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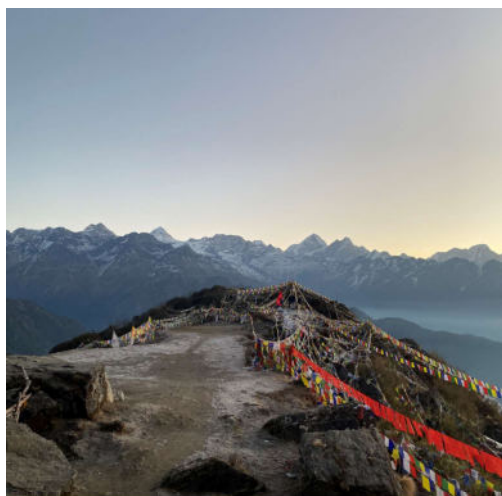
Cardiopulmonary Effects of Normobaric Hypoxia and Sympathetic Activation, and Subsequent Normoxic Recovery in Rats

Hypoxia Symposium, 26th September 2025

Charly Bambar

Introduction

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- hypoxia = reduced supply of oxygen
- possible reasons: ventilation or diffusion disorders, stay at high altitude
- complication: HAPE = high altitude pulmonary edema

Ama Yangri (Nepal): 3770m ASL

Ambient pressure: 490mmHg (cf. 760 mmHg OSL)

Partial pressure of oxygen: 103mmHg (cf. 160 mmHg OSL)

Background and Basic Questions

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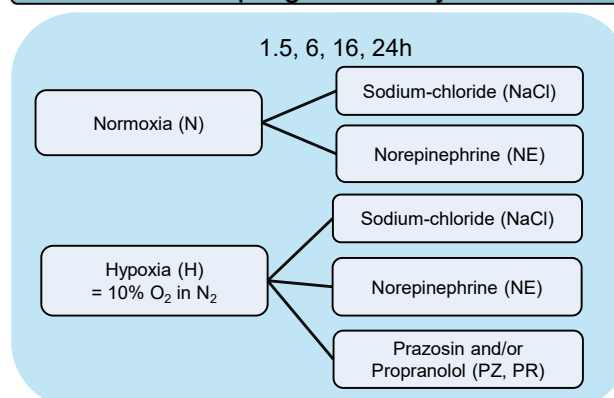
- Systemic hypoxia → sympathetic activity ↑
- excessive catecholamine release → pulmonary edema
- Our basic questions:
 - Effects of hypoxia on **pulmonary edema** and **cardiac function** at different intervals of hypoxia exposure
 - Influence of the **sympathetic system** (norepinephrine and sympathetic blockade)

Previous Experiments

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female Sprague Dawley Rats

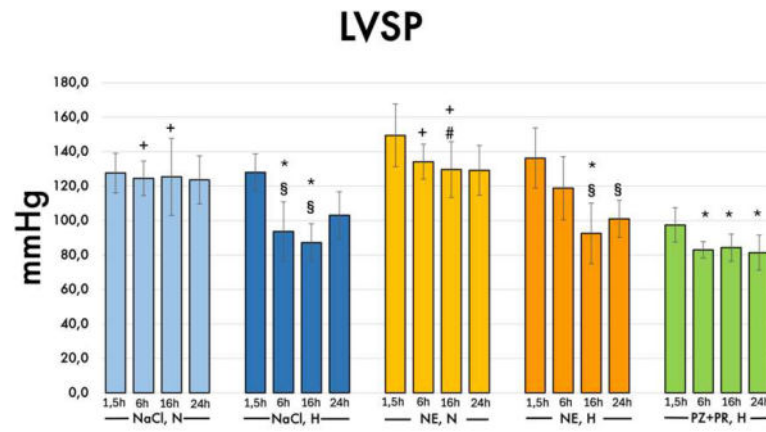
1.5, 6, 16, 24h



Infusion rate = 0.1 ml h⁻¹, NaCl = 0.9%, NE = 0.1 mg kg⁻¹h⁻¹, PZ = 0.1 mg kg⁻¹h⁻¹, PR = 0.16mg kg⁻¹h⁻¹

Previous Results

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Significance marks:

*significant vs. respective NaCl, N

+ significant vs. respective NaCl, H

#significant vs. respective NE, H

§ significant vs. 1.5 h of same treatment.

LVSP = Left Ventricular Systolic Pressure

NaCl = Sodium-Chloride

NE = Norepinephrine

PZ+PR = Prazosin+Propranolol

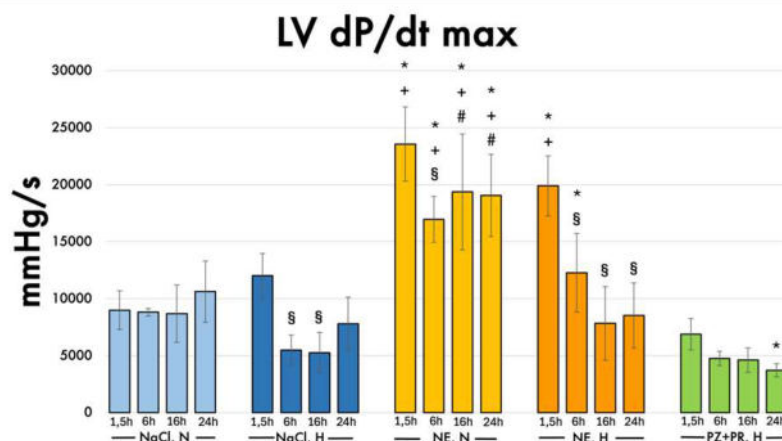
N = Normoxia

H = Hypoxia

from Bölter et al., 2019

Previous Results

6



Significance marks:

*significant vs. respective NaCl, N

+ significant vs. respective NaCl, H

#significant vs. respective NE, H

§ significant vs. 1.5 h of same treatment.

