to generate the physiological action potential and excitability <sup>1</sup>

No muscle force development without proper function of the  $\text{Na}^+/\text{K}^+$ -ATPase

Its dysfunction leads to a loss of muscular force as shown with ouabain, an inhibitor of  $\text{Na}^+/\text{K}^+$ -ATPase

<sup>1</sup>Pirkmajer and Chibalin, 2016 Clausen, 2003, Physiological Reviews

# RISK FACTORS FOR ME/CFS: SODIUM-EFFLUX IS ALSO DECREASED BECAUSE $\text{Na}^+/\text{K}^+$ -ATPASE IS NOT SUFFICIENTLY STIMULATED BY ITS PHYSIOLOGICAL STIMULI (2)



$\text{Na}^+/\text{K}^+$ -ATPase requires 10-20 fold activation during exercise<sup>1</sup> – high ATP consumption

The only hormonal stimuli during exercise are  $\beta$ 2-adrenergic receptors ( $\beta$ 2AdR) and Calcitonin-gene related peptide (CGRP)<sup>1</sup>

- $\beta$ 2AdR are dysfunctional due to desensitization (high sympathetic tone) or autoantibodies
- CGRP decreased due to small nerve fiber neuropathy and TRPM3-dysfunction
- Dysfunction of both also worsens perfusion

$\text{Na}^+$ -EFFLUX ↓

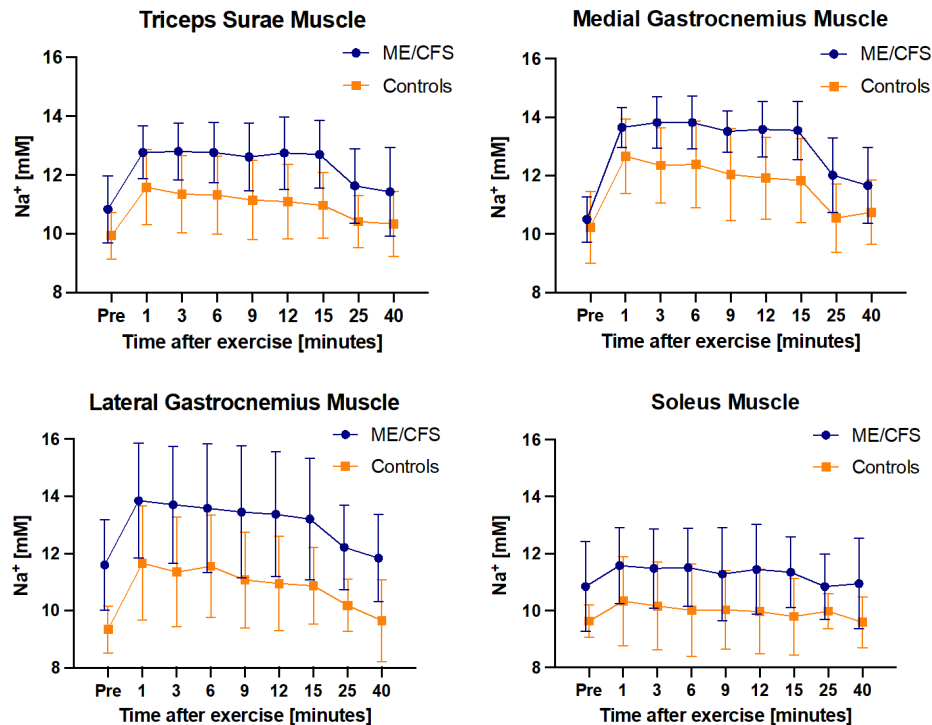
Insufficient  $\text{Na}^+/\text{K}^+$ -ATPase activation during exercise can cause exercise intolerance

<sup>1</sup>Pirkmajer and Chibalin, 2016 Clausen, 2003, Physiological Reviews

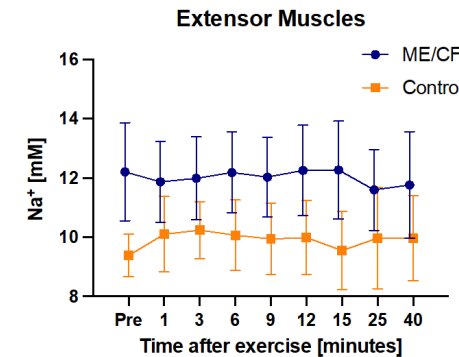
# INTRACELLULAR Na<sup>+</sup> IS ACTUALLY ELEVATED IN SKELETAL MUSCLE IN ME/CFS

Results of a <sup>23</sup>Na Magnetic Resonance Imaging Study <sup>1</sup>

## WORKING MUSCLE (PLANTAR FLEXION)



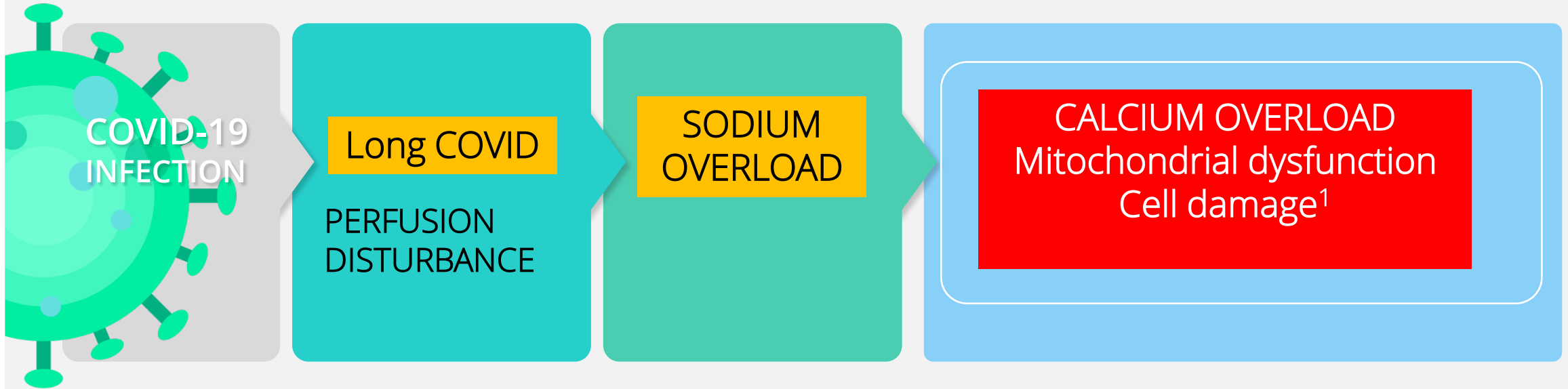
## NON-WORKING LOWER LEG MUSCLE



- 6 ME/CFS patients and 6 controls.
- Approximately 20% increase in intracellular Na<sup>+</sup> measured before and after exercise (not during).
- **Increase in intramuscular Na<sup>+</sup> negatively correlates with hand grip strength.**
- Loss of force (hand grip strength) correlates with prognosis and symptoms in a Post COVID syndrome (PCS) study<sup>2</sup>.

