UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Patofysiologisk lungcirkulation vid COVID-19

Gaetano Perchiazzi, MD, PhD

*The **Hedenstierna Laboratory** – Department of Surgical Sciences, Uppsala University and*
*The **Anaesthesia & Intensive Care Department** – Akademiska Sjukhuset, Uppsala, Sweden*

HEDENSTIERNA LABORATORIET

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

Gaetano Perchiazzi, MD, PhD

Hedenstiernalaboratoriet
Institutionen för kirurgiska vetenskaper
Uppsala Universitet

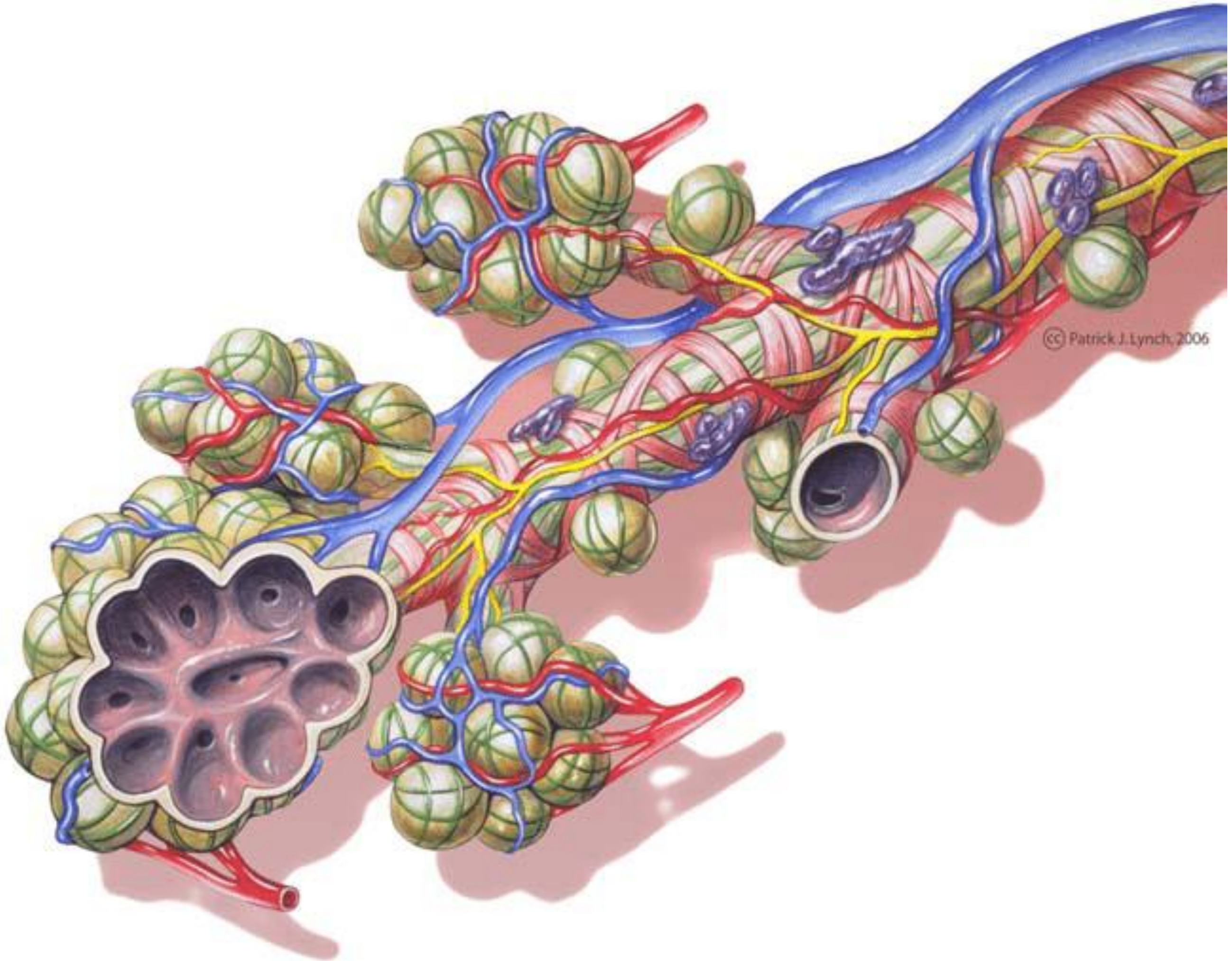
AnOpIVA
Akademiska sjukhuset
75185 Uppsala
SVERIGE

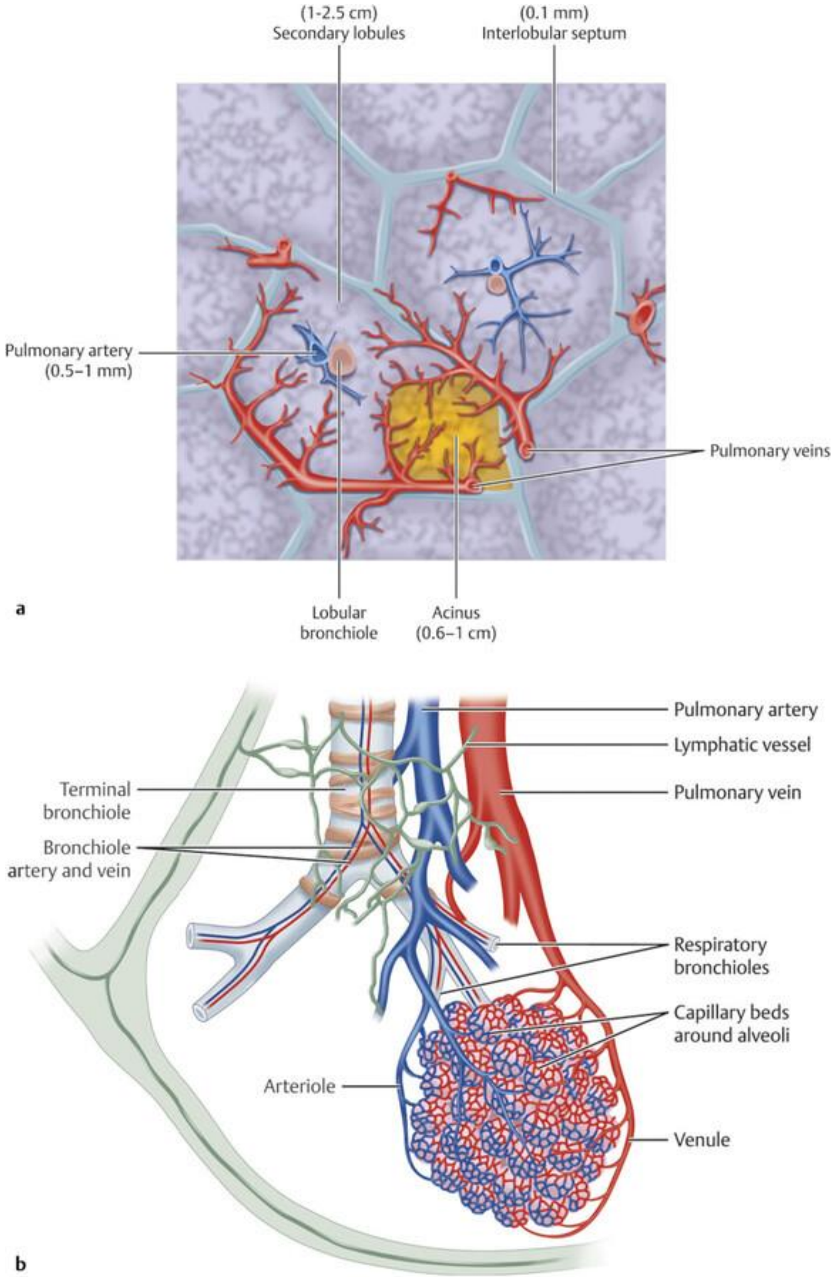
e-mail: gaetano.perchiazzi@surgsci.uu.se

HEDENSTIERNA LABORATORIET

Fysiologi av lung cirkulation

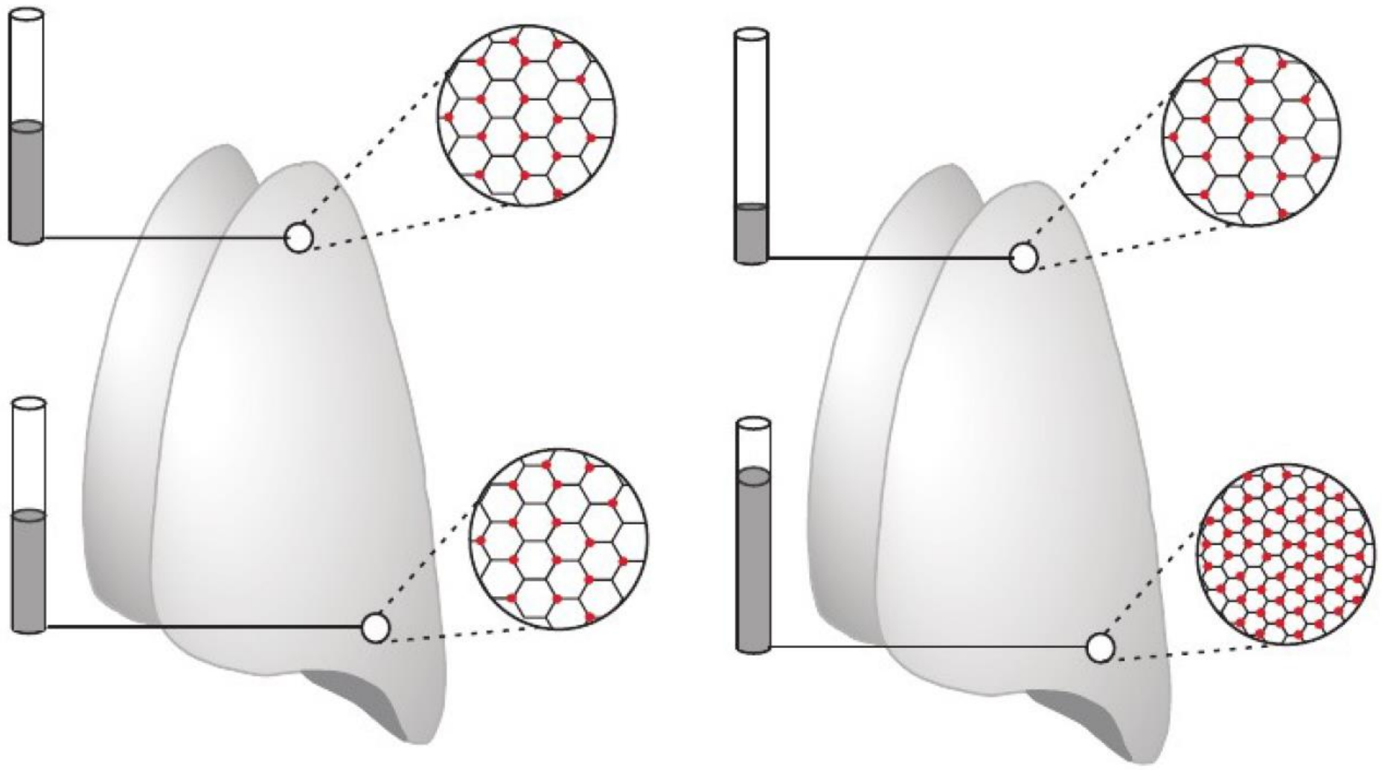
Enhet


(cc) Patrick J. Lynch, 2006


(1-2.5 cm)
Secondary lobules
(0.1 mm)
Interlobular septum
Pulmonary artery
(0.5–1 mm)
Pulmonary veins
a
Lobular
bronchiole
Acinus
(0.6–1 cm)
Pulmonary artery
Lymphatic vessel
Terminal
bronchiole
Pulmonary vein
Bronchiole
artery and vein
Respiratory
bronchioles
Capillary beds
around alveoli
Arteriole
Venule
b