LV dP/dt max = Left Ventricular contractility

NaCl = Sodium-Chloride

NE = norepinephrine

PZ+PR = Prazosin+Propranolol

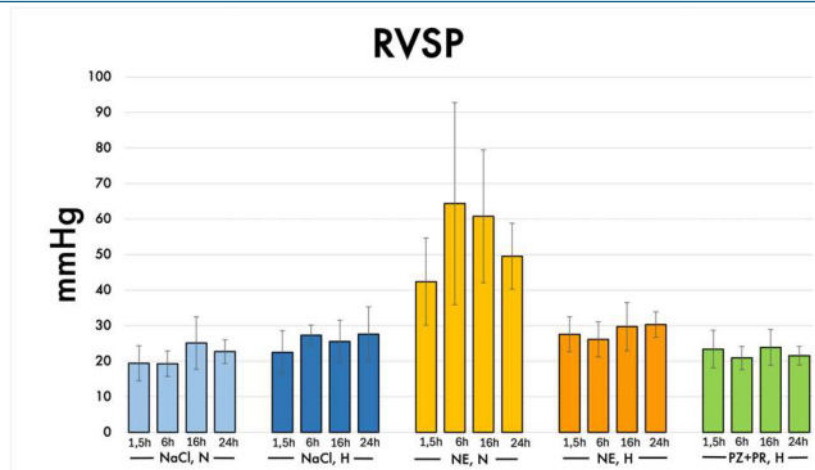
N = Normoxia

H = Hypoxia

from Bölter et al., 2019

Previous Results

7



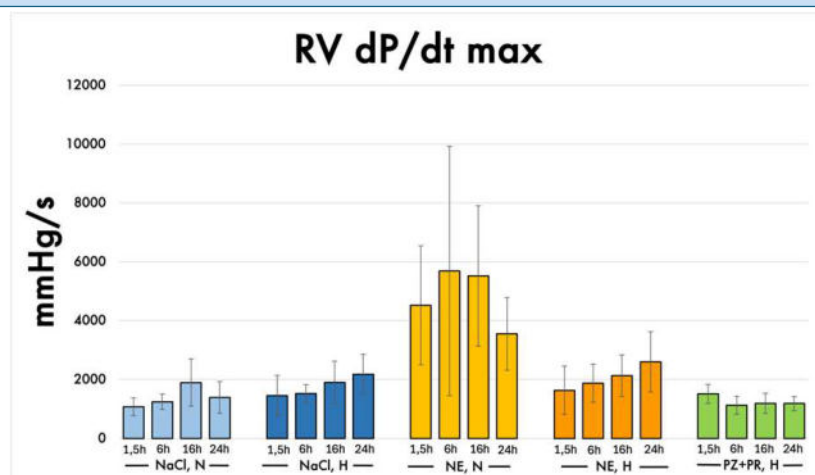
RVSP = Right Ventricular Systolic Pressure
NaCl = Sodium-Chloride
NE = norepinephrine

PZ+PR = Prazosin+Propranolol
N = Normoxia
H = Hypoxia

from Bölter et al., 2019

Previous Results

8



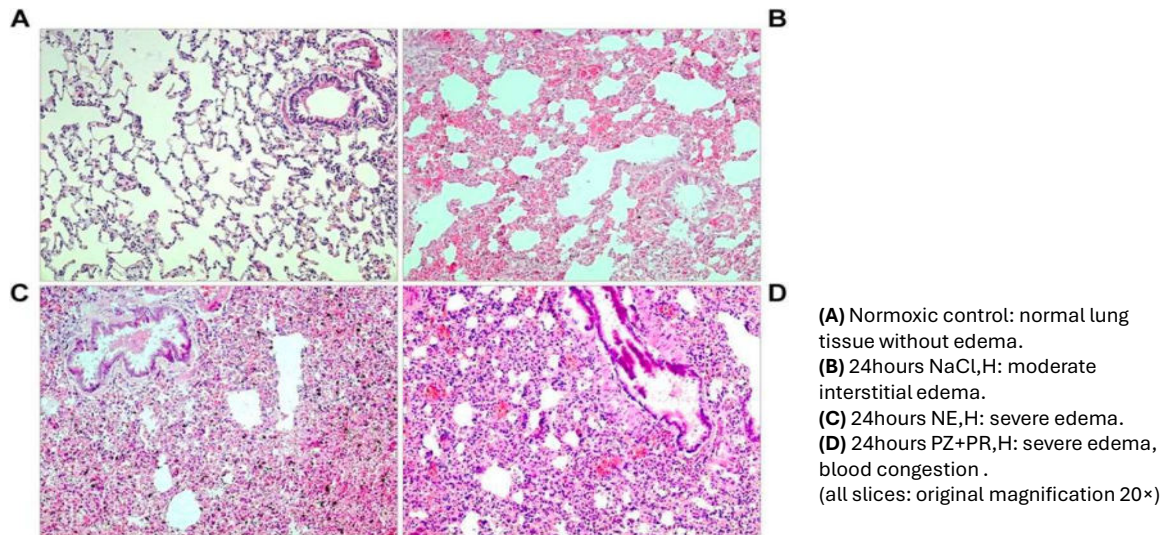
RV dP/dt max = Right Ventricular Contractility
NaCl = Sodium-Chloride
NE = norepinephrine