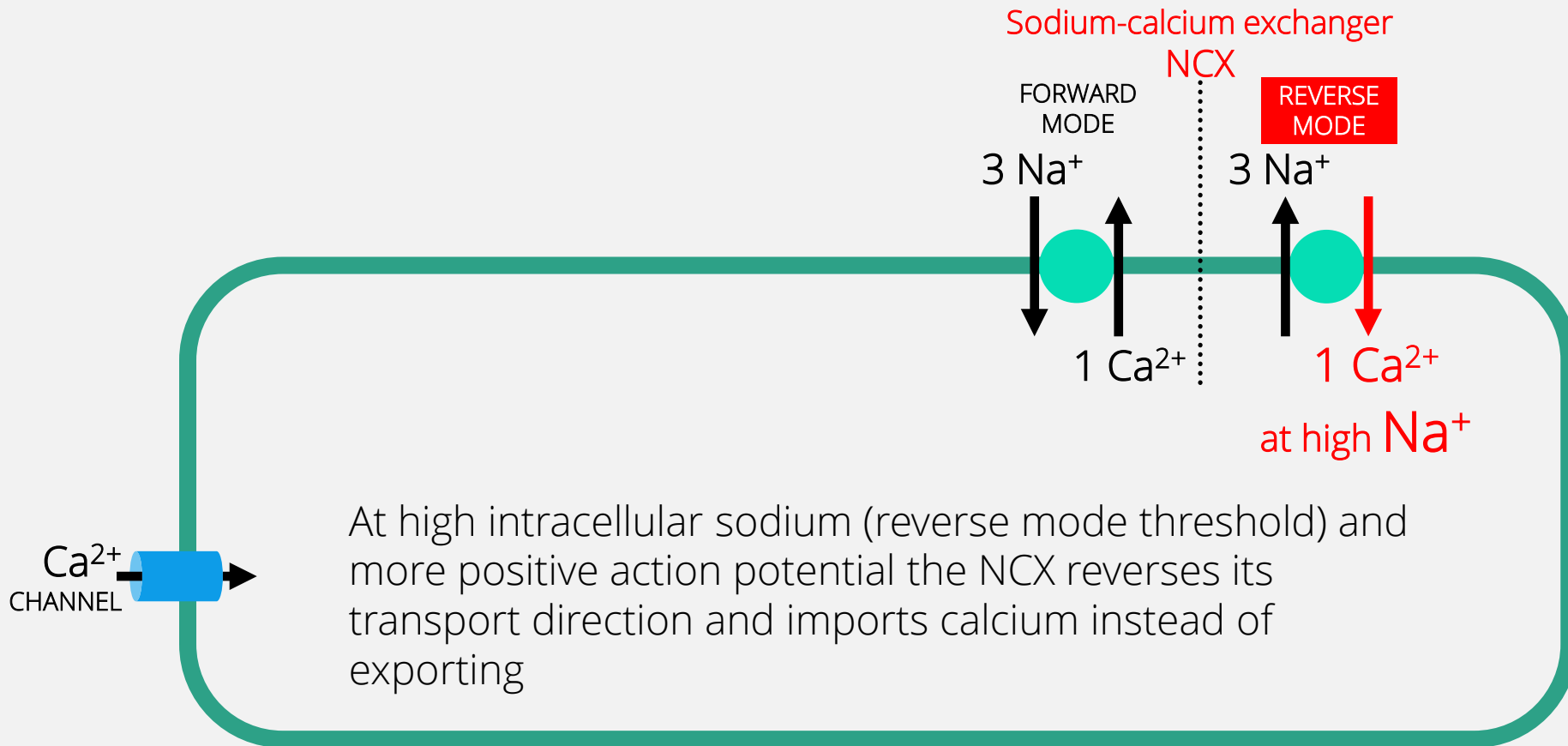
<sup>1</sup>Petter et al., 2022, J Transl Med. <sup>2</sup>Paffrath et al. 2024, J.Clin. Med.  
Triceps surae muscle: Gastrocnemius muscles (lateral and medial heads) and soleus muscle.

# INTRACELLULAR HIGH SODIUM CAUSES CALCIUM OVERLOAD



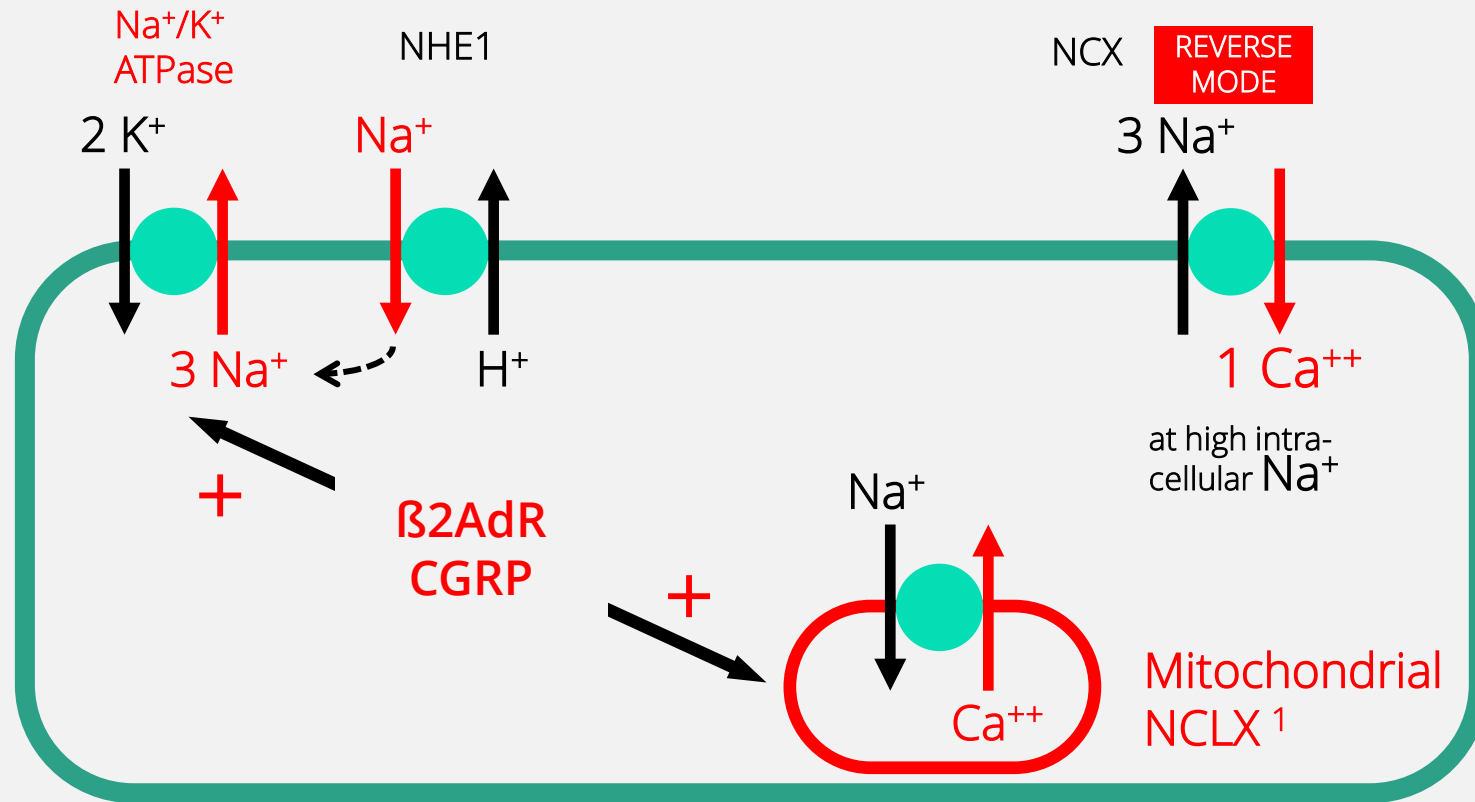
Ischemia-reperfusion-injury is the paradigm of sodium-overload induced calcium-overload and damage

# INTRACELLULAR SODIUM OVERLOAD CAUSES CALCIUM OVERLOAD BY REVERSING THE TRANSPORT DIRECTION OF THE SODIUM-CALCIUM EXCHANGER NCX



- Na<sup>+</sup> loading**
- Na<sup>+</sup> influx ↑
  - Na<sup>+</sup> efflux ↓

# MITOCHONDRIAL CALCIUM EXCHANGER (NCLX) IS NOT SUFFICIENTLY ACTIVATED TO PREVENT MITOCHONDRIAL CALCIUM OVERLOAD



- NCLX as the last protection against mitochondrial calcium overload fails due to dysfunctional β2-adrenergic receptors and low CGRP
- Mitochondria become the most sensitive cellular structures for calcium overload

Mitochondrial calcium overload can even occur at moderately elevated cytosolic calcium levels