Lung ventilation och perfusion

Gas innehållet

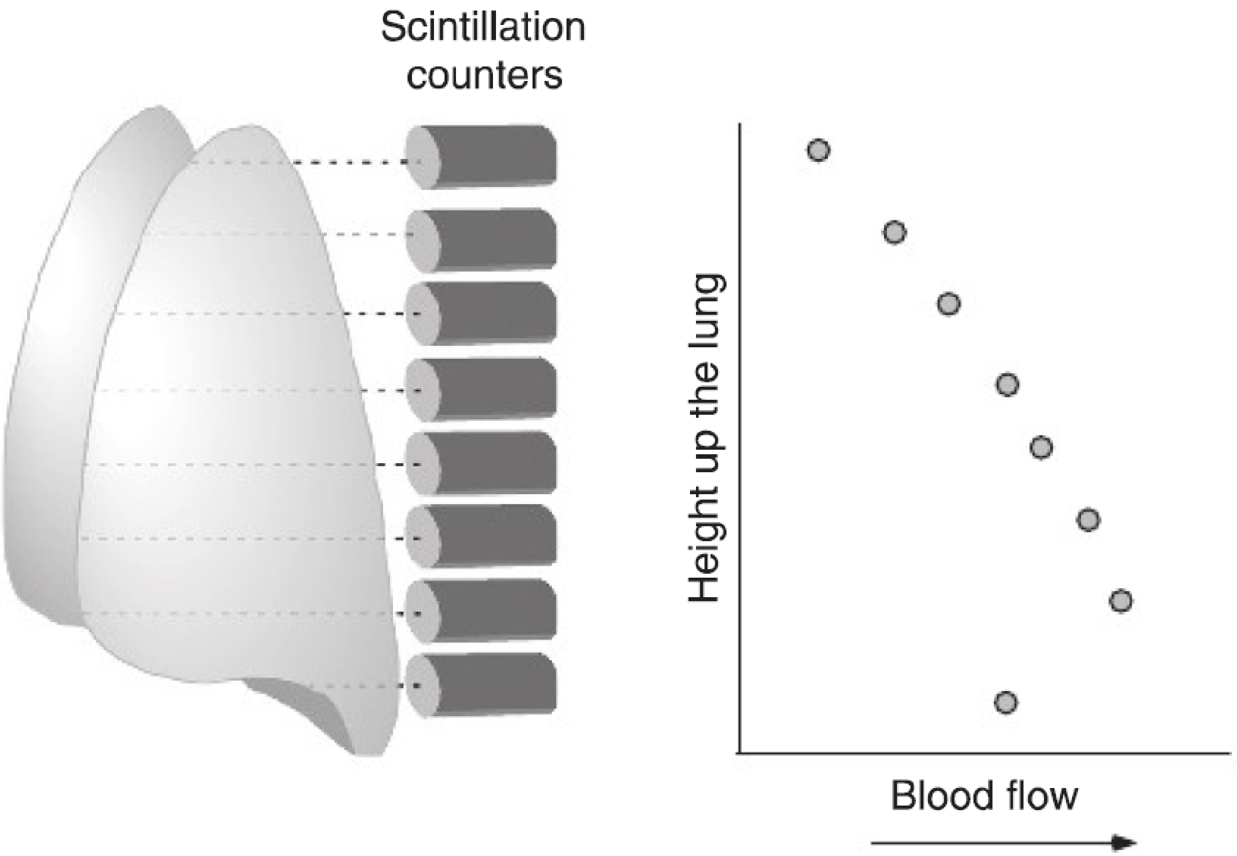


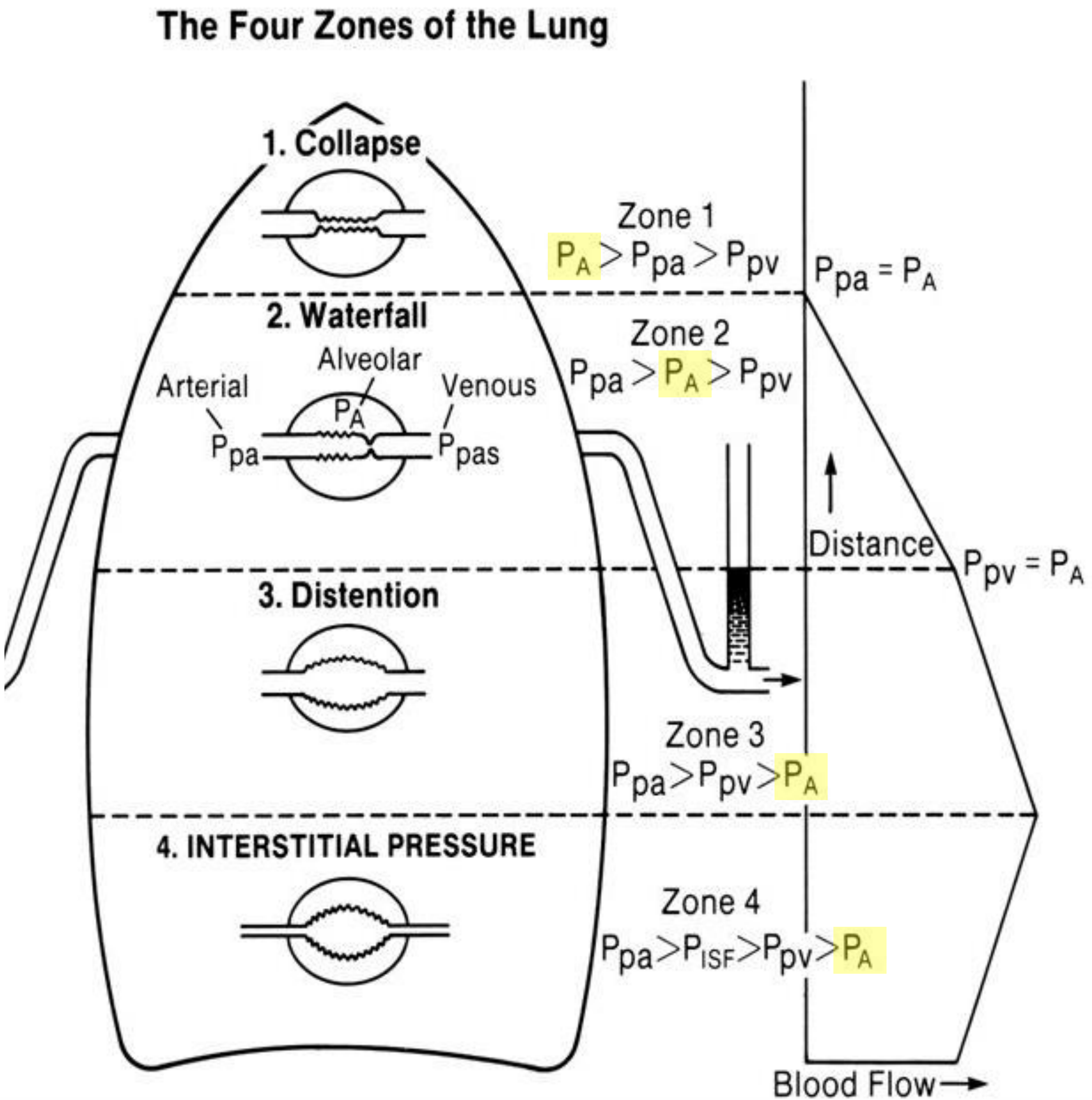
Determinants of Pulmonary Blood Flow Distribution

Robb W. Glenny*[1] and H. Thomas Robertson[1]

Compr Physiol 1:39-59, 2011

Blodflöde

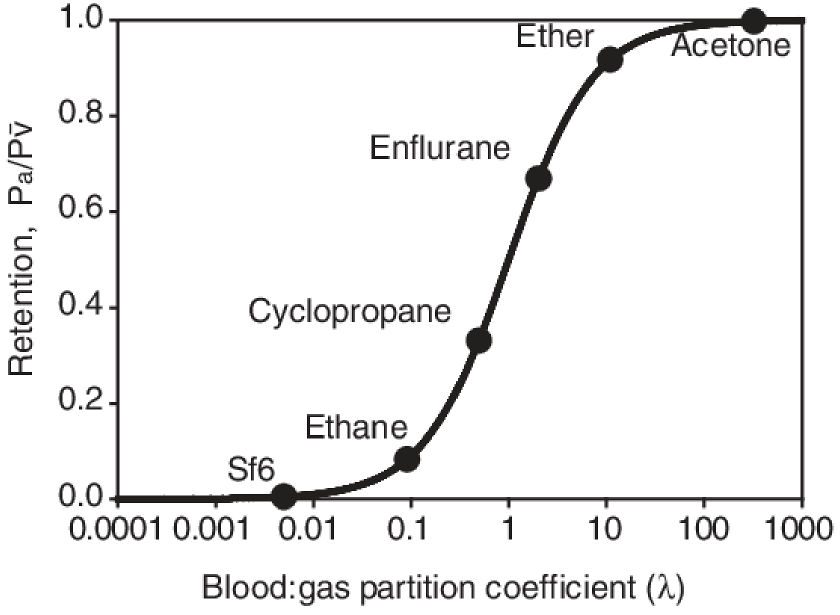

Scintillation counters
Height up the lung
Blood flow

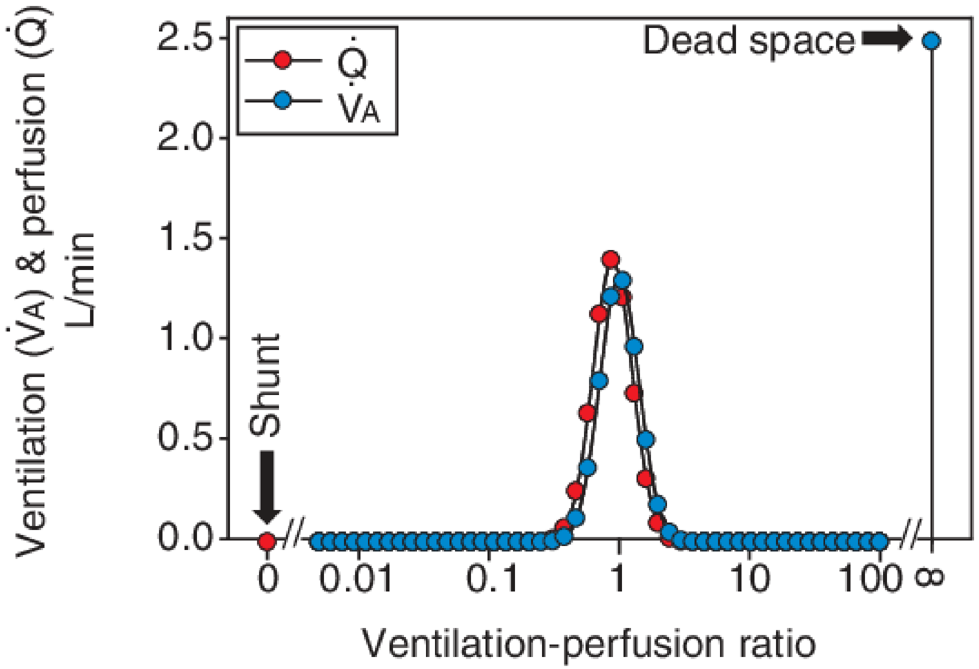

The Four Zones of the Lung
1. Collapse
Zone 1
$P_A > P_{pa} > P_{pv}$
$P_{pa} = P_A$
2. Waterfall
Alveolar
Arterial
Venous
P_A
P_{pa}
P_{pas}
Zone 2
$P_{pa} > P_A > P_{pv}$
Distance
$P_{pv} = P_A$
3. Distention
Zone 3
$P_{pa} > P_{pv} > P_A$
4. INTERSTITIAL PRESSURE
Zone 4
$P_{pa} > P_{ISF} > P_{pv} > P_A$
Blood Flow

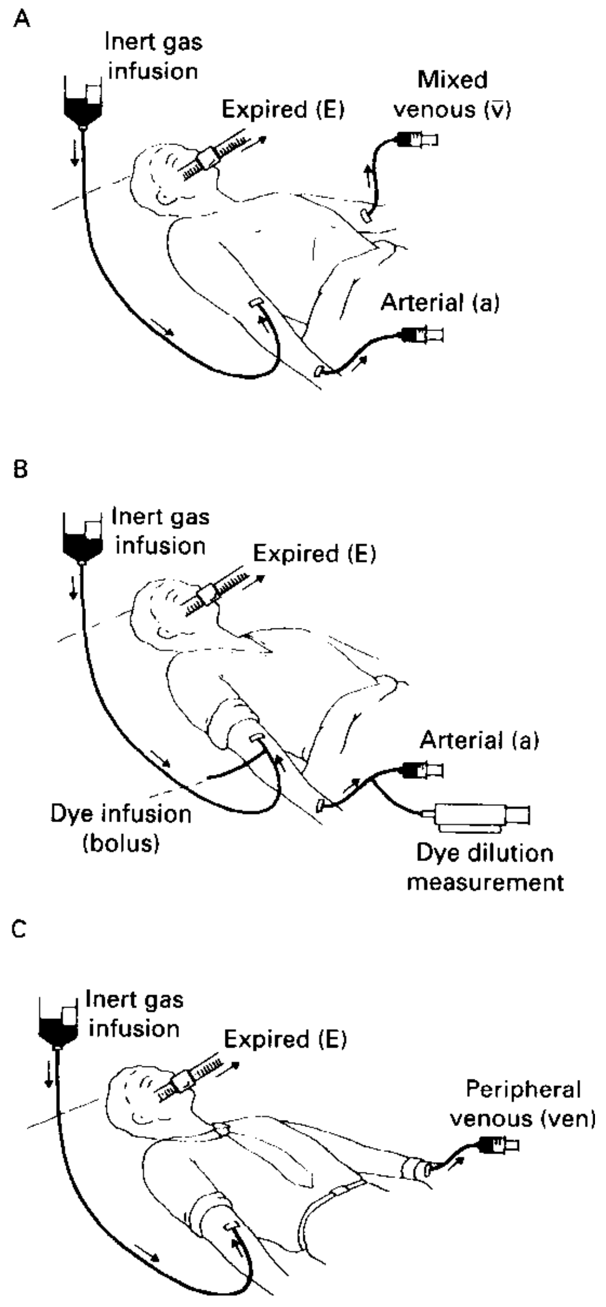
UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

The MIGET

Multiple Inert Gas Elimination Technique

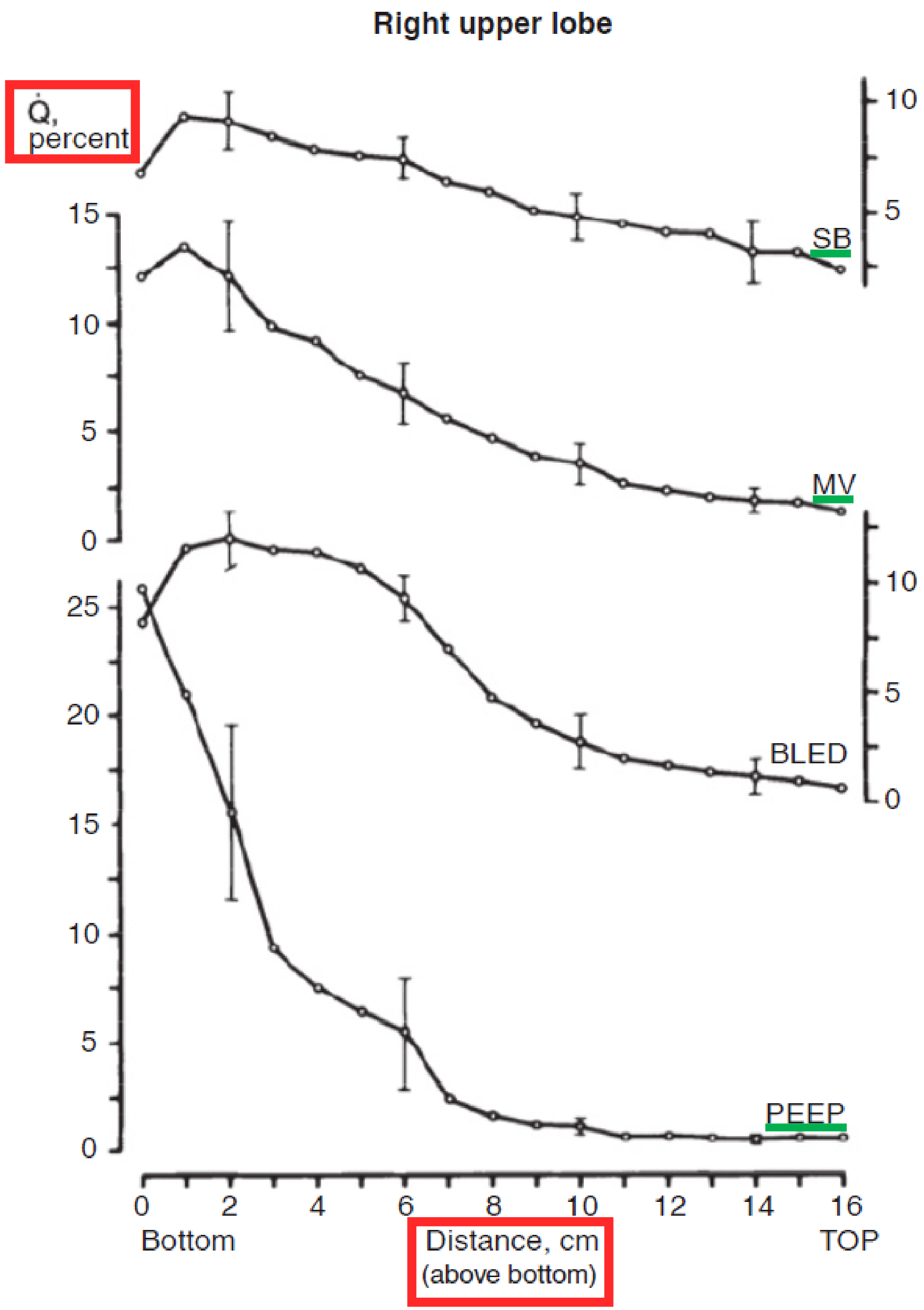






Spatial distribution of pulmonary blood flow in the dog with PEEP ventilation

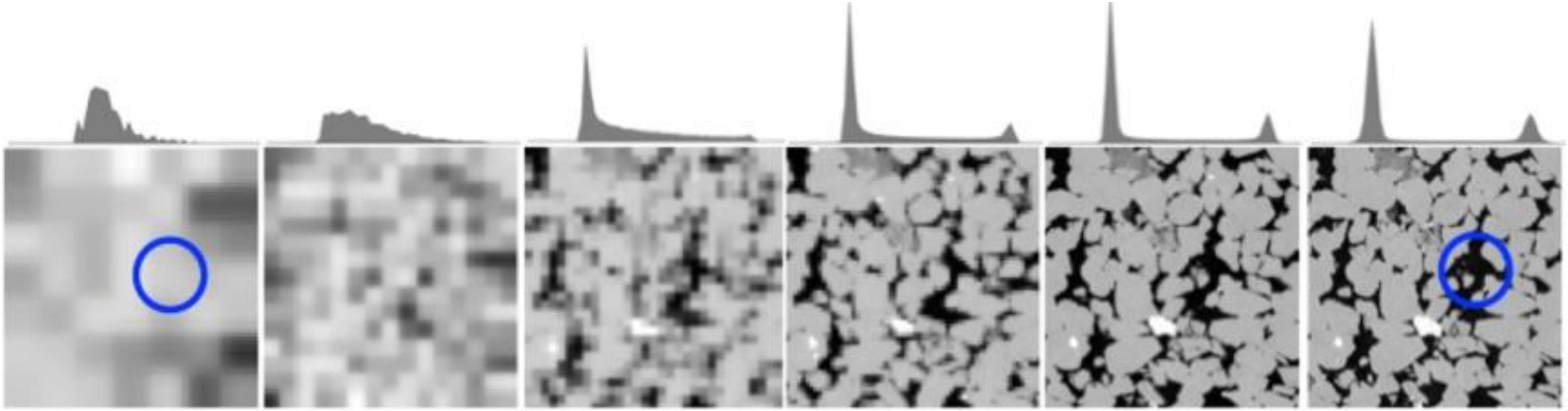
HEDENSTIERNA, GÖRAN, FRANCIS C. WHITE, AND PETER D. WAGNER. *Spatial distribution of pulmonary blood flow in the dog with PEEP ventilation*. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 47(5): 938–946, 1979.—The effects of



Granularity

A *fine-grained* description of a system is a detailed, exhaustive, low-level model of it.