PZ+PR = Prazosin+Propranolol
N = Normoxia
H = Hypoxia

from Bölter et al., 2019

Previous Results

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from Bölter et al., 2019

Most Recent Investigation

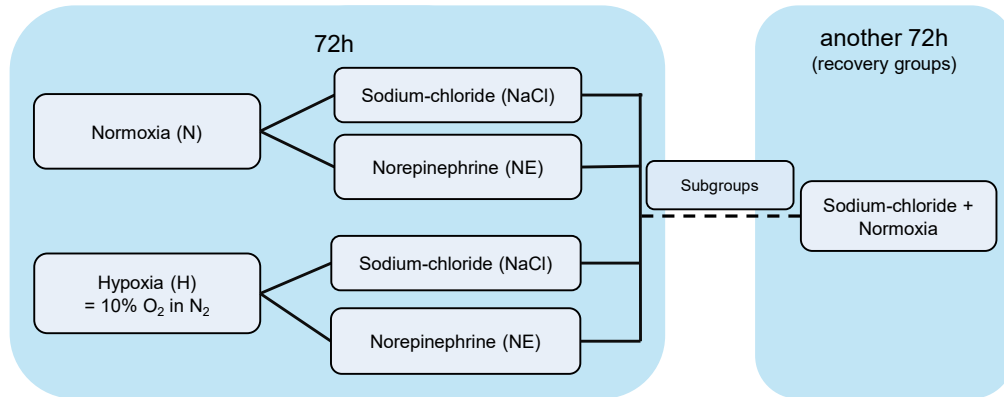
10

- (A) Does **prolonged hypoxia** (72h) lead to adaptation and therefore improvement of **cardiac function**? Can increased **sympathetic stimulation** mitigate the depression of left ventricular function?
 - (B) Is there an **acclimatization** detectable? Is there a change in the general state of the animals (e.g. body weight)?
 - (C) How does **pulmonary edema** develop under prolonged hypoxia?
- General: How do cardiovascular parameters and pulmonary edema develop **after 3 days of recovery**?

Methods

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female Sprague Dawley Rats (n = 98)



Infusion rate = 0.1 ml h⁻¹, NaCl = 0.9%, NE = 0.1 mg kg⁻¹h⁻¹

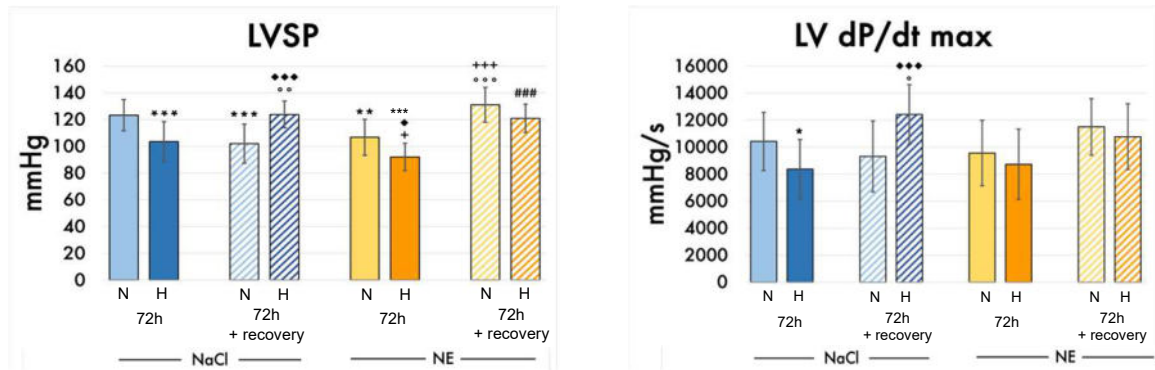
Methods

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- After the experiment:
 - Hemodynamic measurements
 - Blood Gas Analysis
 - Food and water intake, body weight
 - Removal of lung and heart for histological investigation