<sup>1</sup>Kostic et al., 2018, Cell Reports

# THE THREE CONCENTRATION-DEPENDENT EFFECTS OF MITOCHONDRIAL CALCIUM

## STAGE 1: CALCIUM STIMULATES MITOCHONDRIAL ATP PRODUCTION

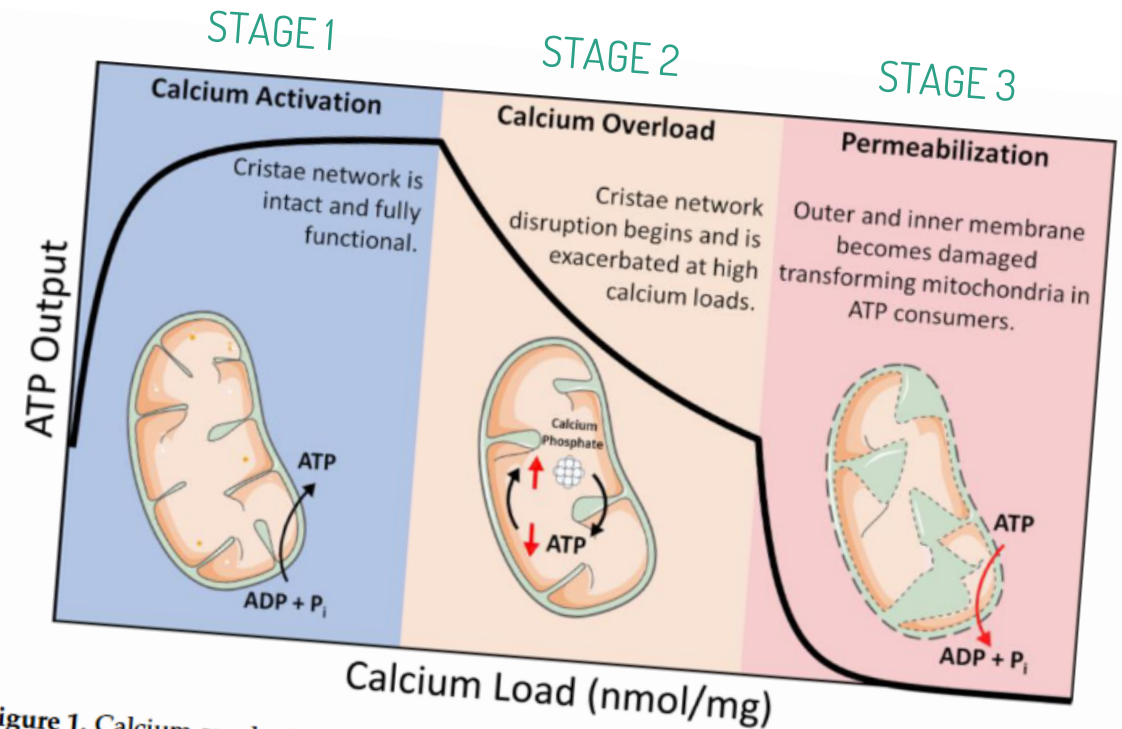
Calcium is essential for the stimulation of mitochondrial OXPHOS stimulating enzymes of the TCA cycle.

## STAGE 2: CALCIUM OVERLOAD DECREASES OXIDATIVE ATP PRODUCTION

Anaerobic glycolysis due to mitochondrial dysfunction causes sodium loading via NHE1 and to a further calcium load and mitochondrial fission.

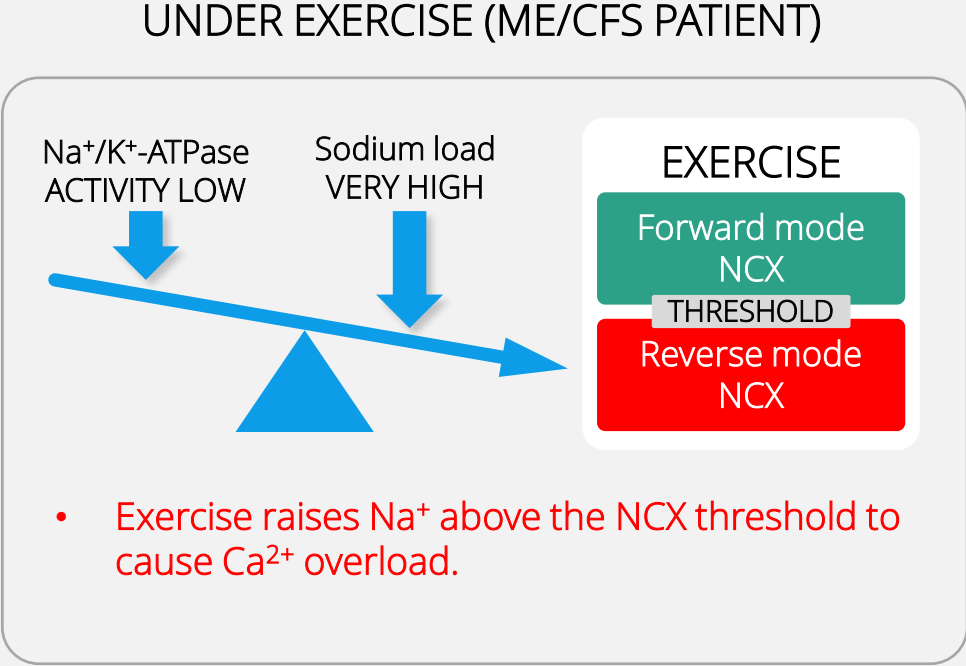
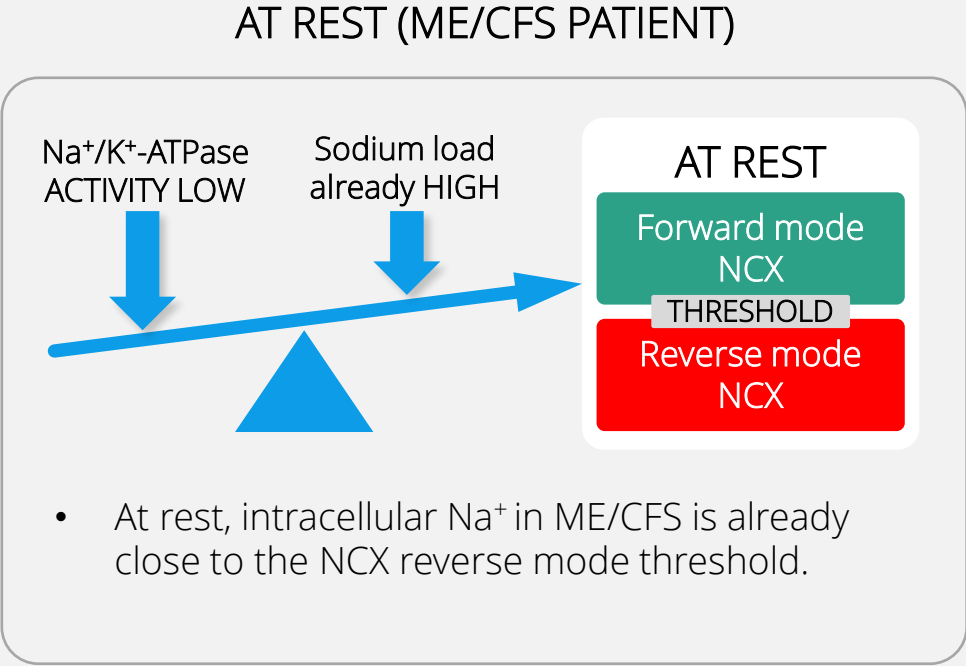
## STAGE 3: CALCIUM OVERLOAD TURNS MITOCHONDRIA INTO ATP CONSUMERS

- In the case of severe calcium overload, mitochondria can change from ATP producers to ATP consumers to maintain mitochondrial homeostasis (futile cycle).
- Severe exercise intolerance?