A *coarse-grained* description is a model where some of this fine detail has been smoothed over or averaged out.



Botha & Sheppard. Mapping permeability in low-resolution micro-CT images: A multiscale statistical approach. Water Resources Research 2016; 52(6): 4377-98.

Recruitability

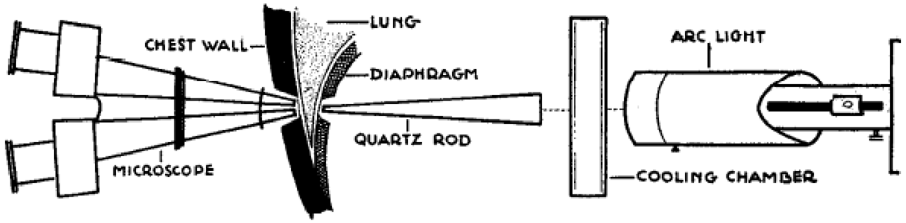
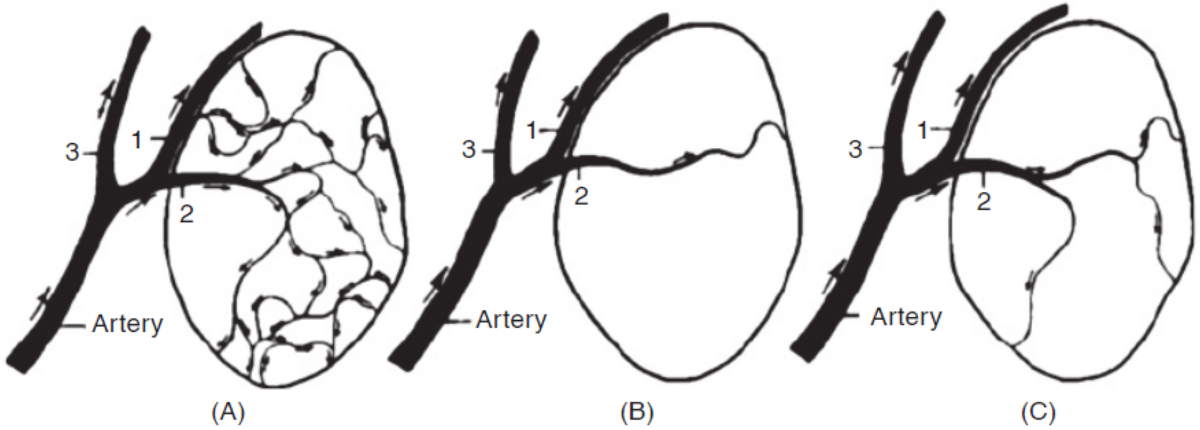
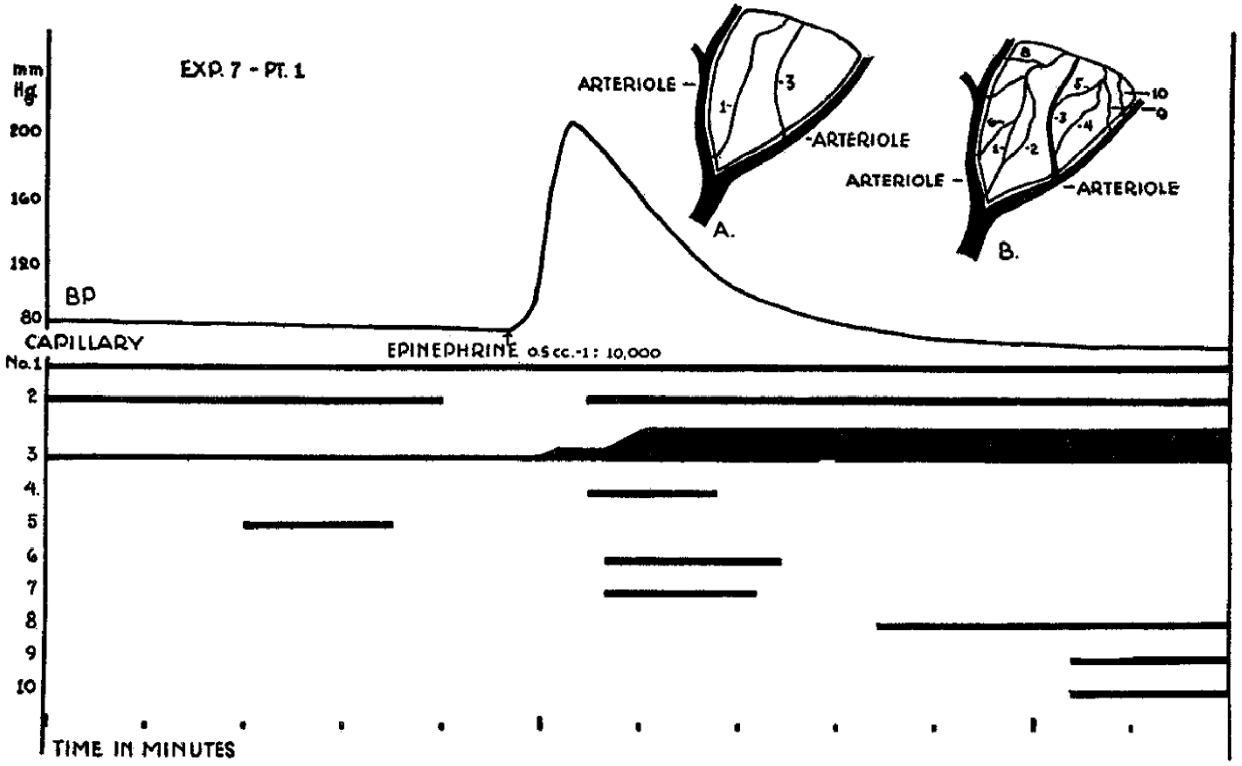


Fig. 1. Shows the detail of the position of the lower border of the lung in relation to the microscope and lighting system.

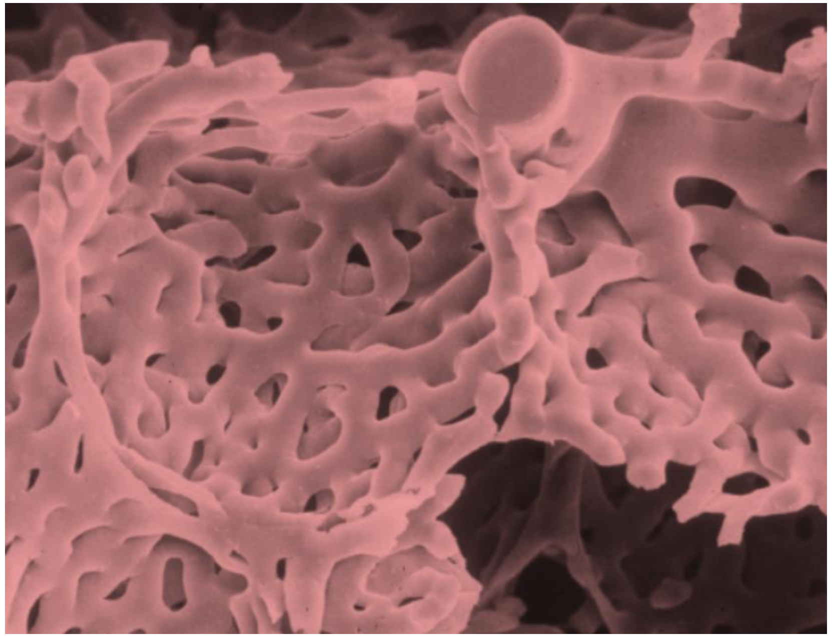


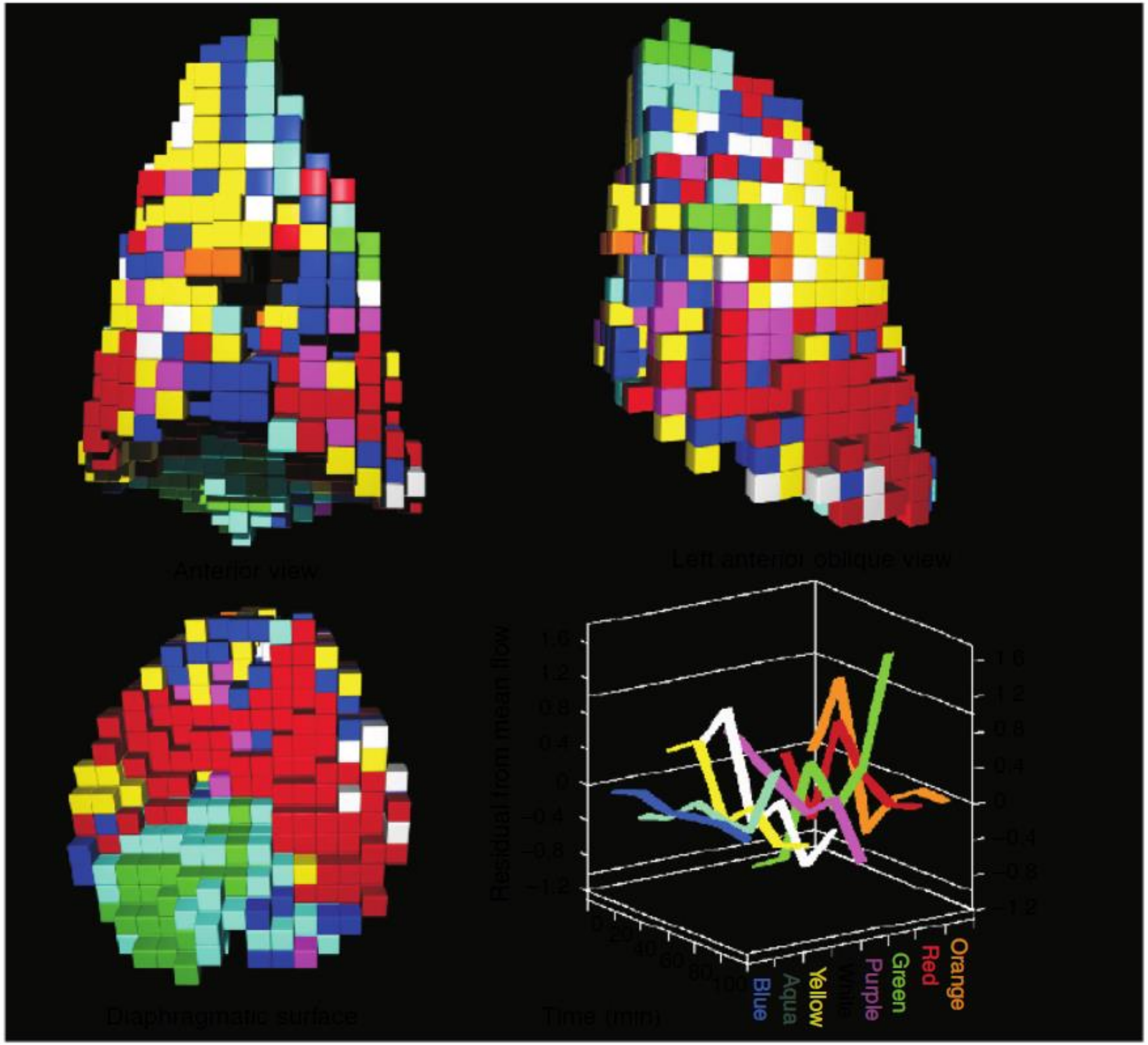


Wearn JT, Ernstene AC, Bromer AW, Barr JS, German WJ, Zschiesche LJ. The normal behavior of the pulmonary blood vessels with observations on the intermittence of the flow of blood in the arterioles and capillaries. *Am J Physiol* 109: 236-256, 1934.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Temporal förändring av den regionala lungperfusionen ”spatially clustered”



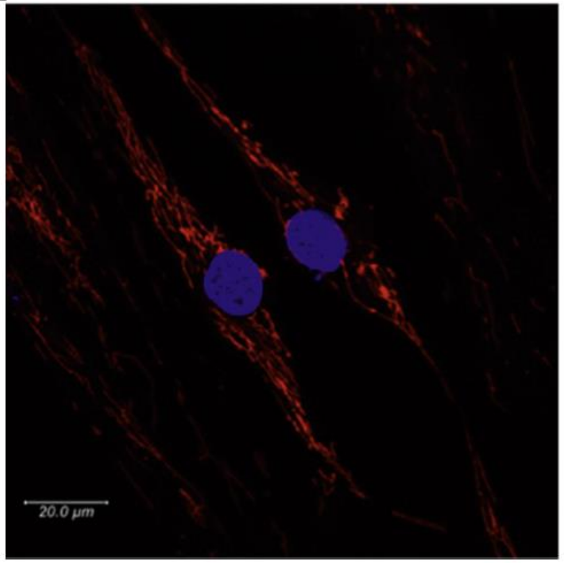


Glenny RW, Polissar NL, McKinney S, Robertson HT. Temporal heterogeneity of regional pulmonary perfusion is spatially clustered. *J Appl Physiol* 79: 986-1001, 1995.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