(A) Results

13



Significance marks:

sign. vs. 72h N, NaCl: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

sign. vs. 72h H, NaCl: ♦ $p < 0.05$; ♦♦♦ $p < 0.001$

sign. vs. 72h N, NE: + $p < 0.05$; +++ $p < 0.001$

sign. vs. 72h H, NE: ### $p < 0.001$

sign. vs. 144h N, NaCl: ° $p < 0.05$; °° $p < 0.01$; °°° $p < 0.001$

LVSP = Left Ventricular Systolic Pressure

LV dP/dt max = Left Ventricular Contractility

NaCl = Sodium-Chloride

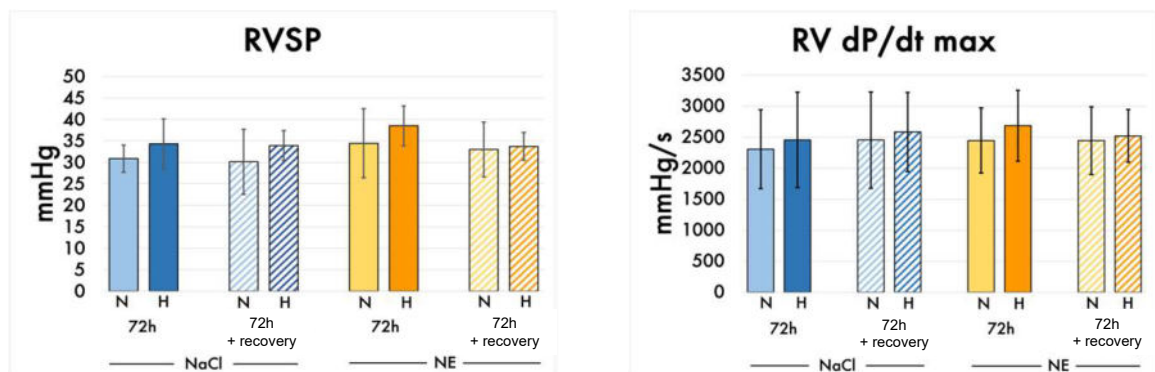
NE = Norepinephrine

N = Normoxia

H = Hypoxia

(A) Results

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RVSP = Right Ventricular Systolic Pressure

RV dP/dt max = Right Ventricular Contractility

NaCl = Sodium-Chloride

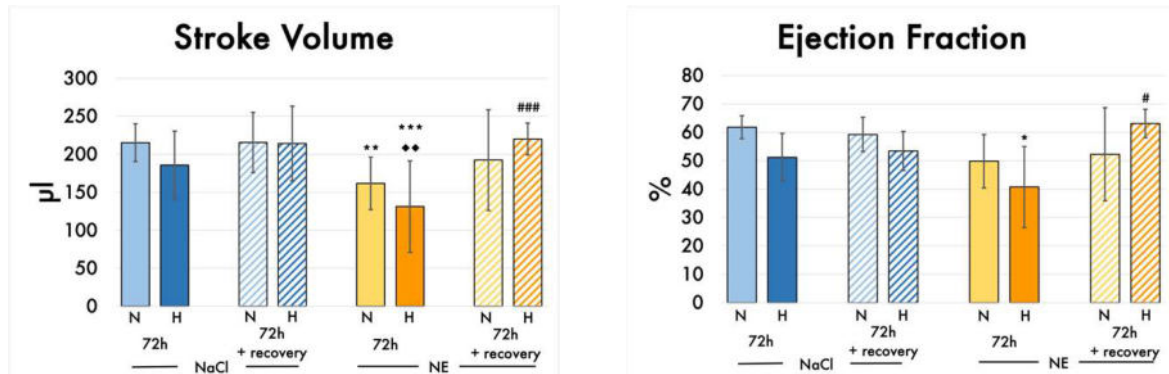
NE = Norepinephrine

N = Normoxia

H = Hypoxia

(A) Results

15



Significance marks:

sign. vs. 72h N, NaCl: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

sign. vs. 72h H, NaCl: ♦♦ $p < 0.01$

sign. vs. 72h H, NE: # $p < 0.05$; ### $p < 0.001$

NaCl = Sodium-Chloride

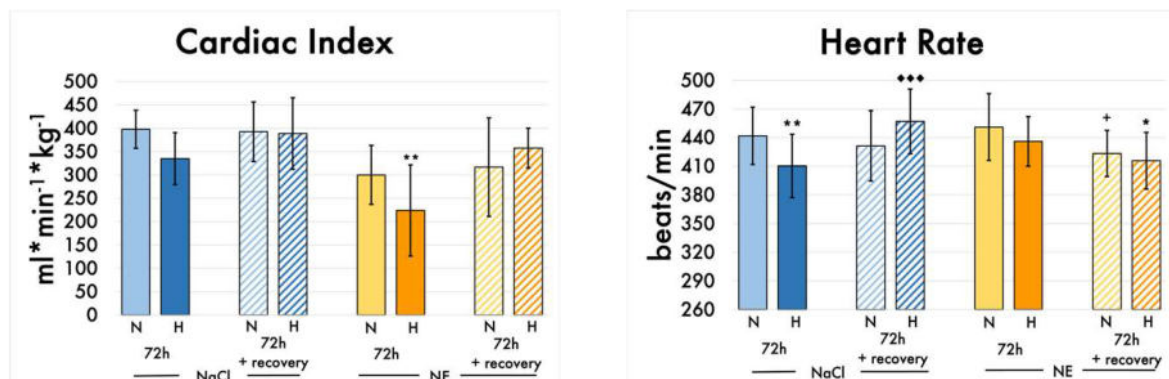
NE = Norepinephrine

N = Normoxia

H = Hypoxia

(A) Results

16



Significance marks:

sign. vs. 72h N, NaCl: * $p < 0.05$; ** $p < 0.01$

sign. vs. 72h H, NaCl: ♦♦♦ $p < 0.001$

sign. vs. 72h N, NE: + $p < 0.05$

NaCl = Sodium-Chloride

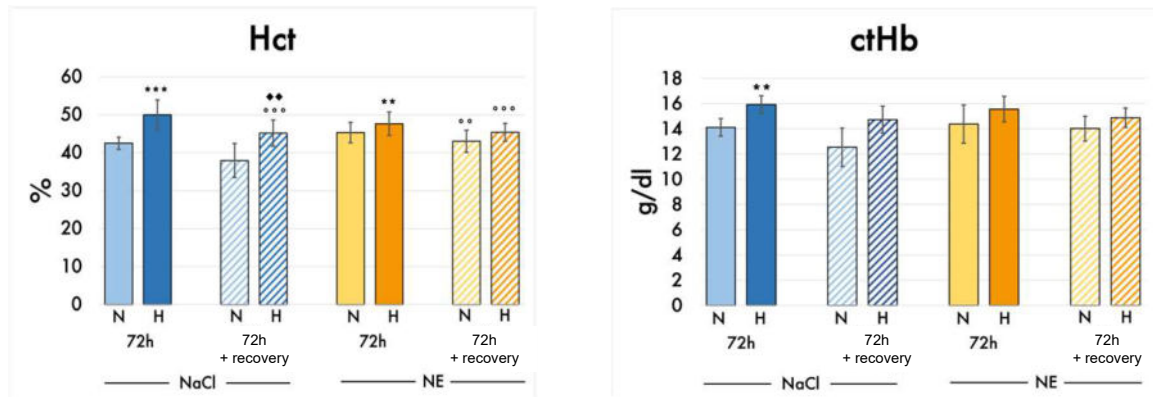
NE = Norepinephrine

N = Normoxia

H = Hypoxia

(B) Results

17



Significance marks:

sign. vs. 72h N, NaCl: ** $p < 0.01$; *** $p < 0.001$

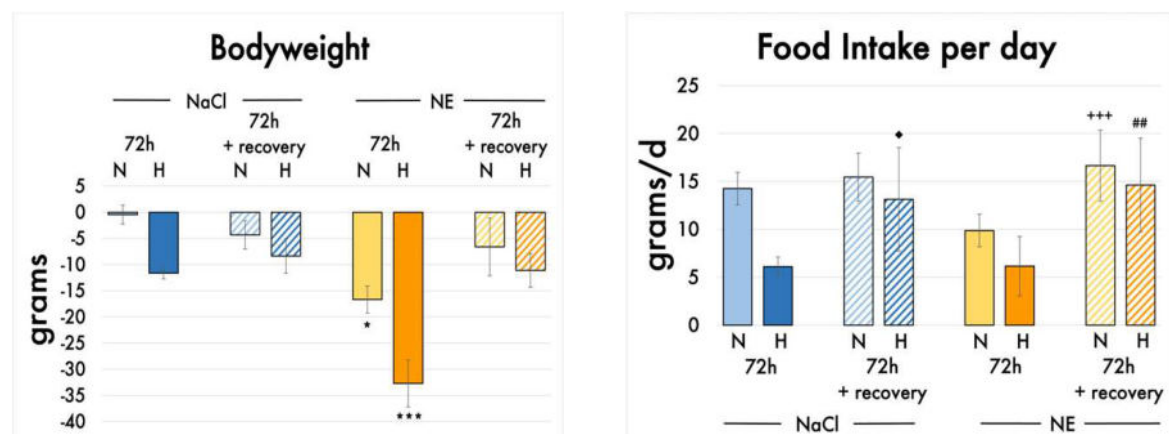
sign. vs. 72h H, NaCl: ♦♦ $p < 0.01$

sign. vs. 144h N, NaCl: °° $p < 0.01$; °°° $p < 0.001$

ctHb = Hemoglobin
Hct = Hematocrit
NaCl = Sodium-Chloride
NE = Norepinephrine
N = Normoxia
H = Hypoxia