**Figure 1.** Calcium overload. In low amounts, calcium enhances mitochondrial function by activating several  $\text{Ca}^{2+}$ -sensitive catabolic enzymes. In moderate amounts, depressed rates of oxidative phosphorylation become observable. **In extreme amounts, mitochondria become structurally compromised and consume ATP in a futile attempt to restore homeostasis.**

# IS THE SODIUM THRESHOLD OF THE REVERSE MODE NCX THE BASE FOR THE CLINICAL PEM THRESHOLD? PATIENT IS ALWAYS CLOSE TO IT

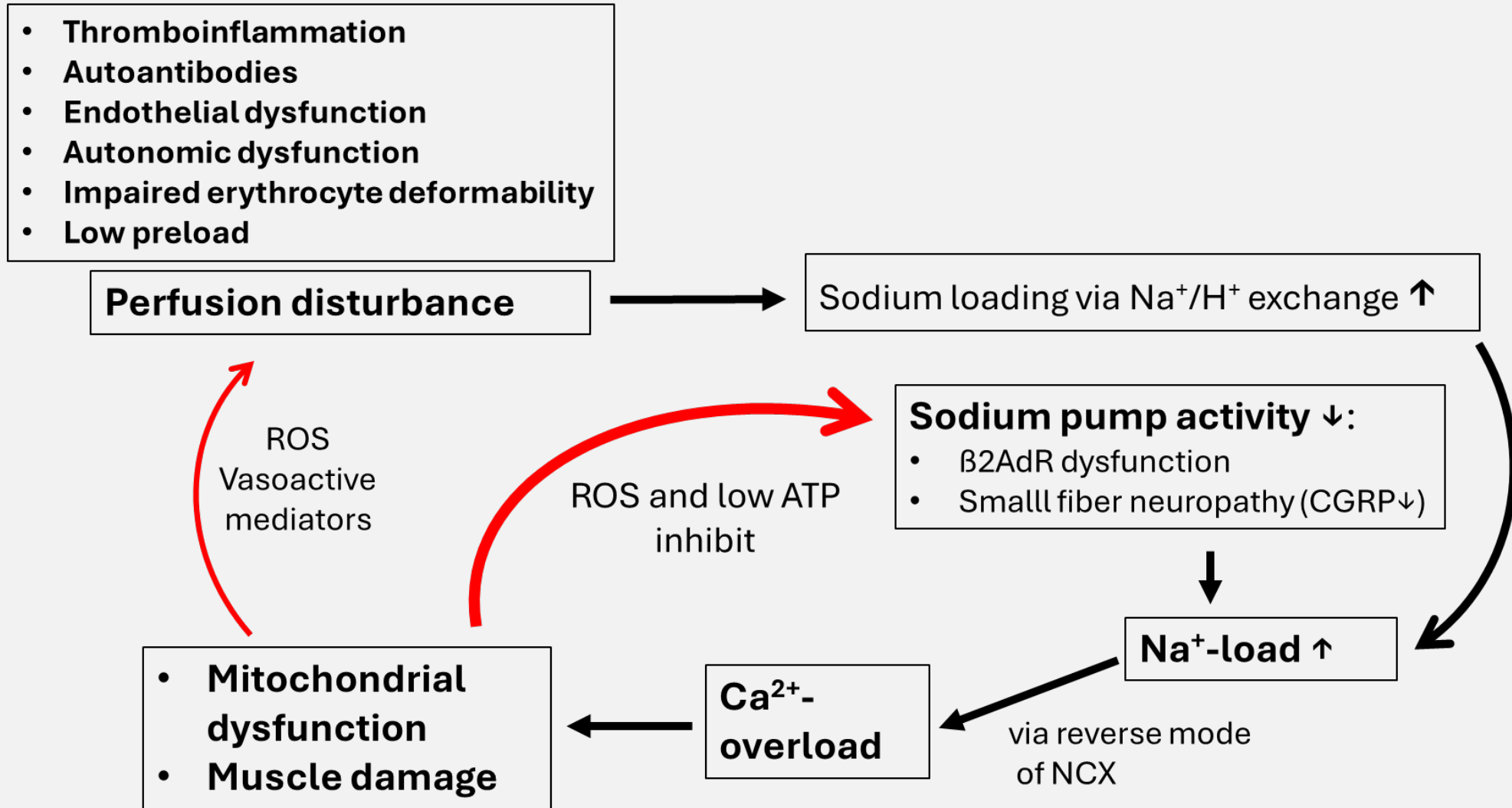


➡ Strict pacing keeps intracellular Na<sup>+</sup> below the reverse mode threshold to prevent calcium overload

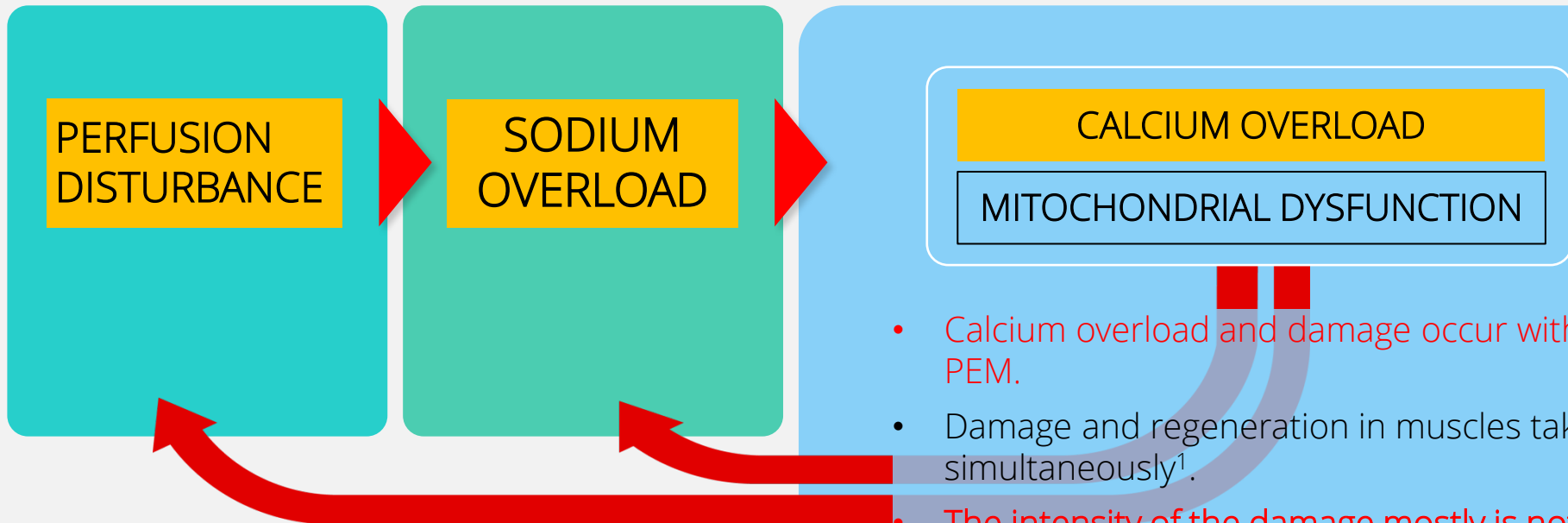
➡ Drugs that keep intracellular Na<sup>+</sup> below the reverse mode threshold could prevent calcium overload

PEM: Post-exertional malaise.