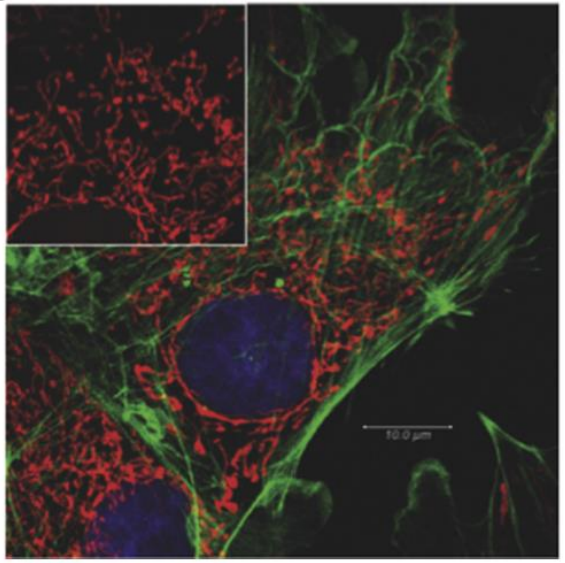
Hypoxic Pulmonary Vasoconstriction

A

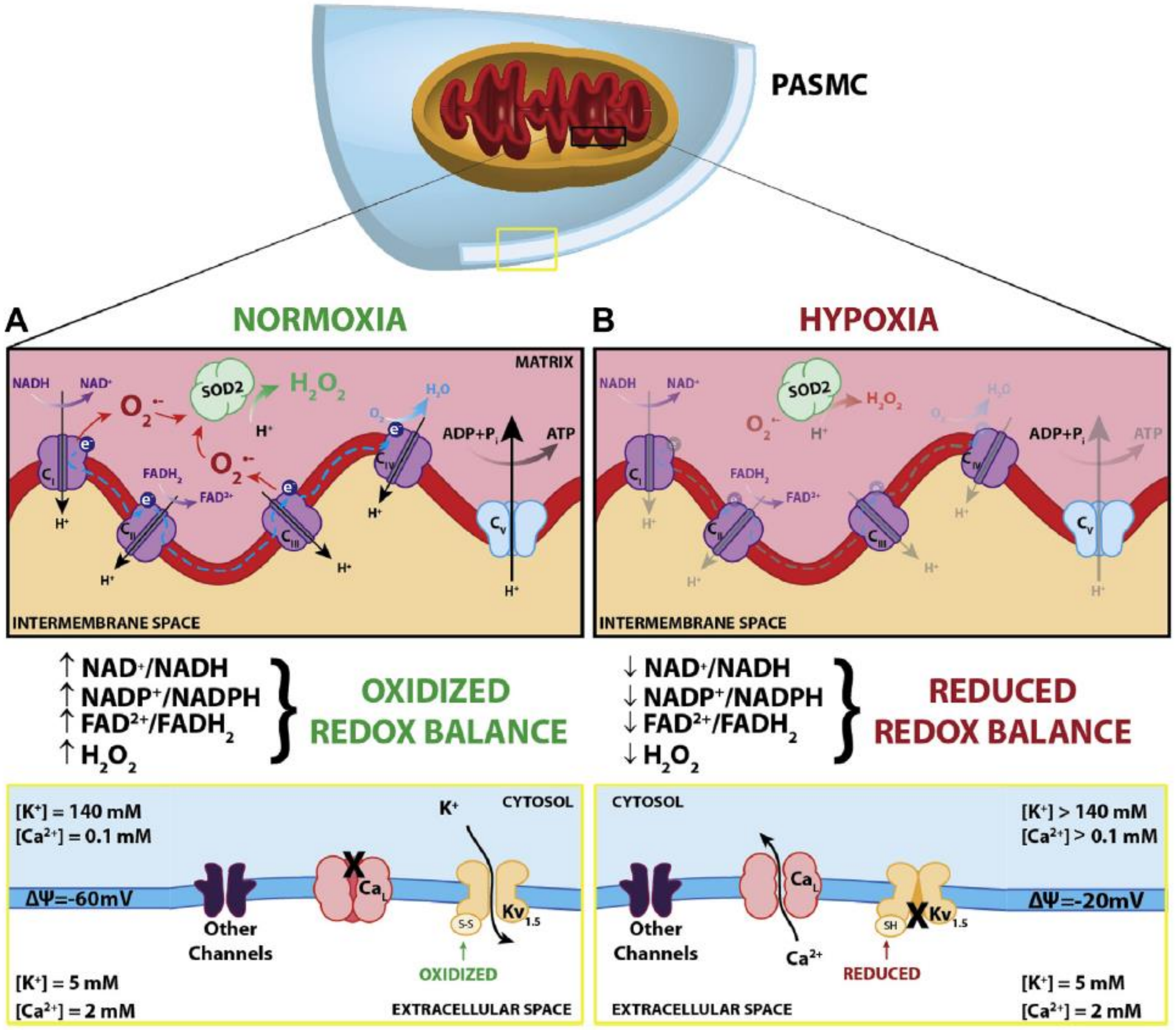


Mitochondria in pulmonary artery smooth muscle cells from a normal patient

B

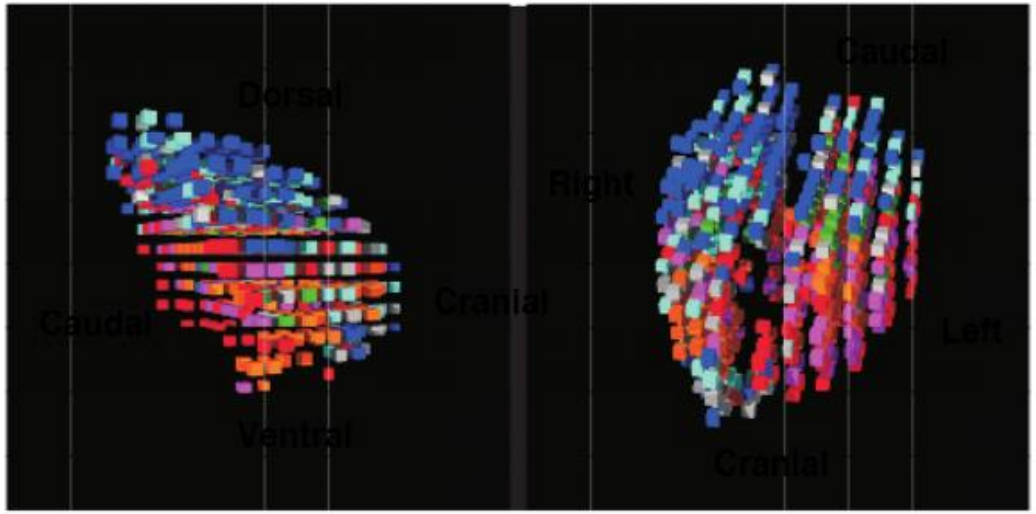


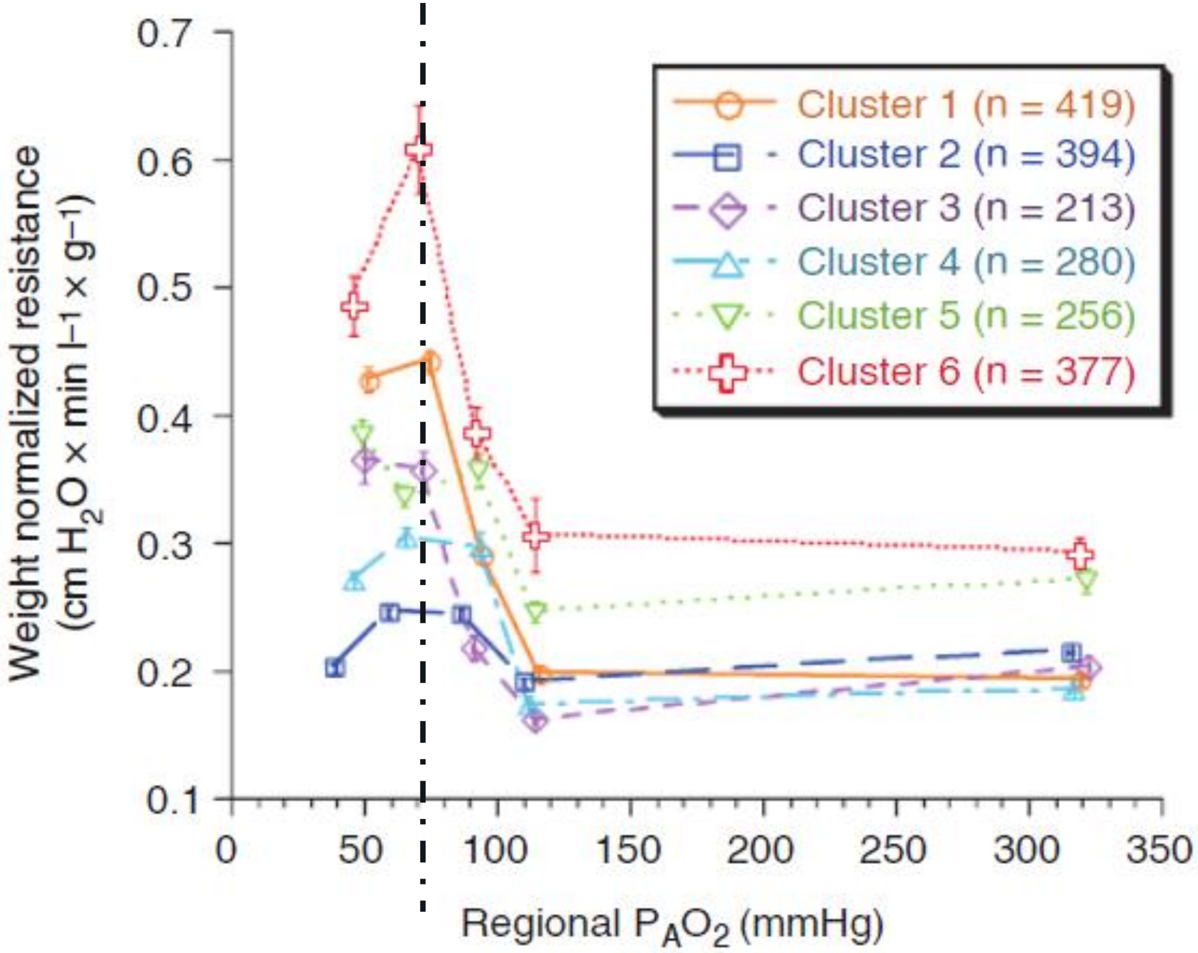
Bovine pulmonary artery endothelial cells stained for mitochondria



Dunham-Snary et al. Hypoxic Pulmonary Vasoconstriction: From Molecular Mechanisms to Medicine. Chest 2017;151:181–192.

Spatial distribution of hypoxic pulmonary vasoconstriction

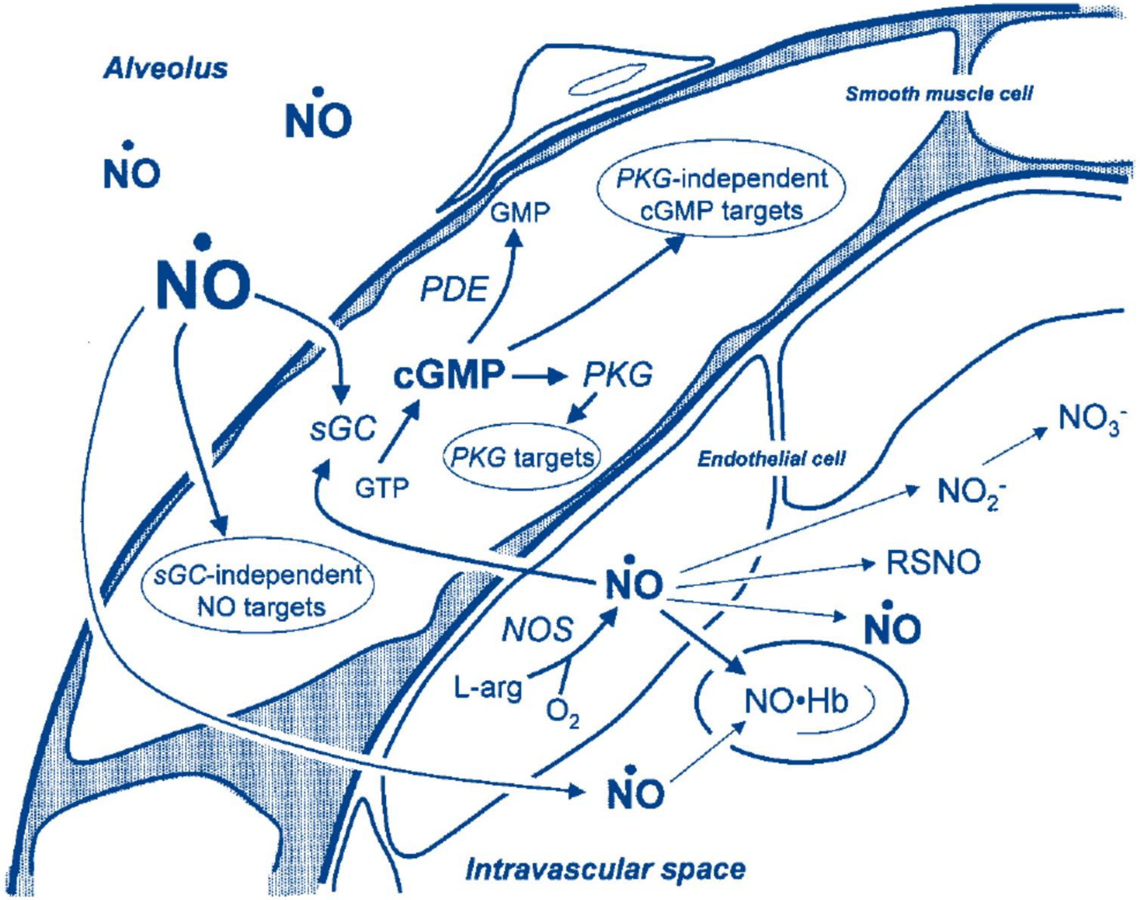




Hlastala et al. Spatial distribution of hypoxic pulmonary vasoconstriction in the supine pig. J Appl Physiol 2004;96:1589–1599.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Teoretisk:



Inhaled Nitric Oxide
A Selective Pulmonary Vasodilator
Current Uses and Therapeutic Potential

Fumito Ichinose, MD; Jesse D. Roberts, Jr, MD; Warren M. Zapol, MD

(*Circulation*. 2004;109:3106-3111.)

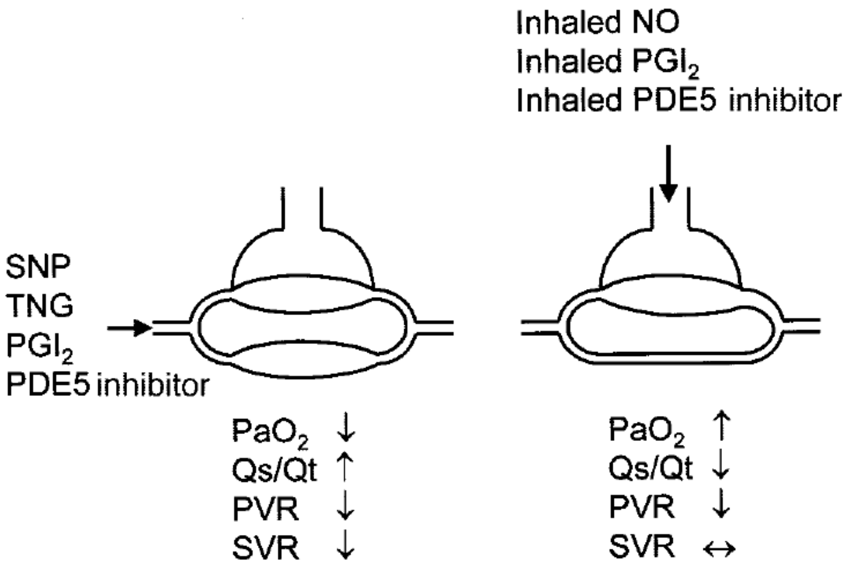


Figure 2. Differing pathophysiological effects of inhaled pulmonary vasodilators and intravenous vasodilators. SNP indicates sodium nitroprusside; TNG, nitroglycerine; PGI_2, prostaglandin I_2; Qs/Qt, right-to-left shunt fraction; and SVR, systemic vascular resistance.