(B) Results

18



Significance marks:

sign. vs. 72h N, NaCl: * $p < 0.05$; *** $p < 0.001$

sign. vs. 72h H, NaCl: ♦ $p < 0.05$

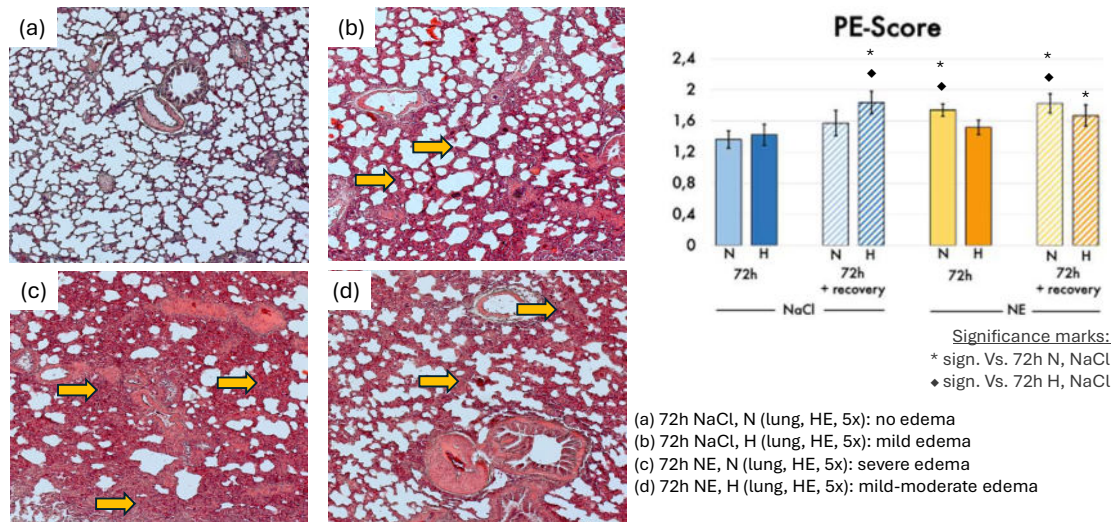
sign. vs. 72h N, NE: +++ $p < 0.001$

sign. vs. 72h H, NE: ## $p < 0.01$

NaCl = Sodium-Chloride
NE = Norepinephrine
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H = Hypoxia

(C) Results

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unpublished data from Sarah Daunheimer

(1) Summary and Outlook

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- Left ventricular function was still reduced after prolonged hypoxia
- Norepinephrine did not prevent hypoxic depression
 - further histological investigation of heart tissue
- 3d of normoxic control conditions restore left ventricular function
 - recovery group after 3d of sympathetic blockade
- Right ventricle was not affected

(2) Summary and Outlook

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- elevated hemoglobin/hematocrit indicate an acclimatization
- pulmonary edema shows no improvement with prolonged hypoxia or norepinephrine, even after the recovery phase
 - immunohistochemistry of the lungs

- Summary
- Outlook



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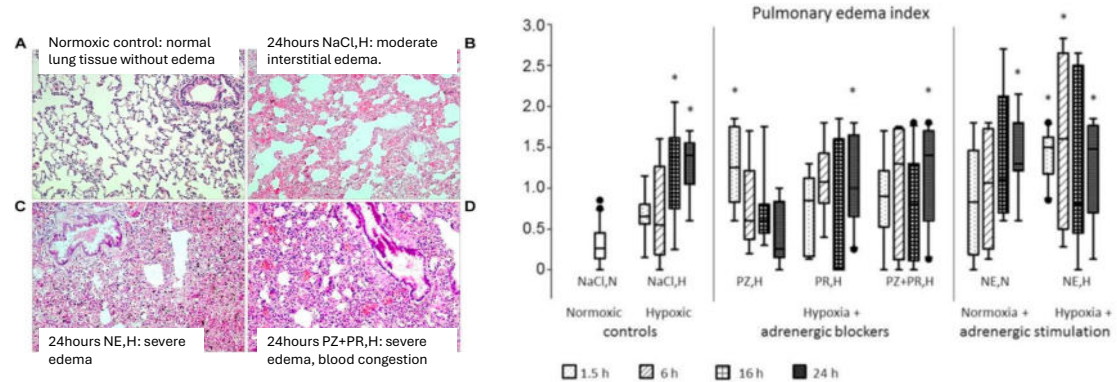
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Discussion - PEI

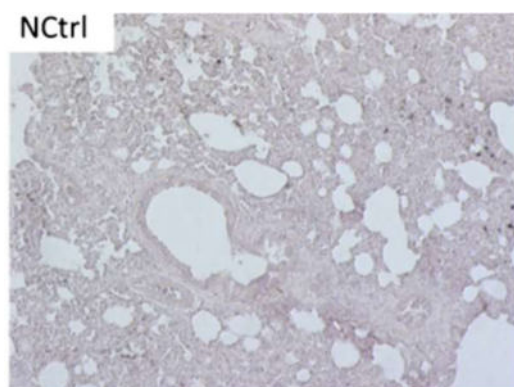
23



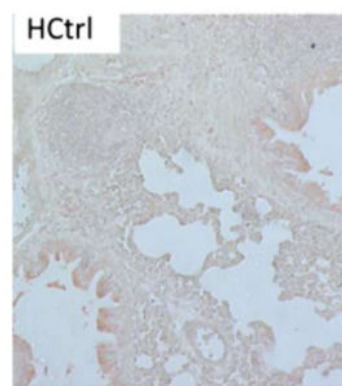
from Bölter, C. et al. (2019)

Discussion – TNF α

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24h NaCl, Normoxia: normal lung tissue without inflammation