# MITOCHONDRIAL DYSFUNCTION LOWERS ATP AND CAUSES EXCESSIVE PRODUCTION OF REACTIVE OXYGEN SPECIES: BOTH INHIBIT $\text{Na}^+/\text{K}^+$ -ATPASE



**CHRONICALLY THE POOL OF INTACT MITOCHONDRIA SHRINKS DUE TO REPEATED AND CUMULATIVE DAMAGE: A VICIOUS CIRCLE THAT STABILIZES ME/CFS**



- Calcium overload and damage occur with every PEM.
- Damage and regeneration in muscles take place simultaneously<sup>1</sup>.
- The intensity of the damage mostly is not very high, but it is repetitive and hence cumulative.
- Therefore, preventable by an appropriate drug

**THE POOL OF INTACT MITOCHONDRIA SHRINKS WHICH AUGMENTS THE VICIOUS CIRCLE**  
 Anaerobic metabolism<sup>1</sup> ↑, protons ↑, sodium ↑, calcium ↑ (until overload), **damage ↑**, pool of intact mitochondria ↓, **regenerative capacity of mitochondria ↓**

**THERAPEUTIC STRATEGY:** Inhibit damage mechanisms to enable undisturbed regeneration.

<sup>1</sup>Appleman et al., 2024; Nature Communications

# SKELETAL MUSCLE PATHOLOGICAL FINDINGS IN PATIENTS WITH POST COVID SYNDROME WITH PEM OR ME/CFS

Arranged according to the investigational method; Scheibenbogen and Wirth, 2025, J Cachexia Sarcopenia Muscle.

CLINICAL SIGNS	SKELETAL MUSCLE FORCE TEST	EXERCISE (ENDURANCE) TEST	BIOPSIES FROM SKELETAL MUSCLE	IMAGING (MRI)
<ul style="list-style-type: none"> <li>Fatigue, early exhaustion, muscle weakness, muscle pain, fasciculations and cramps. [6-8]</li> </ul>	<ul style="list-style-type: none"> <li>Muscular force impaired assessed via hand grip strength (HGS) and leg strength. [7]                             <ul style="list-style-type: none"> <li>HGS correlates with symptom severity and prognosis.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Metabolic changes during exercise: Early appearance of anaerobic metabolism. [9]</li> <li>Diminished oxygen uptake and extraction. [10]</li> </ul>	<ul style="list-style-type: none"> <li>Skeletal muscle biopsies show signs of muscular damage and regeneration. More damage one day after exercise. [9]                             <ul style="list-style-type: none"> <li>Biopsies exclude obstructed capillaries, viral presence and autoimmune myositis.</li> </ul> </li> <li>Evidence for muscle mitochondrial dysfunction. [9, 13, 22, 24, 26]</li> <li>Electron microscopy from skeletal muscle biopsies show changes in mitochondrial morphology and mitochondrial damage. [13, 22]                             <ul style="list-style-type: none"> <li>Mitochondrial damage shows a particular localization pattern. Subsarcolemmal mitochondria are affected. in contrast to interfibrillary mitochondria.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Intracellular sodium in skeletal muscle is elevated and negatively correlated with hand grip strength in a <sup>23</sup>Na MRI study in resting or exercising muscle depending on muscle type. [12]                             <ul style="list-style-type: none"> <li>Rise in intracellular sodium is a precondition for the damage by calcium.</li> <li>pH changes.</li> </ul> </li> </ul>

Clear evidence of an acquired mitochondrial myopathy

# Decrease in Cardiac Output and Strongly Reduced Oxygen Consumption Become Apparent Only with Exercise Testing

TABLE 2 Peak exercise parameters by group.

Characteristic	Control	PASC	CFS	p Value
<b>Peak hemodynamics</b>				
Heart rate, bpm	127 [100, 171]	133 [125, 152]	123 [111, 137]	0.432
RAP, mmHg	4 [2.5, 7.5]	3 [1, 6]	3 [1, 6]	0.739
mPAP, mmHg	23 [21, 24]	19 [16.5, 28]	19 [18, 27]	0.367
PCWP, mmHg	13 [7.5, 13.5]	8 [6, 11]	9 [6, 15]	0.192
CO, L/min	19.2 [10.8, 22]	14.2 [12, 16.6]	12.07 [10.7, 15.2]	0.101
CI, L/min/m <sup>2</sup>	9.7 [7.5, 11]	7.6 [6.2, 9.5]	6.9 [5.6, 9]	0.011 <sup>a</sup>
<b>Blood gas analysis</b>				
PaO <sub>2</sub> , mmHg	100 [86.5, 103.5]	98 [95, 107]	105 [97, 111]	0.262
PaCO <sub>2</sub> , mmHg	46 [37.5, 47.5]	45 [37, 57]	38 [35, 44]	0.095
PvO <sub>2</sub> , mmHg	26 [22, 37]	26 [24, 32]	29 [27, 31]	0.026 <sup>a</sup>
SaO <sub>2</sub> %	97 [95.5, 98.5]	97 [92, 100]	99 [97, 100]	0.231
SvO <sub>2</sub> %	37 [32, 43]	40 [34, 49]	53 [46, 58]	0.004 <sup>a,c</sup>
HCO <sub>3</sub> <sup>-</sup> , mEq	23 [22, 25]	24 [23, 25]	24 [22, 26]	0.719
Lactate, mmol/L	5.3 [4.7, 9.3]	5.2 [4.7, 6.9]	2.6 [1.8, 3.2]	0.004 <sup>a,c</sup>
<b>Cardiopulmonary exercise parameters</b>				
VO <sub>2</sub> peak, mL/min	2048 [1608, 2376]	1361 [1015, 1677]	1115 [932, 1201]	0.003 <sup>a,c</sup>
VO <sub>2</sub> peak, % predicted	116.8 [106, 196]	68.8 [56.9, 87.7]	51.1 [48.8, 61.2]	<0.001 <sup>a-c</sup>
VCO <sub>2</sub> peak, mL/min	2132 [1774, 2929]	1279 [921, 1695]	1170 [1064, 1227]	<0.001 <sup>a,b</sup>
SER	0.6 [0.45, 0.76]	0.59 [0.5, 0.6]	0.47 [0.32, 0.54]	0.034

“The functional limitations of PASC and CFS/ME are not evident at rest and therefore require exercise testing to disclose. “

In line with exercise intolerance....

“PASC and CFS/ME share multicomponent, multi-organ pathophysiology with the predominant component being the contracting neuromuscular system.”

## Severe ME/CFS and Possible Causes of Bedriddenness

1. Skeletal muscle weakness and symptoms (myasthenia, fasciculations, cramps)
2. Severe orthostatic intolerance:  
OI is a risk factor for ME/CFS and further aggravated by ME/CFS; cerebral blood flow decreased already at 20 degrees of head-up tilt testing <sup>1</sup>
3. Hypersensitivities to light, noise and odors
4. Severe symptoms and PEM