Vägen från Asbaugh till Wuhan

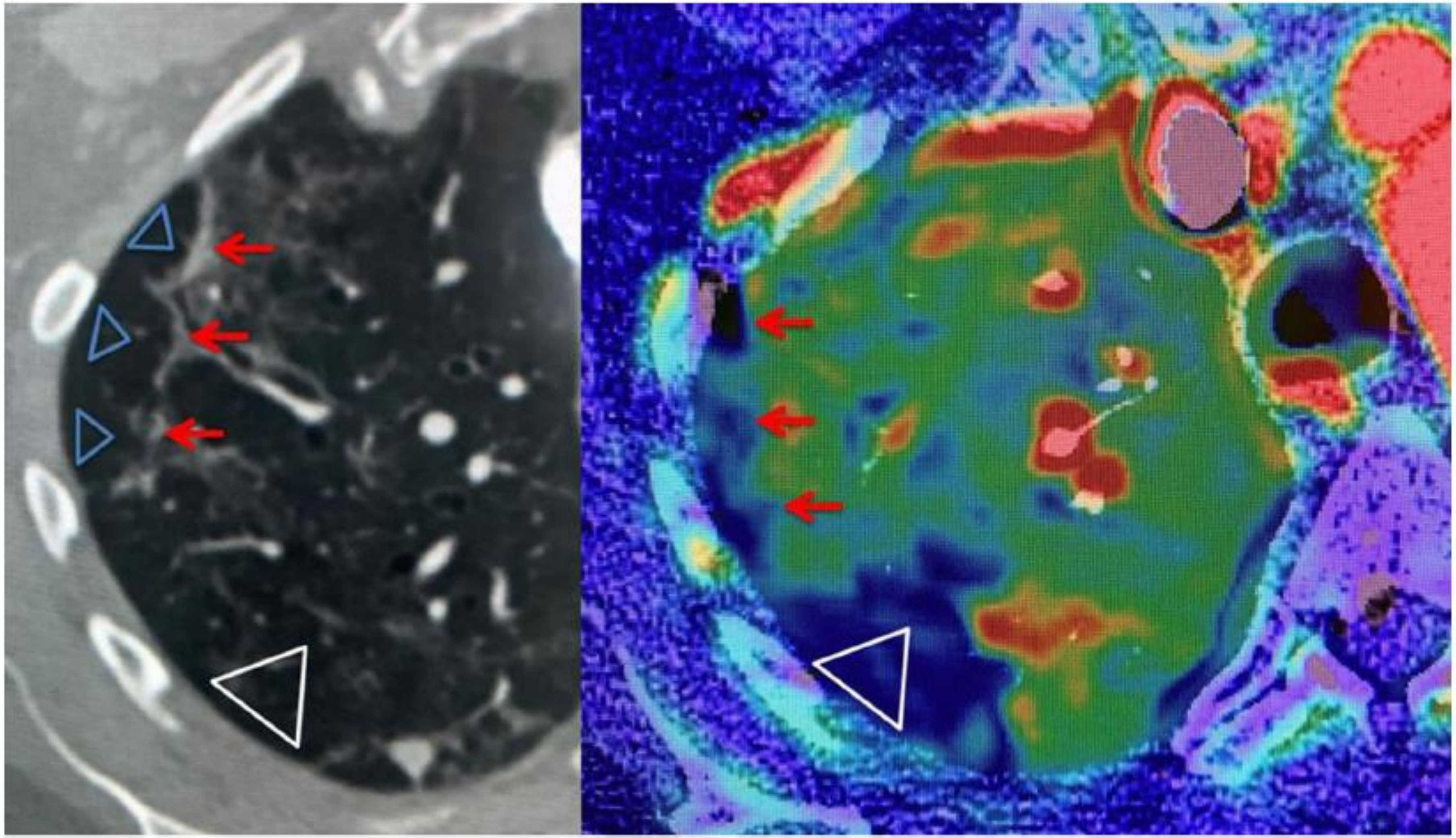
ACUTE RESPIRATORY DISTRESS IN ADULTS

DAVID G. ASHBAUGH
M.D. Ohio State
ASSISTANT PROFESSOR OF SURGERY

The Lancet · Saturday 12 August 1967

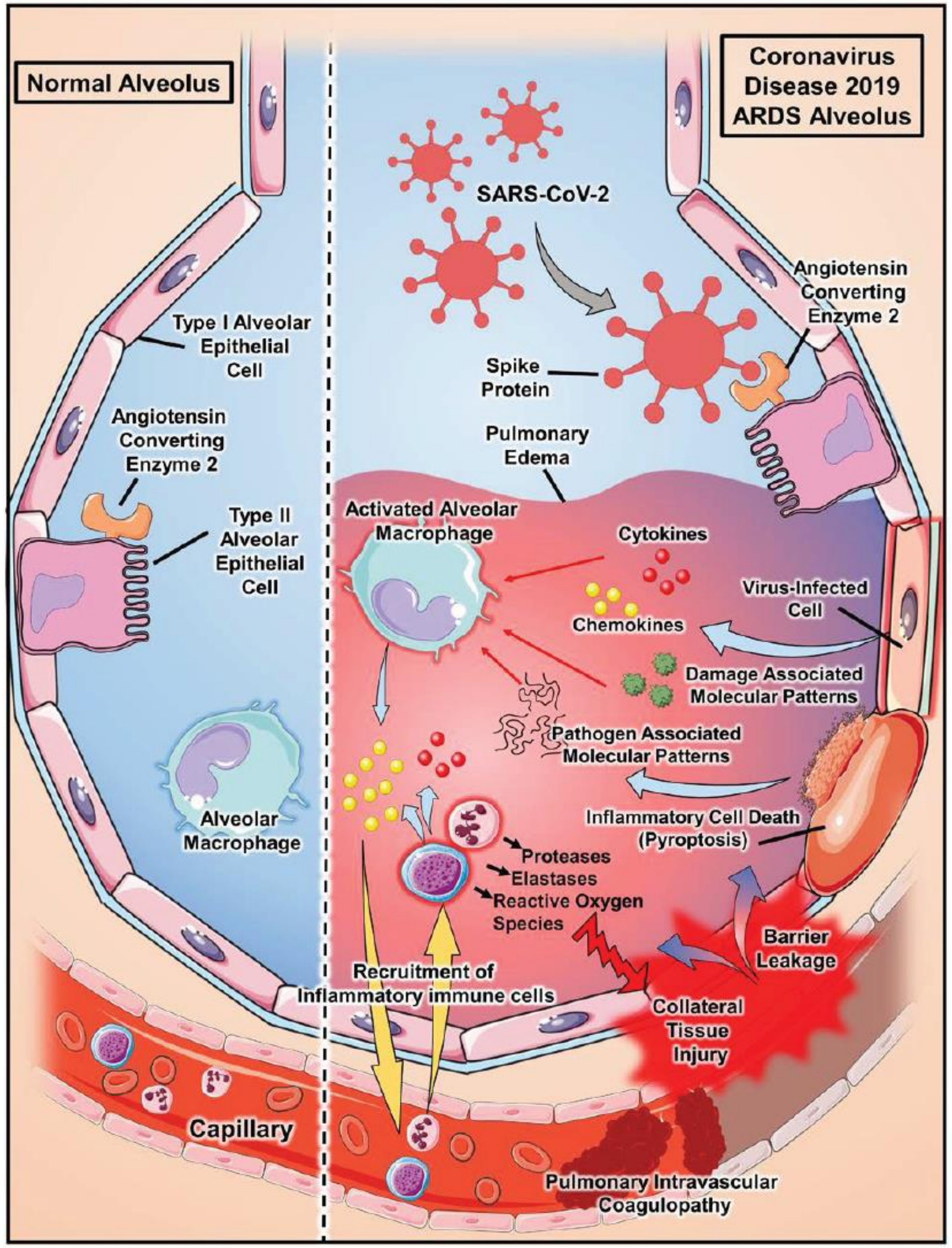
HECTOR RETAMAL/AFP

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET



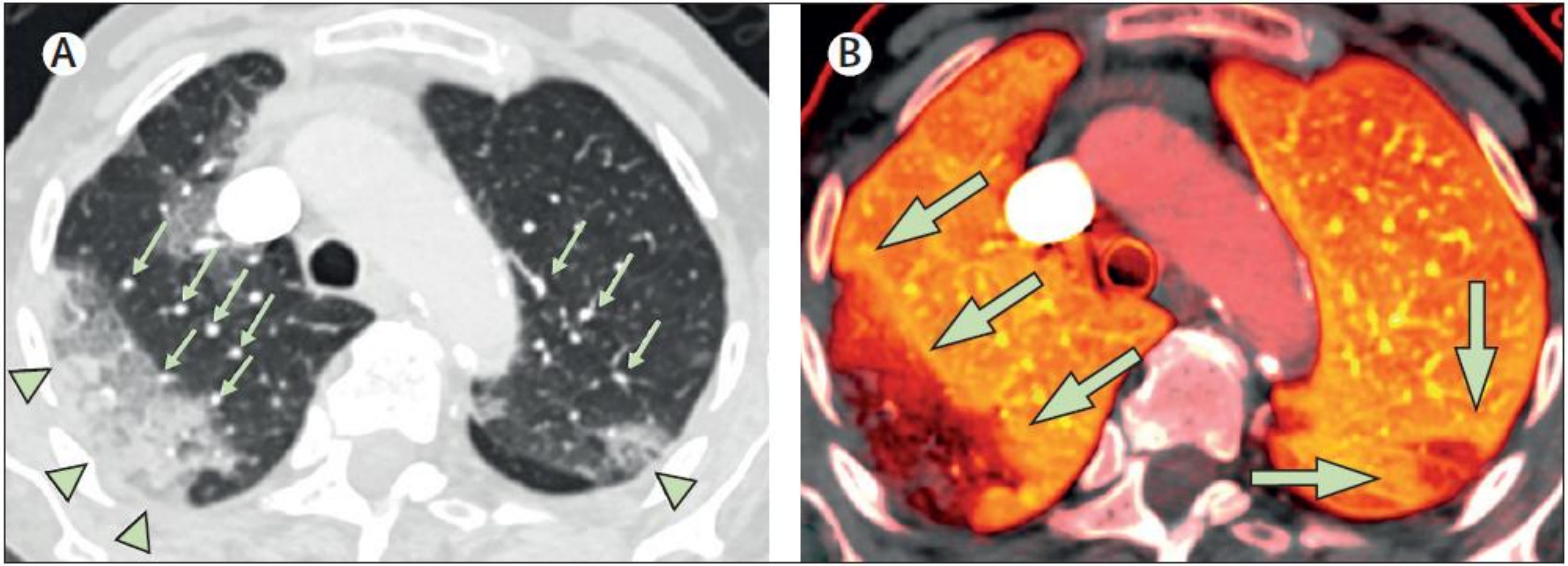
Oudkerk et al. The vascular nature of COVID-19. Br J Radiol 2020;93: 20200718.

Discussion:
alveolo-centric vs vaso-centric disease



Williams GW, et al. Acute Respiratory Distress Syndrome. Anesthesiology. 2021 Feb 1;134(2):270-282

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET



Lang et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis 2020;20:1365–1366.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

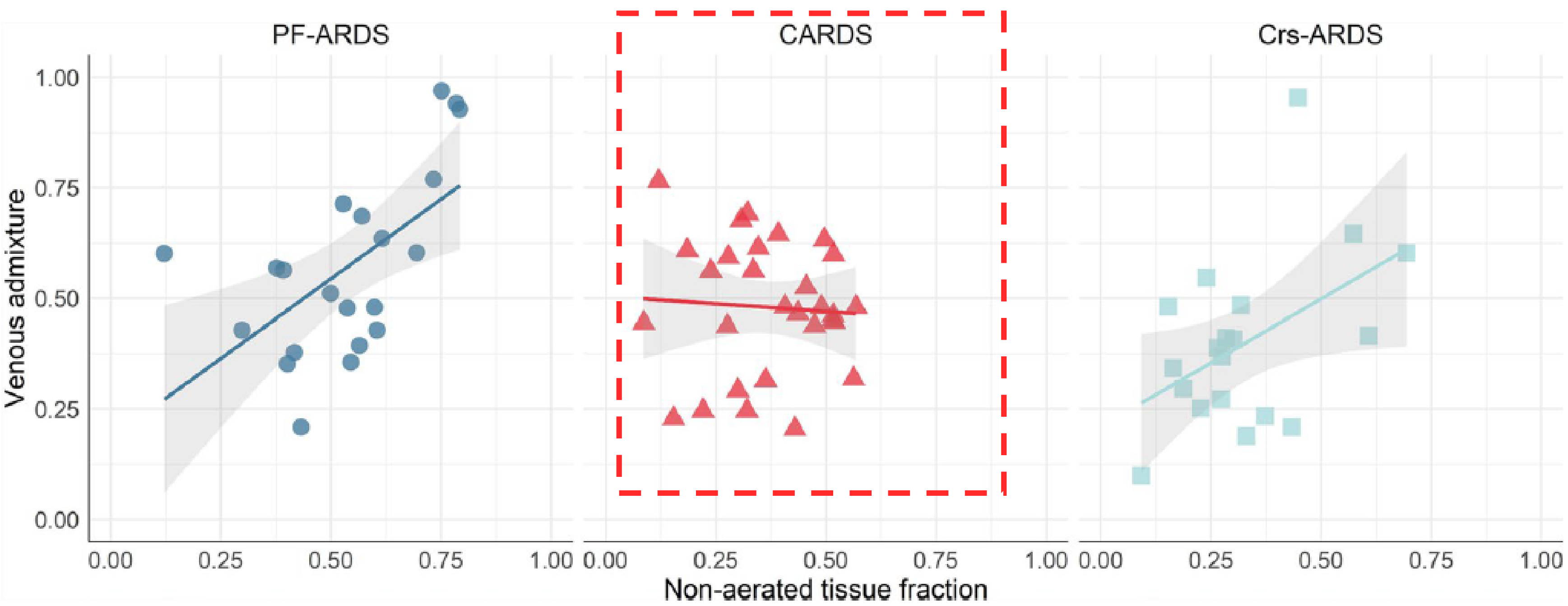
Intensive Care Med (2020) 46:2187–2196
https://doi.org/10.1007/s00134-020-06281-2

ORIGINAL

Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study

Davide Chiumello[1], Mattia Busana[2], Silvia Coppola[1], Federica Romitti[2], Paolo Formenti[1], Matteo Bonifazi[2], Tommaso Pozzi[1], Maria Michela Palumbo[2], Massimo Cressoni[3], Peter Herrmann[2], Konrad Meissner[2], Michael Quintel[2], Luigi Camporota[4], John J. Marini[5] and Luciano Gattinoni[2*]

Venous admixture



UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Vad orsakar viruset?