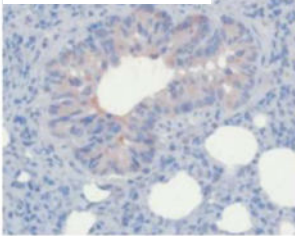
24h NaCl, Hypoxia: mild-to-moderate expression of TNF α

from Kowalleck, U. et al. (2022)

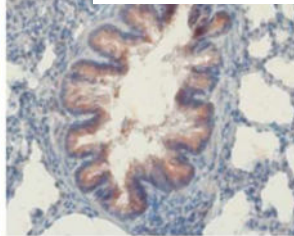
Discussion – TNF α

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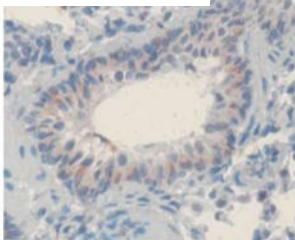
72h NaCl, N



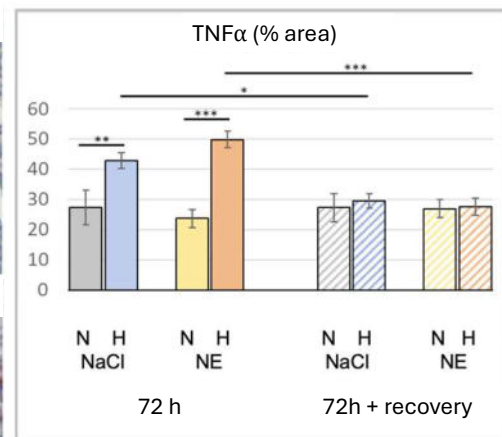
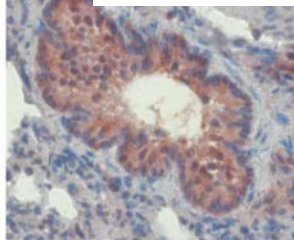
72h NaCl, H



72h NE, N



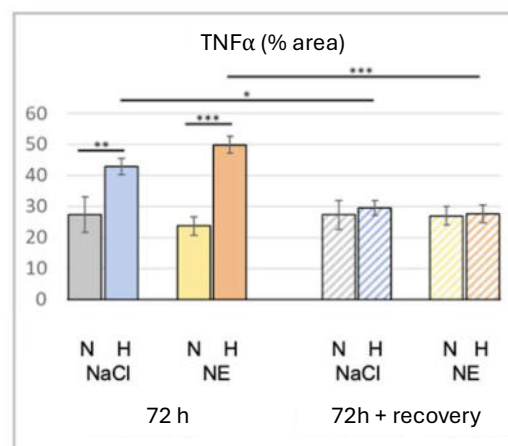
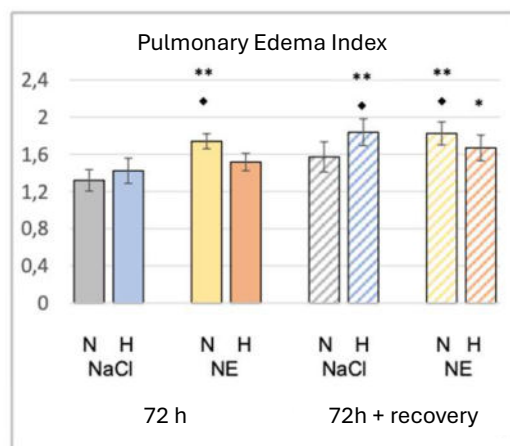
72h NE, H



unpublished data from Sarah Daunheimer

Discussion – comparison PEI vs. Inflammation

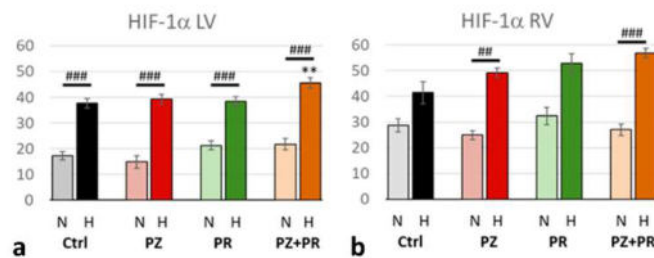
26



unpublished data from Sarah Daunheimer

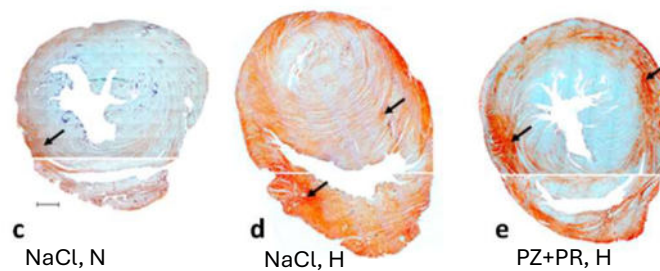
Discussion – HIF-1 α

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(a,b): Abundance of hypoxia-inducible factor (HIF)-1 α in the LV (a) and RV (b) expressed as percentage of positive area related to the total area of the free walls of LV and RV, respectively