<sup>1</sup> van Campen et al.; Healthcare 2020

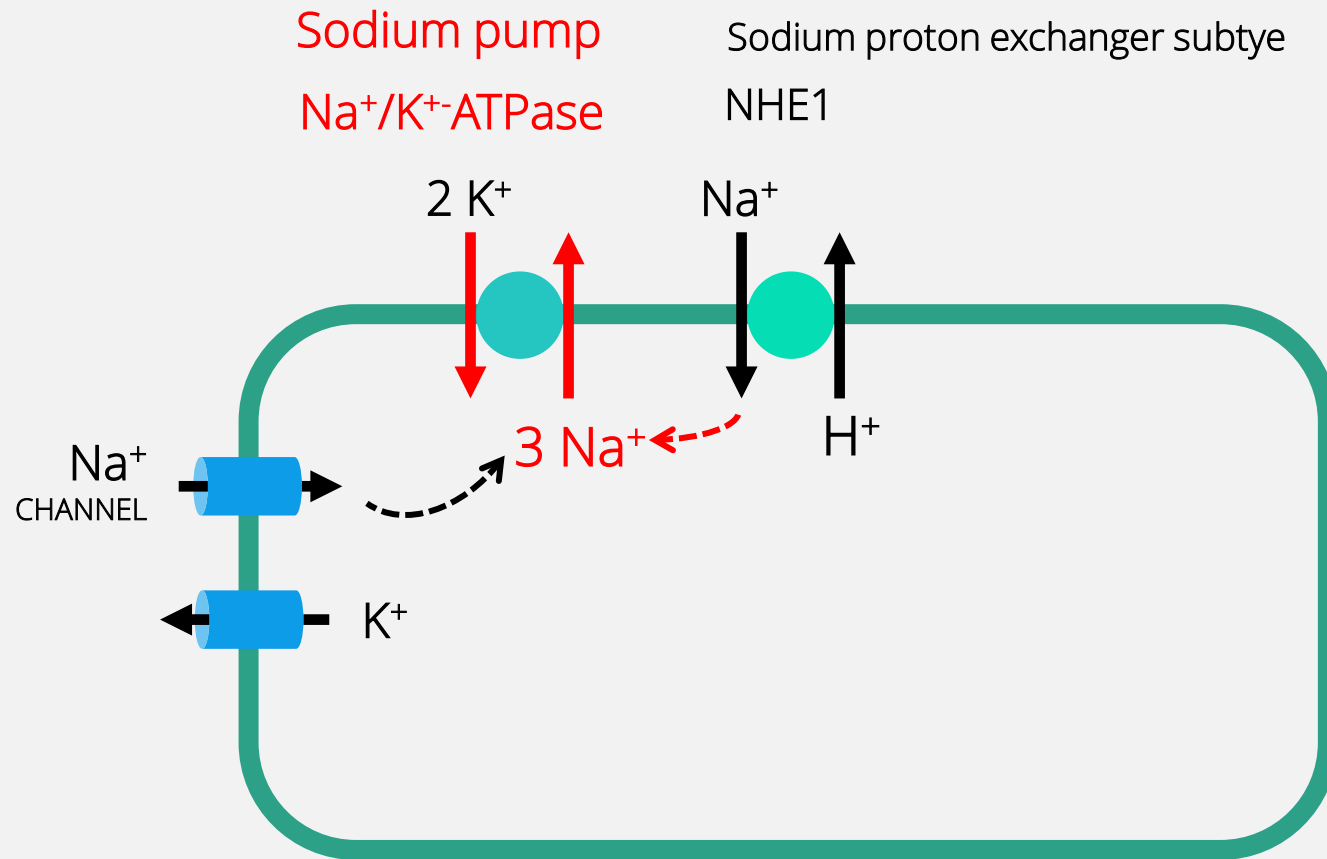
# Possible Causes of Skeletal Muscle Weakness

Neurological investigations exclude motor nerve damage pointing to an intrinsic (single) muscular cause for severe loss of force and fasciculations (hyperexcitability)

- 1. Atrophy due to inactivity in the intention to avoid PEM and due to immobilization (deconditioning)**  
No atrophy of skeletal muscle found in ME/CFS in contrast to 6 weeks bedrest<sup>1</sup>. Skeletal muscle adaptations in long COVID are distinct from those occurring after deconditioning.  
Calcium signaling involved in muscle hypertrophy<sup>2</sup> might prevent atrophy<sup>2</sup>
- 2. Central fatigue:** would spare muscle, not cause damage or PEM, cannot explain strong loss of force
- 3. Skeletal muscle damage ✓** Skeletal muscle damage has been shown<sup>3</sup> and may contribute but may not be big enough to cause a severe loss of force. Biopsies needed for clarification
- 4. Lack of energy due to mitochondrial dysfunction and hypoperfusion ✓✓** can explain severe fatigue and loss of endurance and force endurance, but does not explain neither strong loss of force (after a rest) nor fasciculations
- 5. Electrophysiological causes: ✓✓✓** leading to insufficient excitation and recruitment of muscle fibers upon neuromuscular activation can explain strong loss of force and fasciculations

<sup>1</sup>Charlton et al. 2025, MedRxiv preprint <sup>2</sup>Semsarian et al., 1999, Nature <sup>3</sup>Appleman et al., 2024; Nature Communications

# PHYSIOLOGICAL ROLE OF THE $\text{Na}^+/\text{K}^+$ -ATPASE FOR FORCE DEVELOPMENT



$\text{Na}^+/\text{K}^+$ -ATPase generates the physiological action potential and excitability <sup>1</sup>

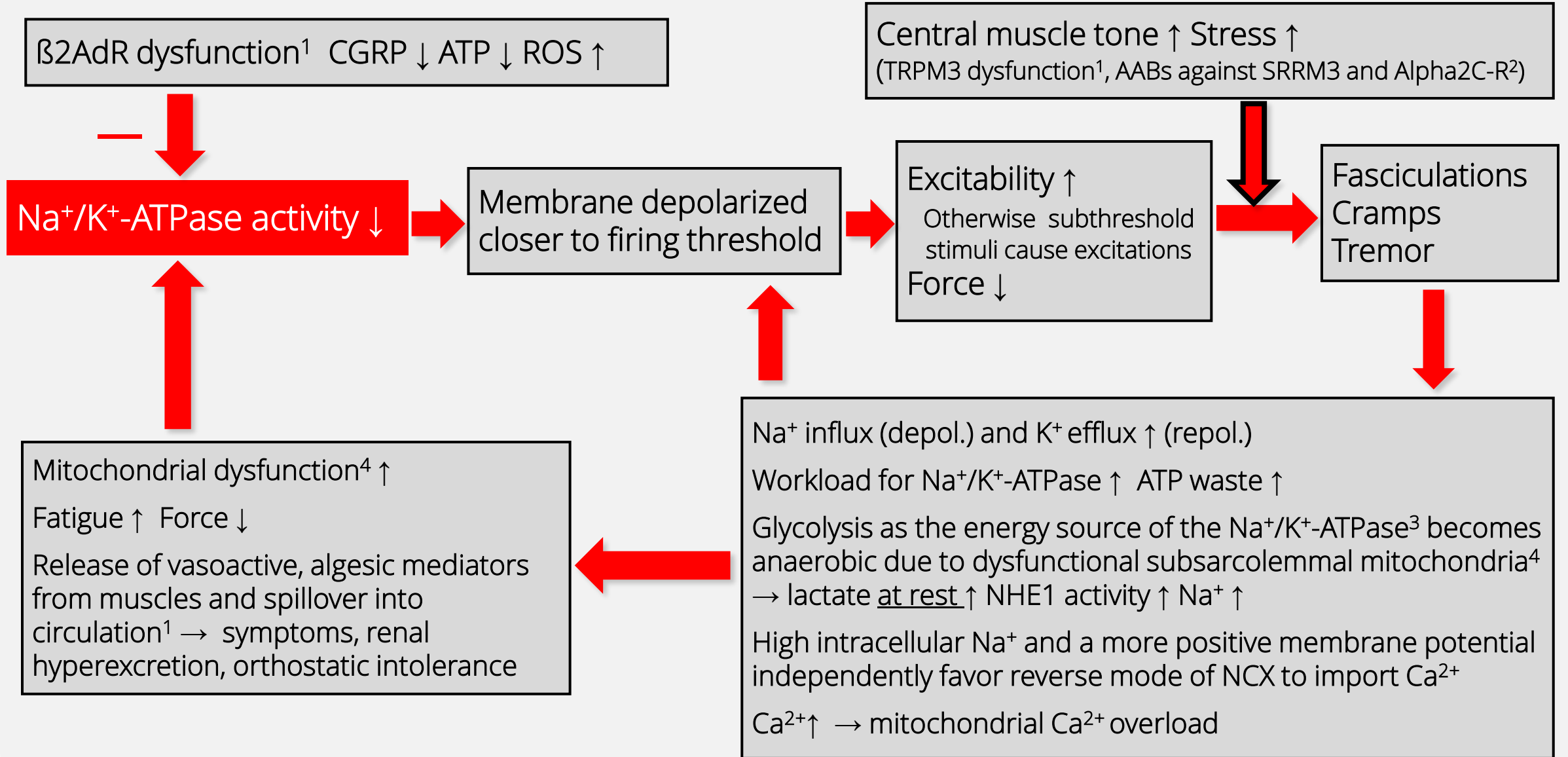
Even during strong exercise in healthy subjects  $\text{Na}^+/\text{K}^+$ -ATPase can become insufficient raising intracellular sodium, lowering cellular potassium and raising interstitial potassium.