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

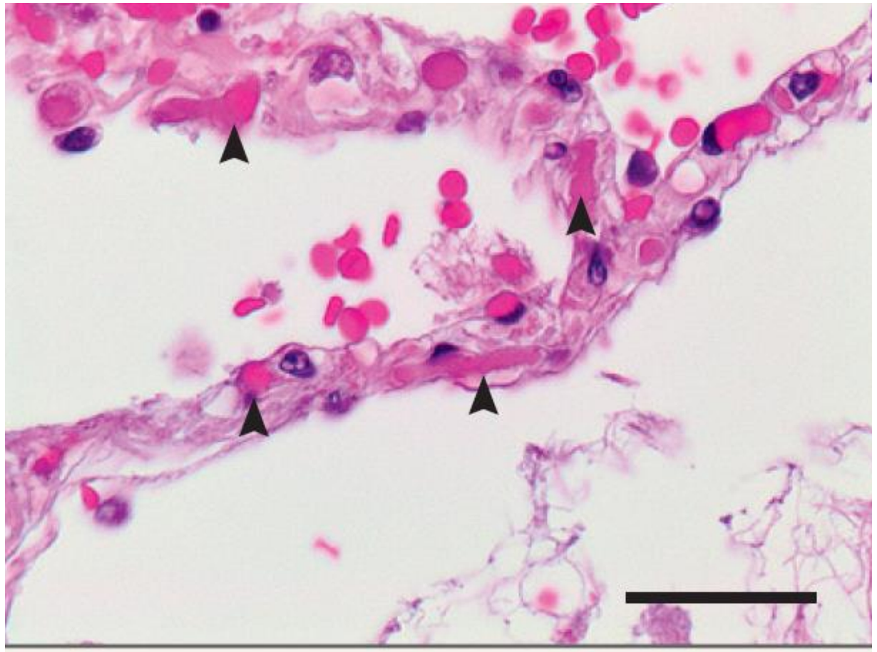
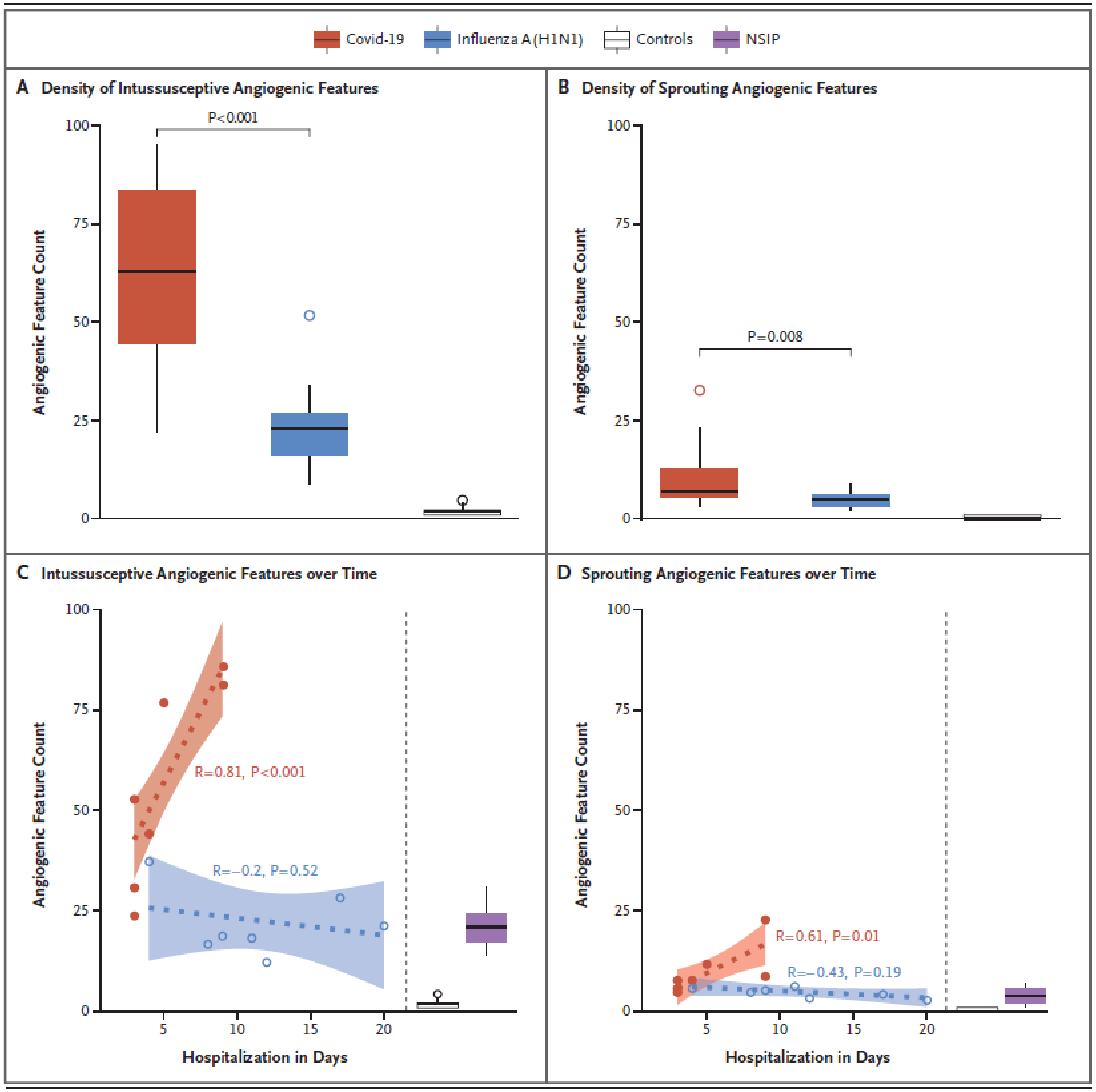


Figure 2. Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.



COVID-19:

- Severe endotelial injury
- Vascular trombosis, microangiopathy , occlusion of capillary
- New vessel growth

N Engl J Med 2020;383:120-8.

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

ESC European Society of Cardiology

European Heart Journal (2020) **41**, 3038–3044
doi:10.1093/eurheartj/ehaa623

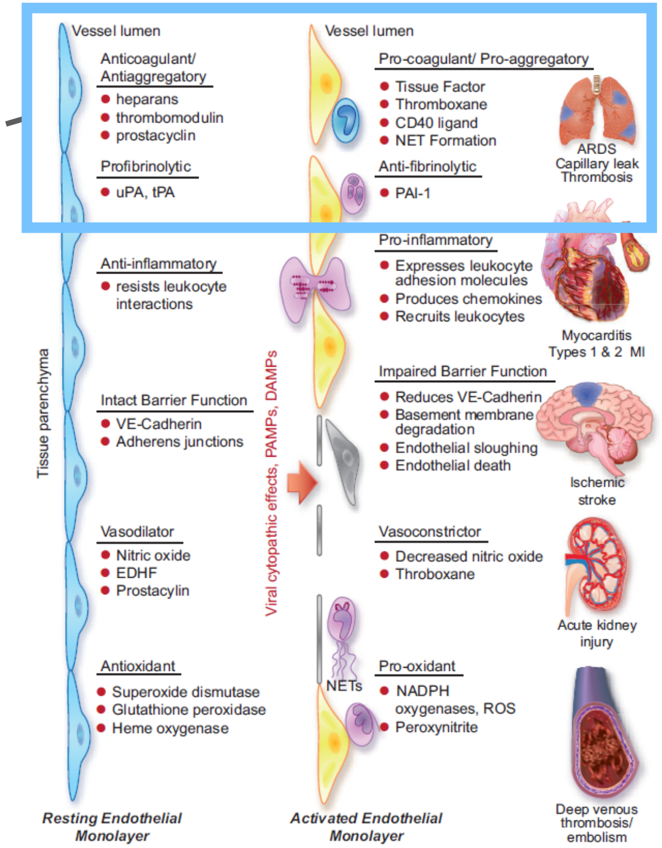
VIEWPOINT
Disease management

COVID-19 is, in the end, an endothelial disease

Peter Libby [1]* and Thomas Lüscher [2]

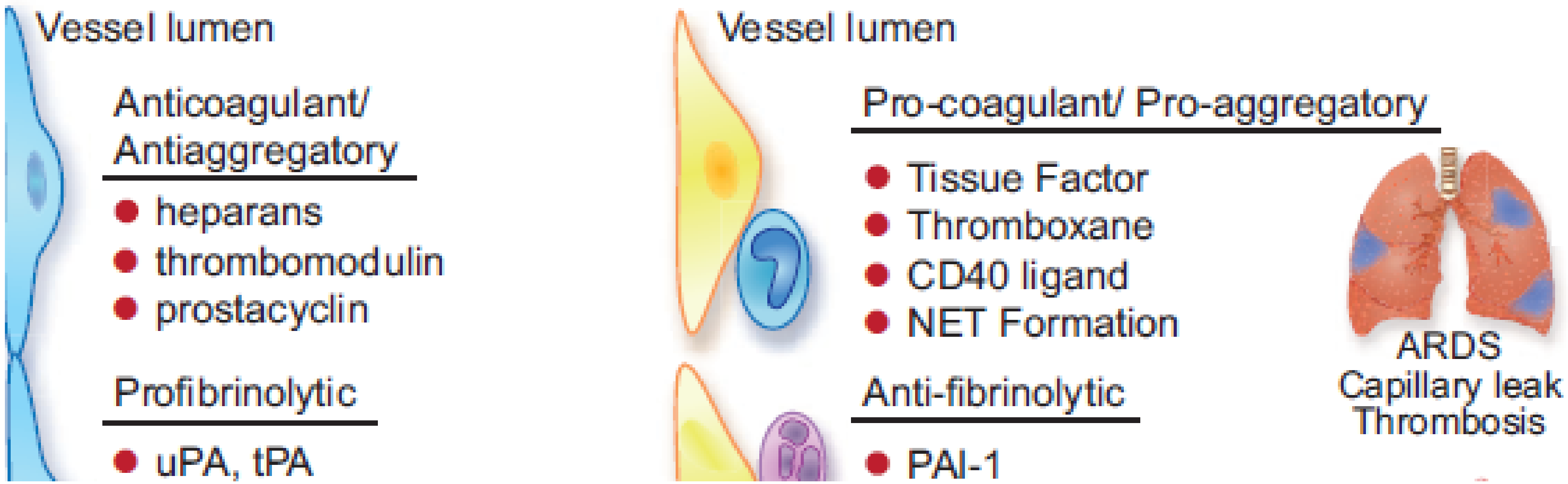
[1]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; and [2]Heart Division, Royal Brompton & Harefield Hospital and National Heart and Lung Institute, Imperial College, London, UK

Received 17 June 2020; revised 7 July 2020; editorial decision 14 July 2020; accepted 17 July 2020



Mediators of inflammation OR damage-associated molecular patterns derived from dead or dying cells