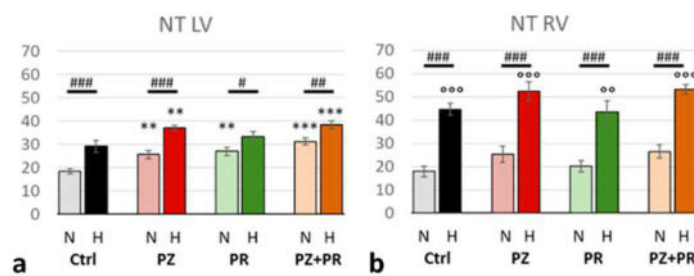
Significance marks:
sign. between hypoxic and normoxic group: ### p < 0.001



from Neubert, E. et al. (2023)

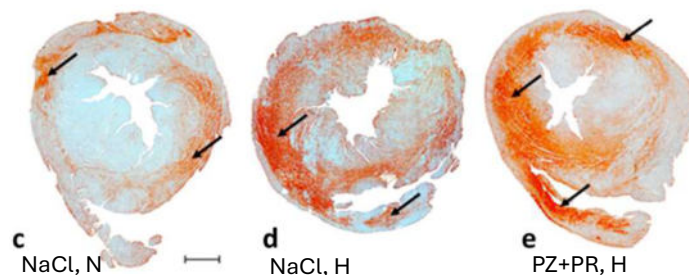
Discussion – NT

28



(a,b): Abundance of nitrotyrosine (NT) in the LV (a) and RV (b) expressed as percentage of positive area related to the total area of the free walls of LV and RV, respectively

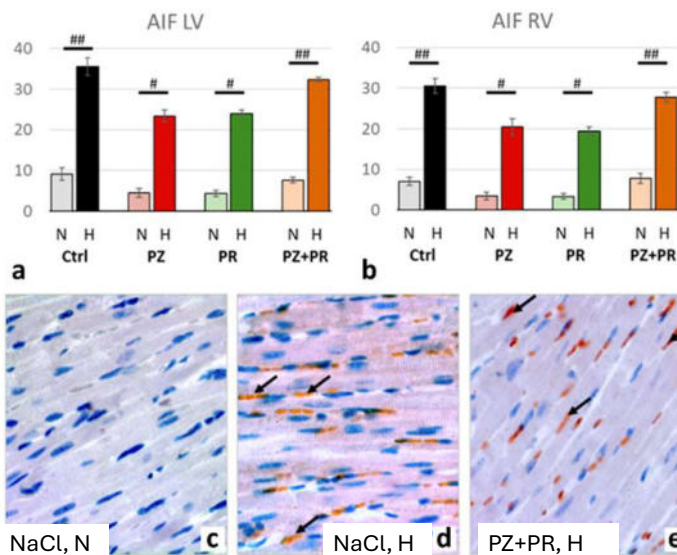
Significance marks:
sign. between hypoxic and normoxic group: ### p < 0.001
sign. vs. related normoxic or hypoxic control: ** p < 0.001; p < 0.001
sign. between LV and RV: °° p < 0.01; °°° p < 0.001



from Neubert, E. et al. (2023)

Discussion – AIF

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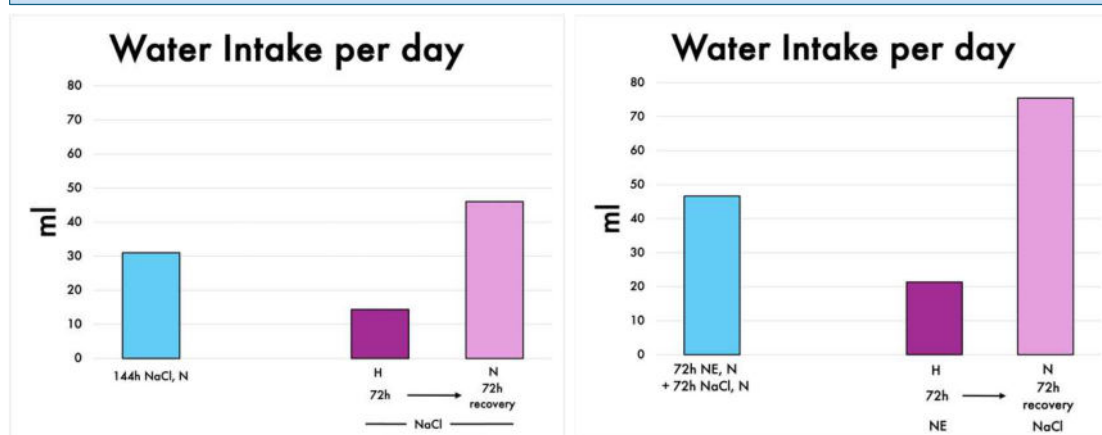
(a,b): Abundance of apoptosis-inducing factor (AIF) in the LV (a) and RV (b) expressed as percentage of positive cell nuclei related to the total number of counted nuclei in the LV and RV, respectively

Significance marks:
sign. between hypoxic and normoxic group:
p < 0.001

from Neubert, E. et al. (2023)

Discussion – Water Intake

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NaCl = Sodium-Chloride
NE = norepinephrine
N = Normoxia
H = Hypoxia