The ensuing depolarization causes inactivation of part of the sodium channels impairing action potential propagation, fiber recruitment **and loss of force:**  
**Electrophysiological fatigue**

Pharmacological inhibition by ouabain leads to a total loss of force in vitro

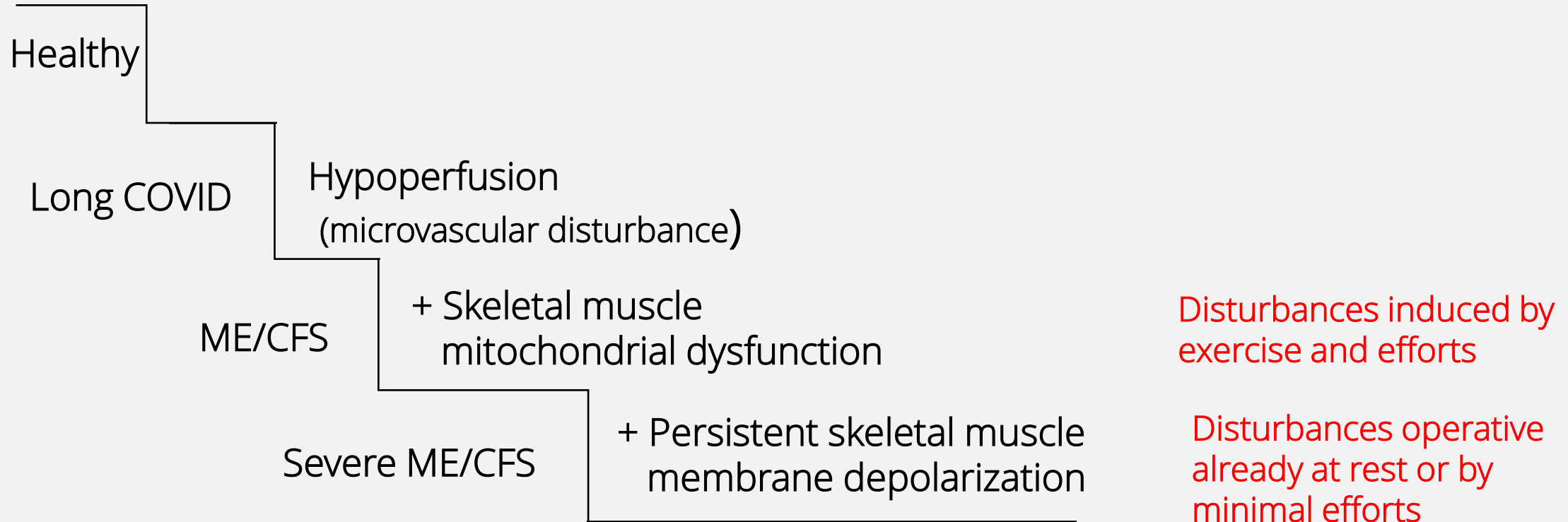
<sup>1</sup>Pirkmajer and Chibalin, 2016 Clausen, 2003, Physiological Reviews

# IS SKELETAL MUSCLE OF THE SEVERELY ILL IN A STATE OF DEPOLARIZATION?



<sup>1</sup>Wirth and Löhn, 2024 <sup>2</sup> Hoheisel et al., 2025 <sup>3</sup>Pirkmajer and Chibalin, 2016 <sup>4</sup>Bizjak et al., 2024

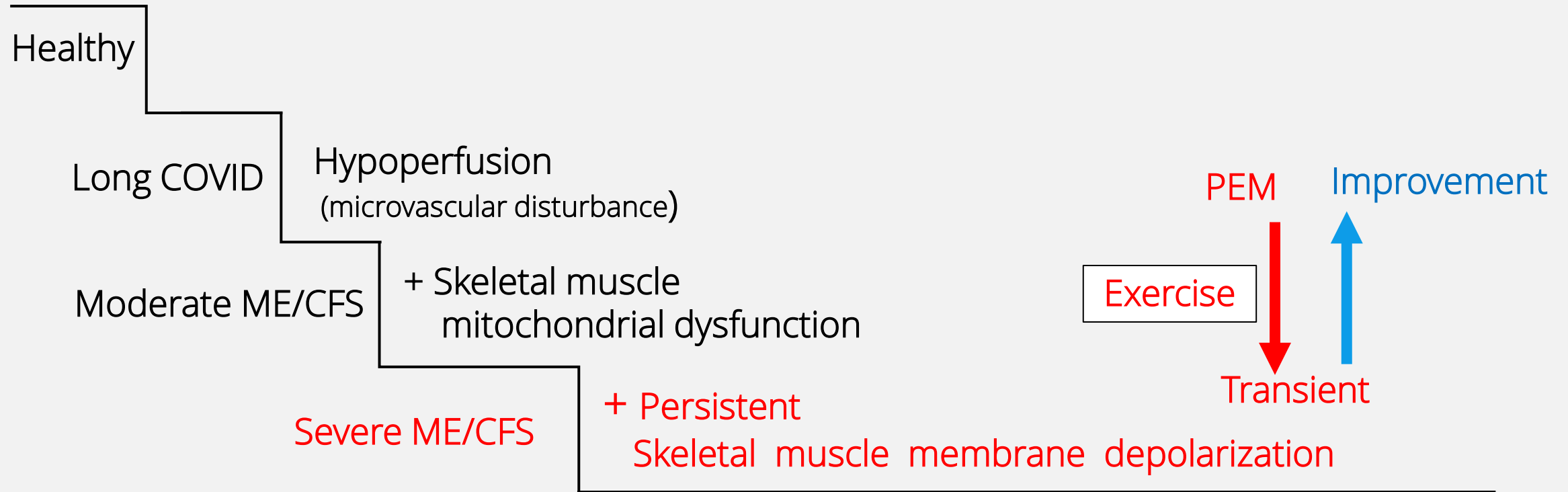
# A STEP MODEL TO EXPLAIN THE SITUATION OF THE SEVERELY ILL ME/CFS PATIENT



Insufficient  $\text{Na}^+/\text{K}^+\text{ATPase}$  activity keeps the sarcolemma in a state of depolarization, even at rest

Depolarization sensitizes to central rises in muscle tone to explain why mental stress can cause muscle symptoms

# DURING PEM OF LONGER DURATION IN PATIENTS WITH MODERATE ME/CFS SKELETAL MUSCLE DEPolarIZATION COULD ALSO BE PRESENT BUT BE TRANSIENT



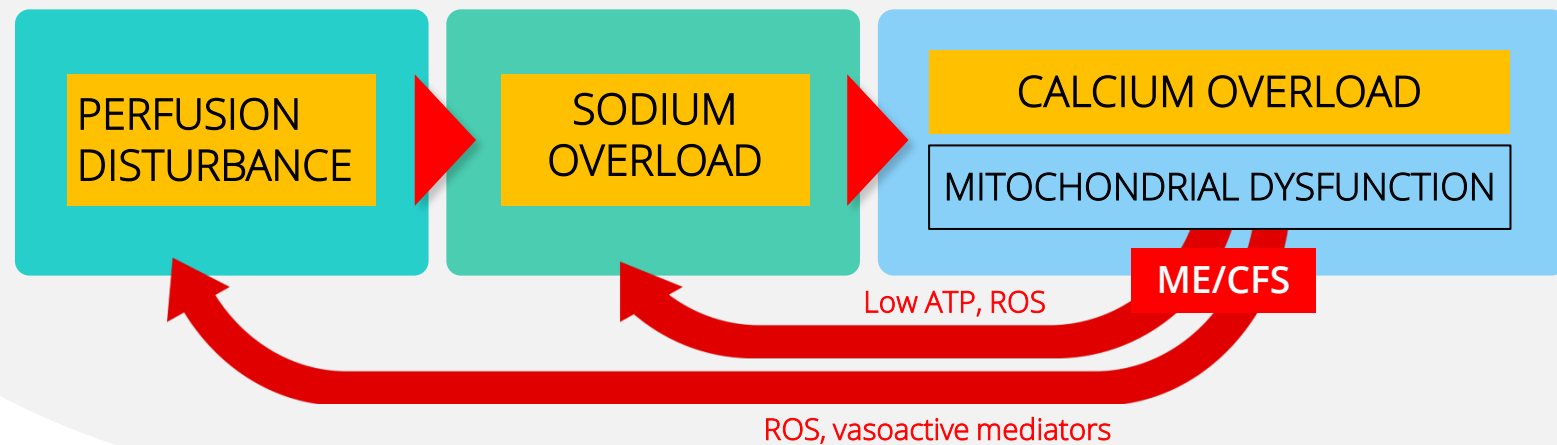
M-wave alterations (EMG) were found after exercise test in a patient group with lower grip strength and more symptoms: the decreased amplitude and prolonged duration can be explained by depolarization