Resting → **Activated**



UPPSALA UNIVERSITET

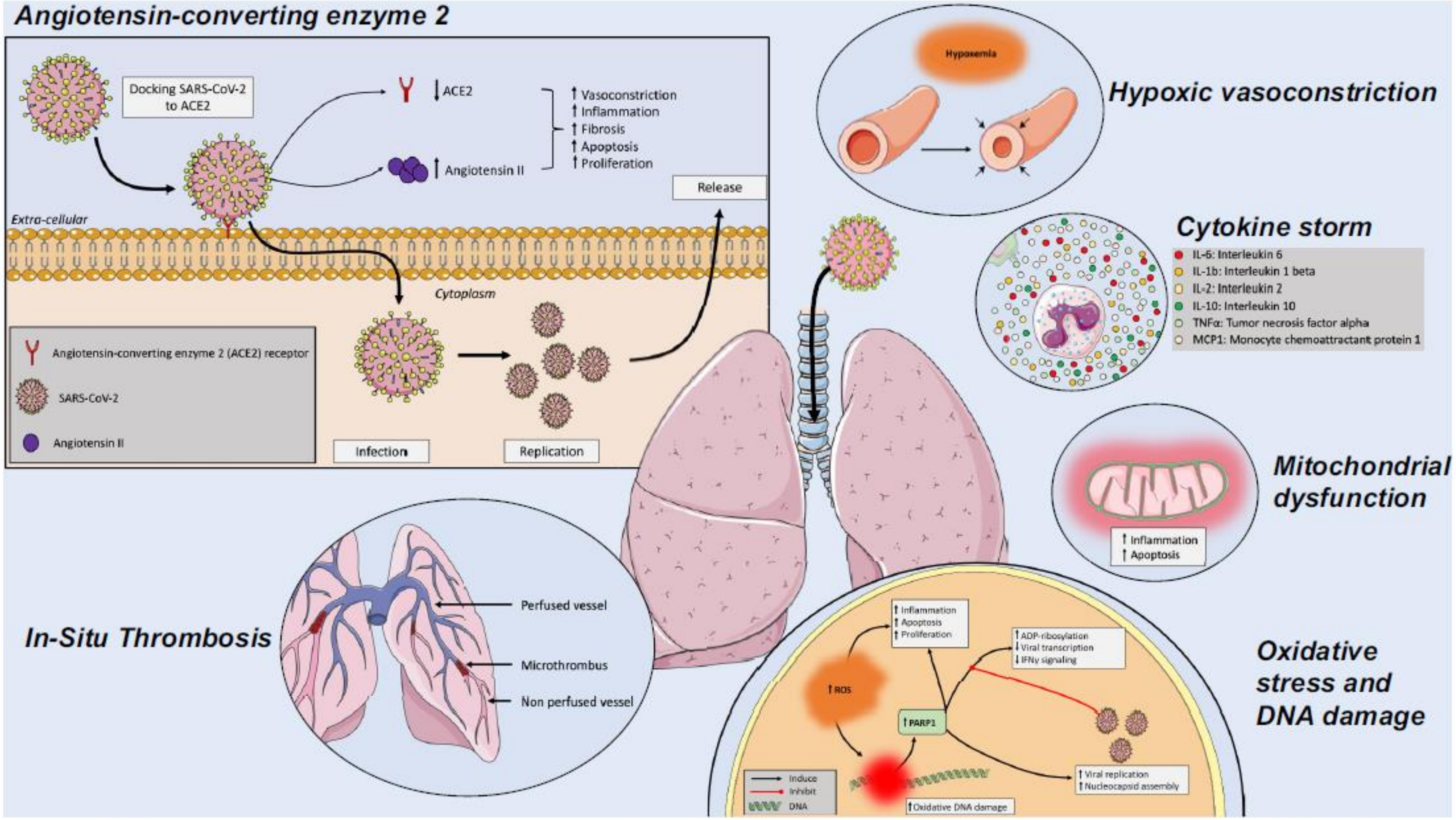
AKADEMISKA SJUKHUSET

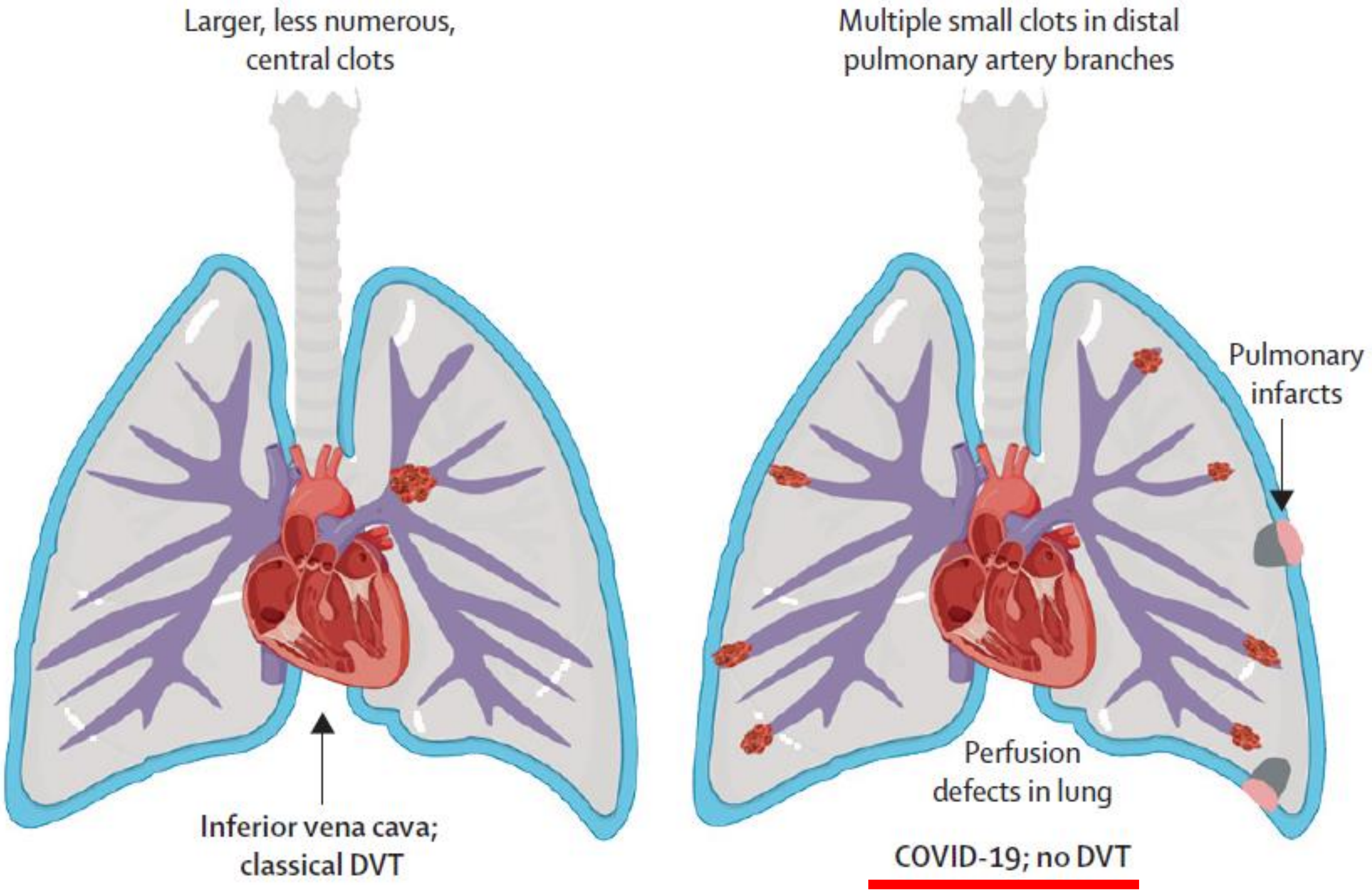
Am J Physiol Lung Cell Mol Physiol 319: L277–L288, 2020.
First published June 17, 2020; doi:10.1152/ajplung.00195.2020.

REVIEW | *The Pathophysiology of COVID-19 and SARS-CoV-2 Infection*

Novel insights on the pulmonary vascular consequences of COVID-19

François Potus,[1,2,3,4]* Vicky Mai,[1,2,3]* Marius Lebret,[1,2,3] Simon Malenfant,[1,3] Emilie Breton-Gagnon,[1,2,3] Annie C. Lajoie,[1,2,3] Olivier Boucherat,[1,2,3] Sébastien Bonnet,[1,2,3]* and Steeve Provencher[1,2,3]*



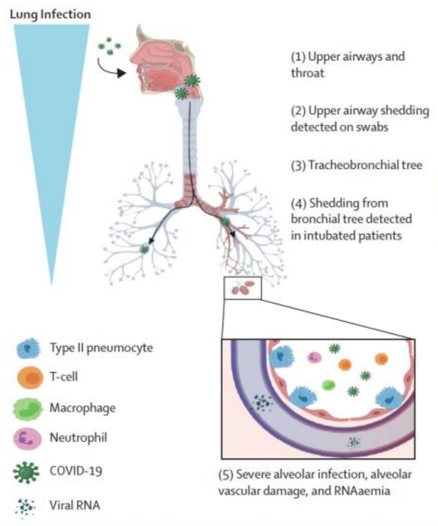


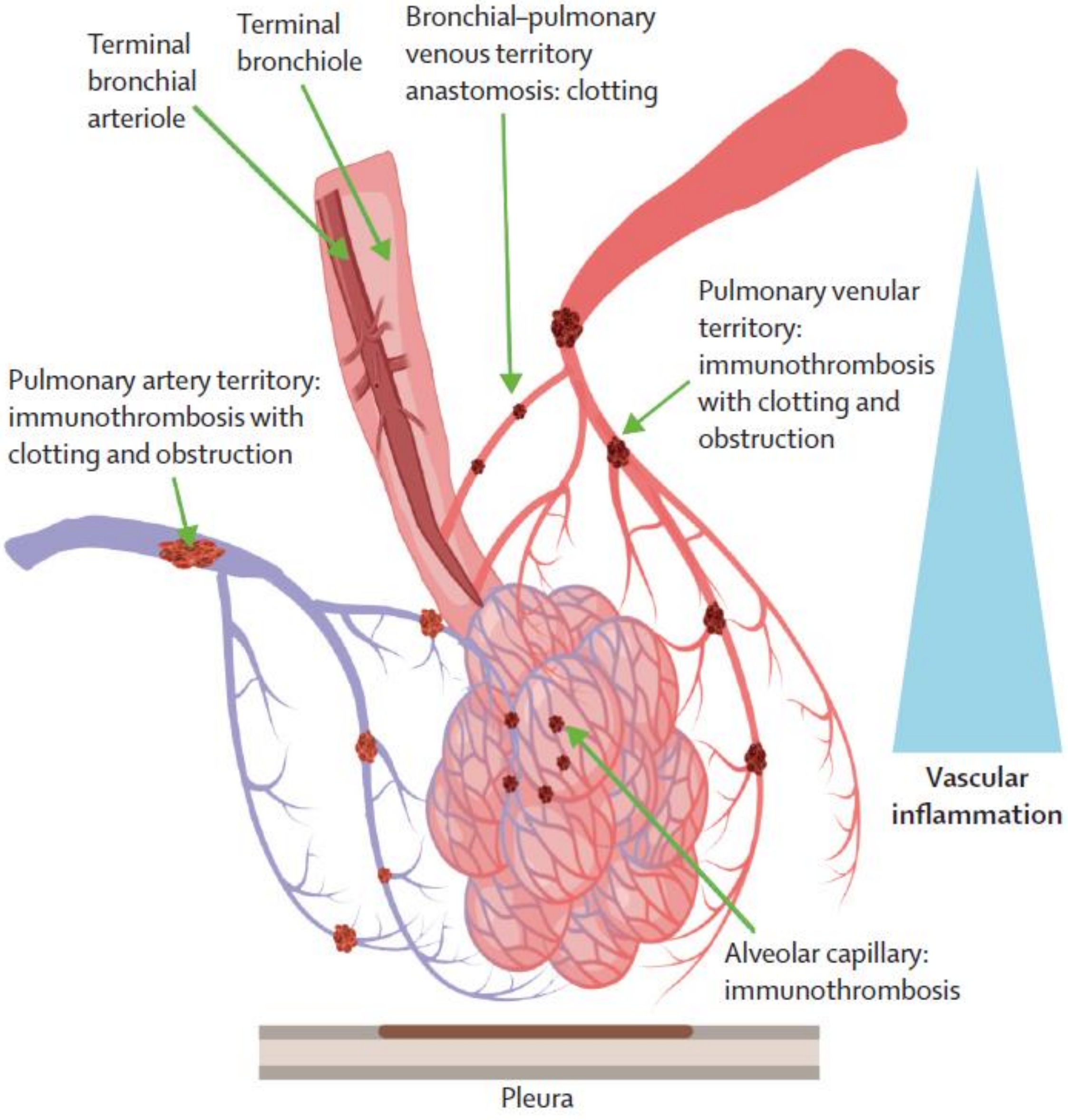
Pulmonary vascular territory immunothrombosis

The clot composition in severe COVID-19 is rich in megakaryocytes, platelets, neutrophils including NETotic neutrophils, and other immune

....something local....

McGonagle et al. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. Lancet Respir Med 2021;9:665–672.





The lung parenchyma receives oxygen input from a **triad of sources**:
dual blood supply from the pulmonary and bronchial arteries,
and a third supply directly from the alveoli

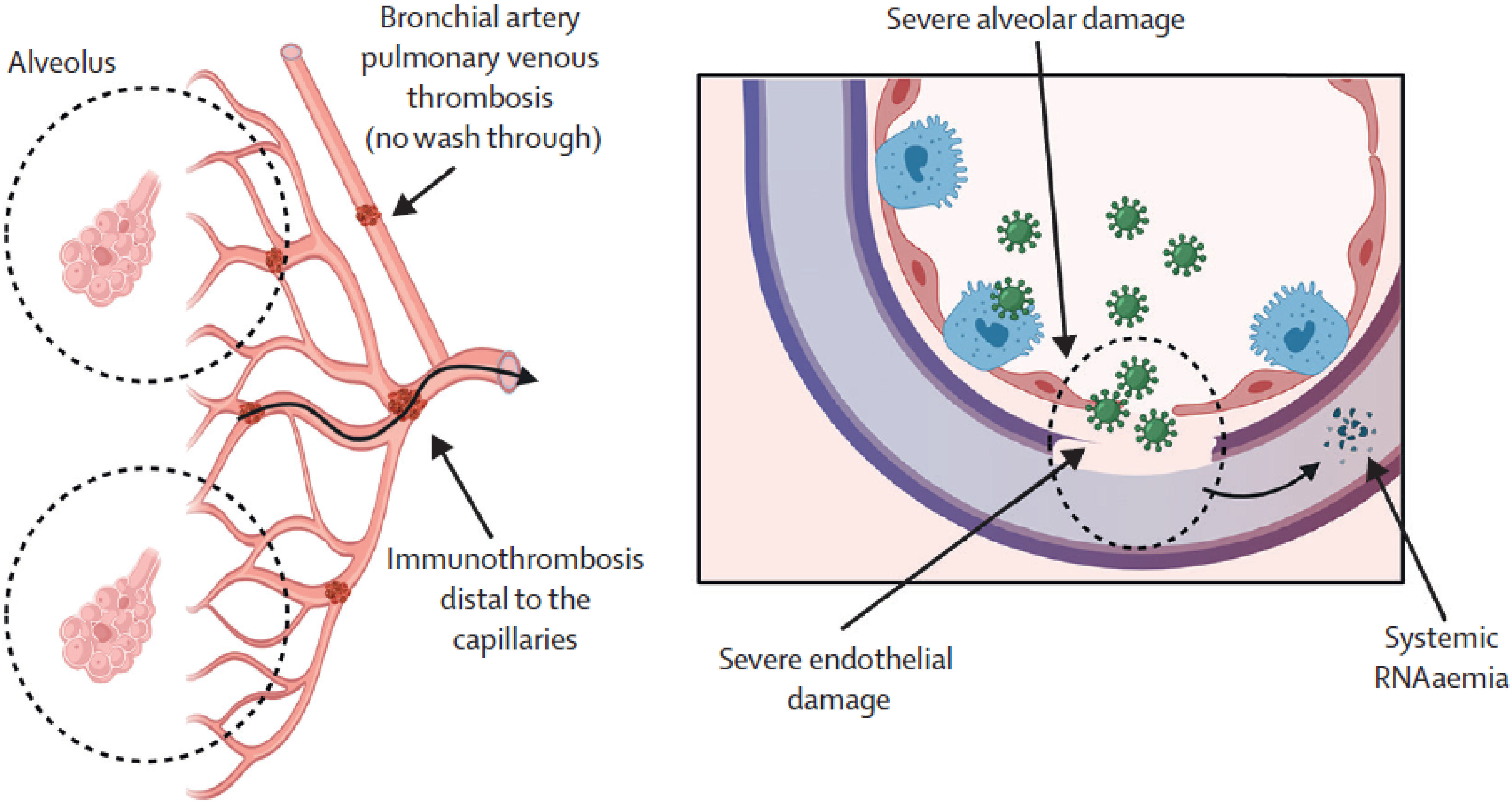
They are all involved in the local immunothrombosis

*The classical embolic occlusion of the pulmonary artery **removes only one component** of the tri compartmental model—the one that supplies **deoxygenated blood** and therefore little oxygenation to the parenchyma*

while the remaining two sources (the bronchial artery and direct oxygenation from the alveoli) remain unscathed and provide sufficient oxygenation to prevent infarction

McGonagle et al. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. Lancet Respir Med 2021;9:665–672.