<sup>1</sup>Retornanz et al.; 2023, Clinical Biochemanics

# DIFFERENT TRIGGERS IN THE PRESENCE OF VARIOUS RISK FACTORS CAN CAUSE SODIUM-INDUCED CALCIUM OVERLOAD AS THE FINAL COMMON PATHWAY

Infection ⚡ Trauma ⚡ Stress

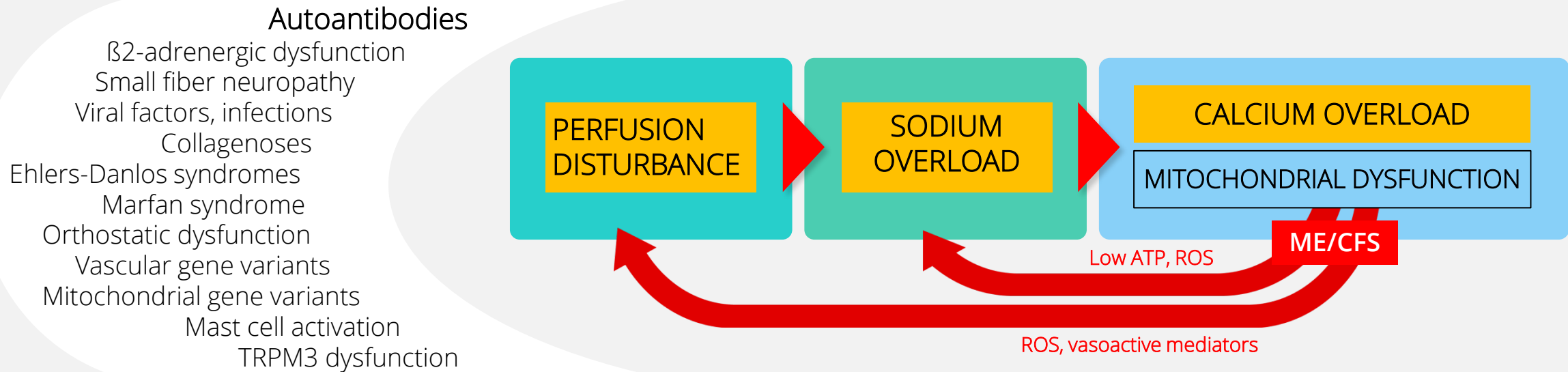
- Autoantibodies**
- β2-adrenergic dysfunction
  - Small fiber neuropathy
  - Viral factors, infections
  - Collagenoses
  - Ehlers-Danlos syndromes
  - Marfan syndrome
  - Orthostatic dysfunction
  - Vascular gene variants
  - Mitochondrial gene variants
  - Mast cell activation
  - TRPM3 dysfunction



- Regardless of the triggering mechanism the same vicious circle is operative as the final pathway
- Main disturbance causing the cardinal symptoms: exercise intolerance with PEM

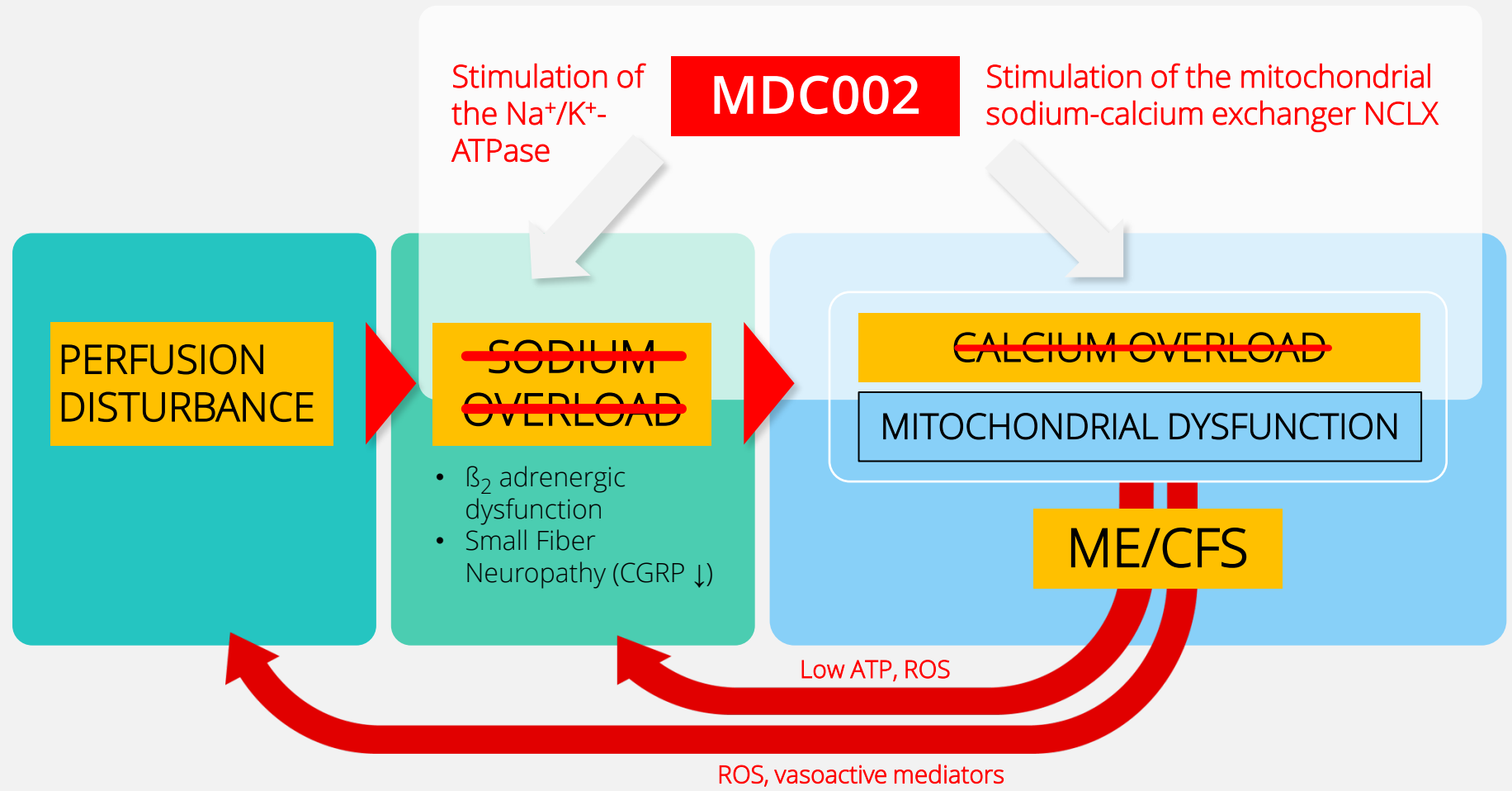
# TRIGGERS DISEAPPEAR BUT THE VICIOUS CIRCLE PERSISTS DUE TO RISK FACTORS

## Particular role of autoimmunity



Disease concept seems sufficiently validated to derive a therapeutic strategy

# THERAPEUTIC CONCEPT: BREAKING THE VICIOUS CIRCLE THAT MAINTAINS ME/CFS AND RESTORING RESTING MEMBRANE POTENTIAL



Additional effects: MDC002 raises skeletal muscle and cerebral blood flow

CGRP: Calcitonin gene-related peptide; ROS: Reactive oxygen species