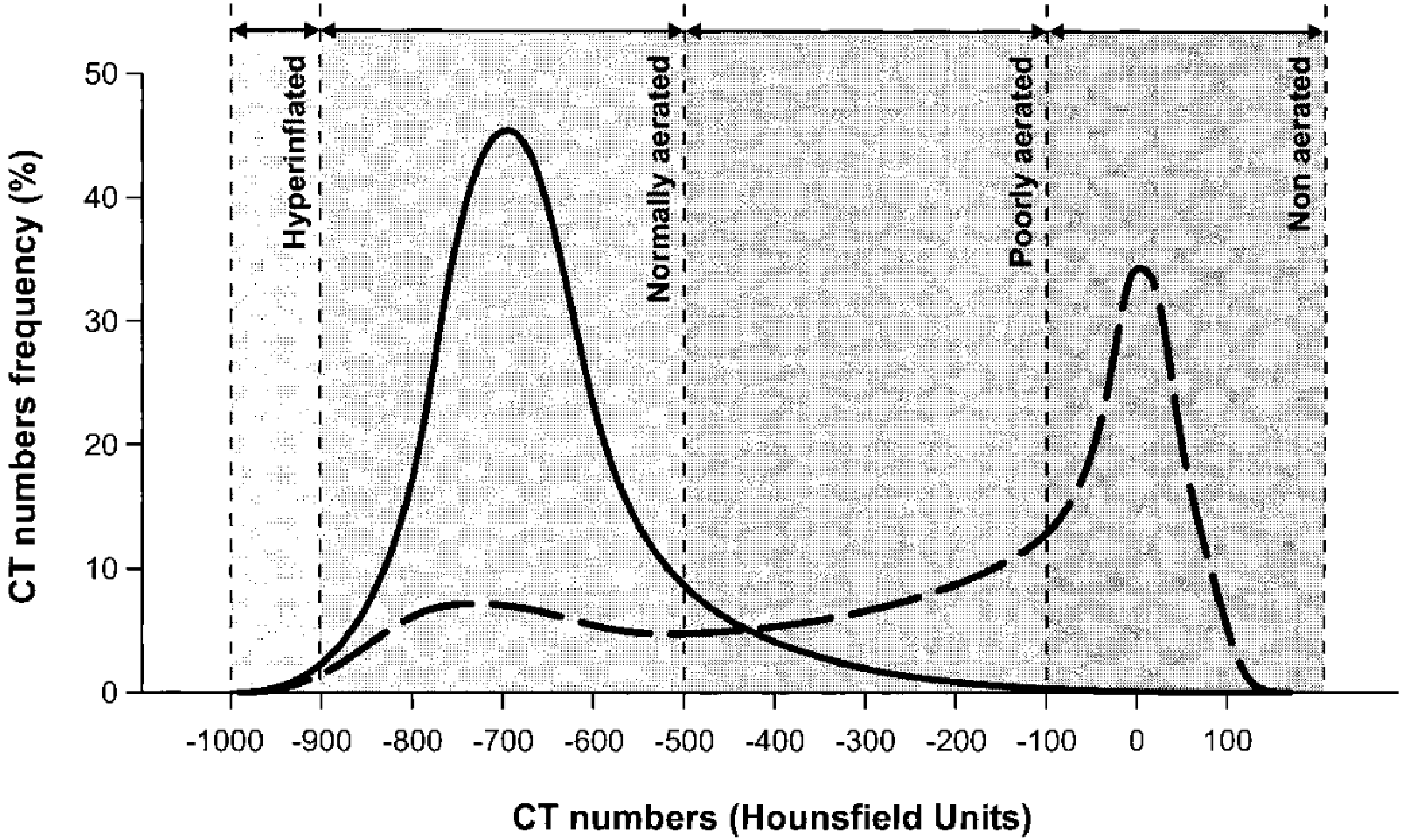
UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET



McGonagle et al. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. Lancet Respir Med 2021;9:665–672.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

COMPUTED TOMOGRAPHY



Gattinoni L, Caironi P, Pelosi P, et al.: State of the Art What Has Computed Tomography Taught Us about the Acute Respiratory Distress Syndrome ? 2001; 164:1701–1711

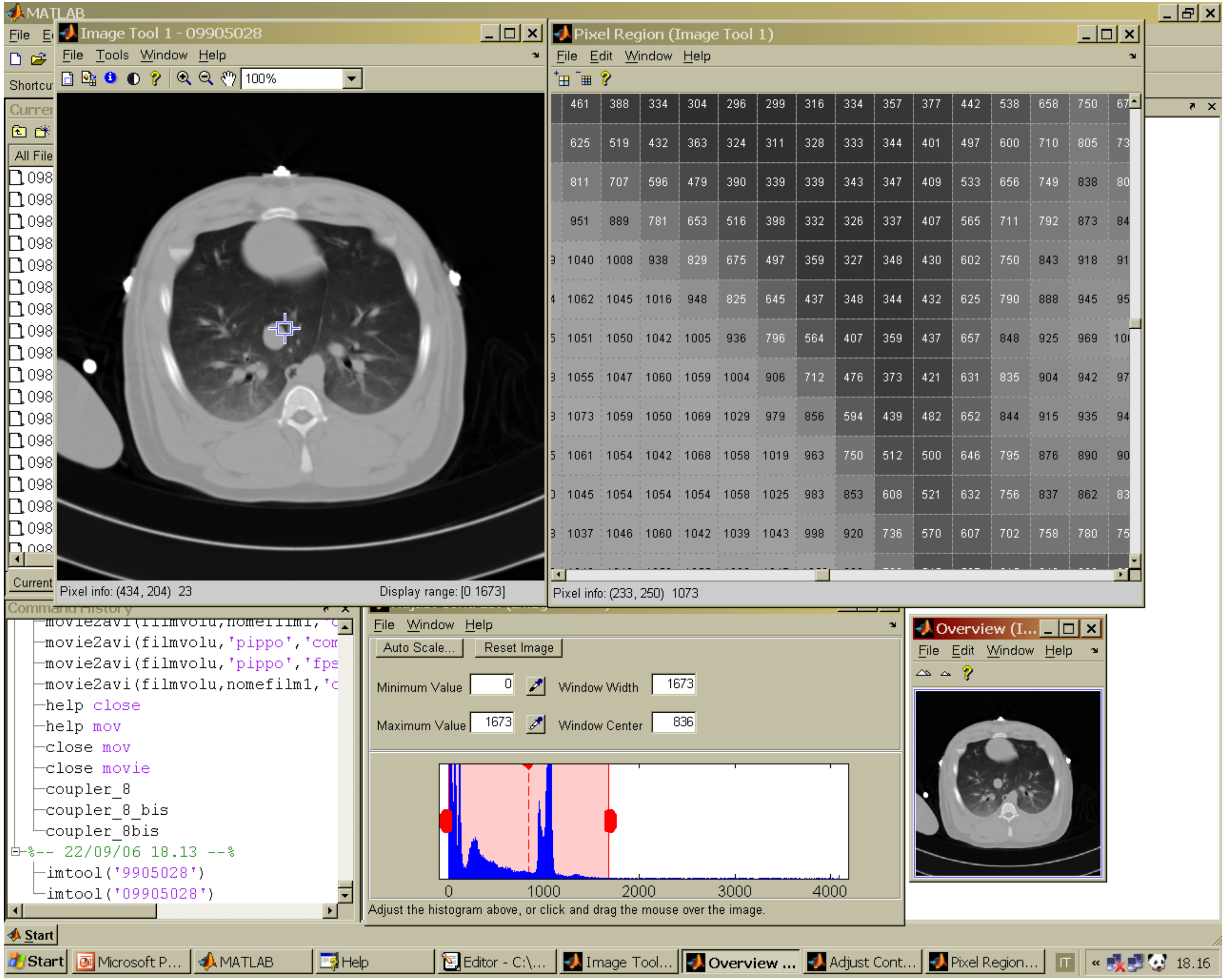
UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

Software:

MatLab ver. 7

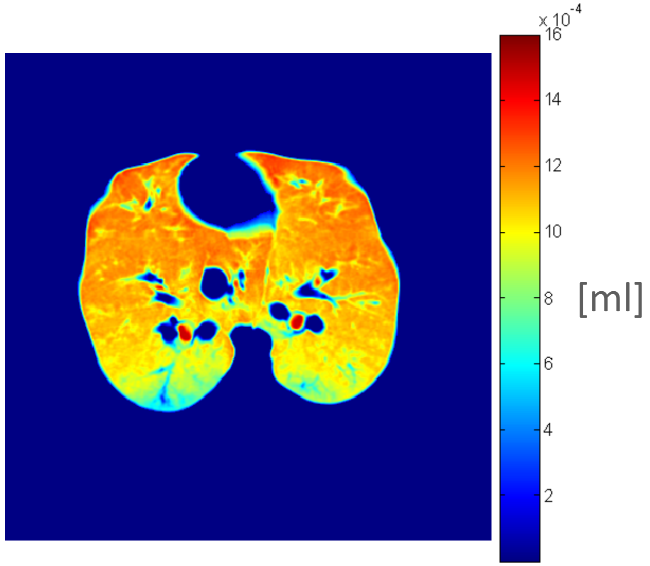
Image Processing Toolbox



Volume map of the lung

manual outlining of the lung

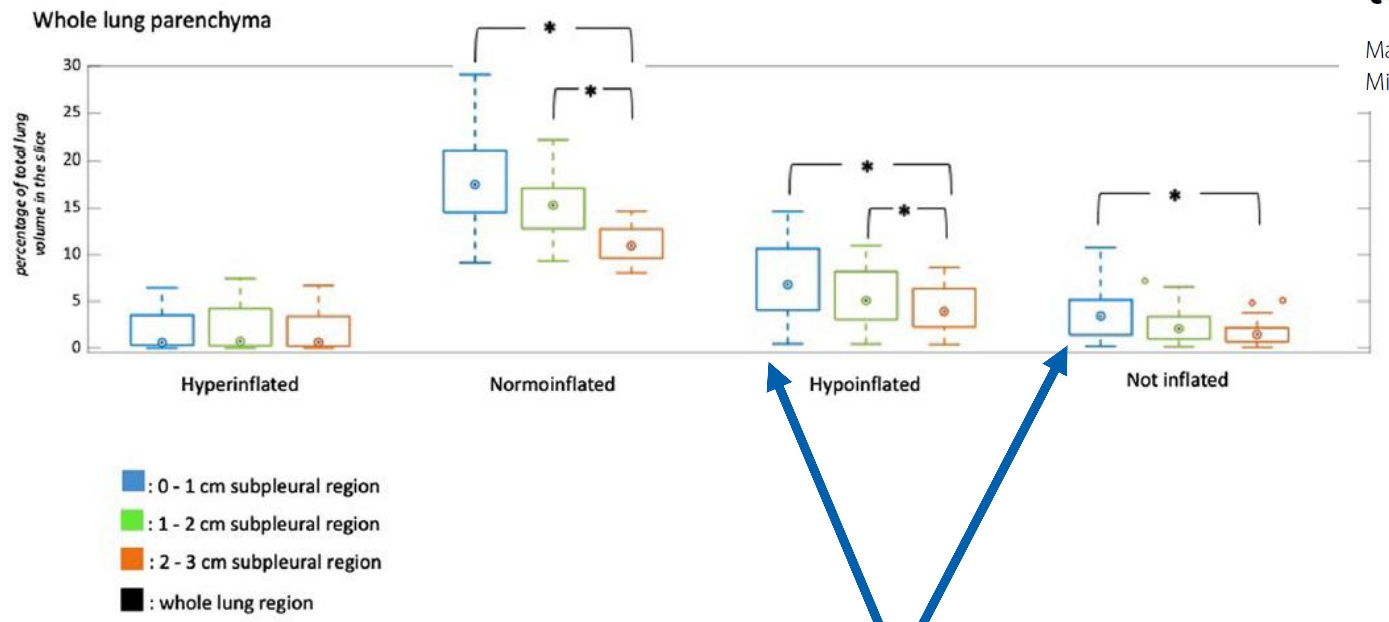
calculation of gas content voxel-by-voxel



By using matrix mathematics, it is possible to calculate and present the gas volume map of the lung

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

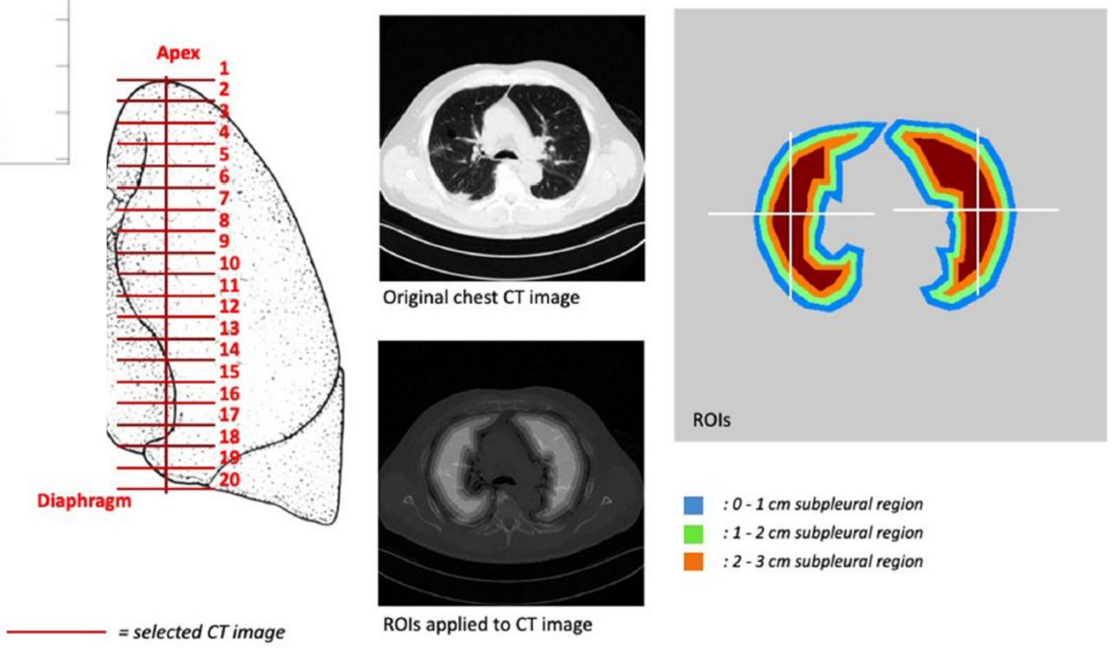


In a cohort of COVID-19 patients with severe respiratory failure, a predominant subpleural distribution of lung injury was observed, associated with a variable involvement of more central regions.

RESEARCH Open Access

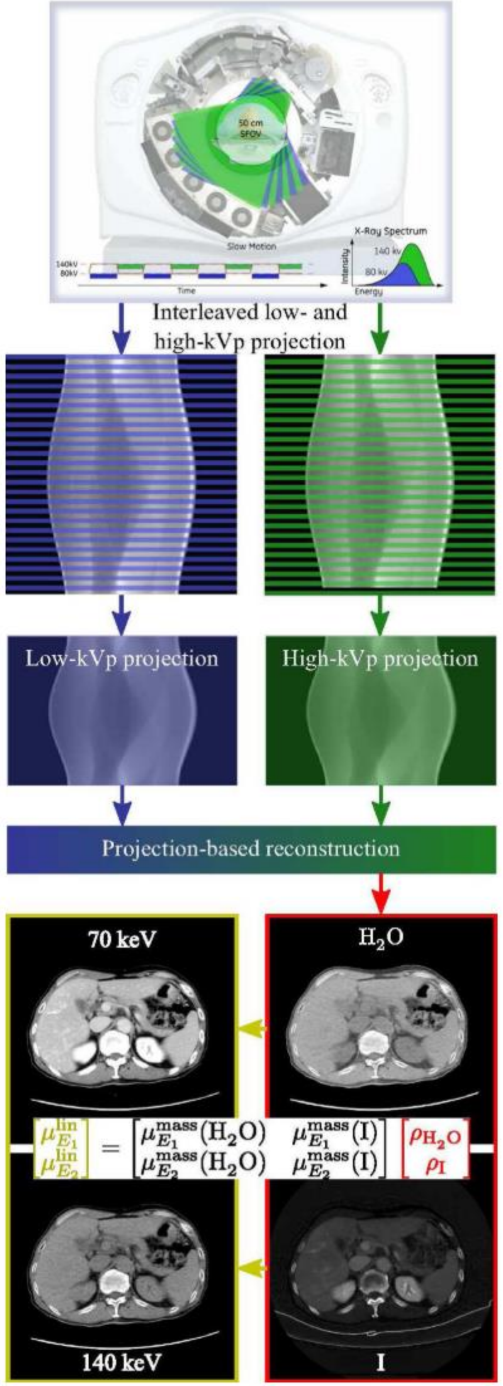
A quantitative analysis of extension and distribution of lung injury in COVID-19: a prospective study based on chest computed tomography

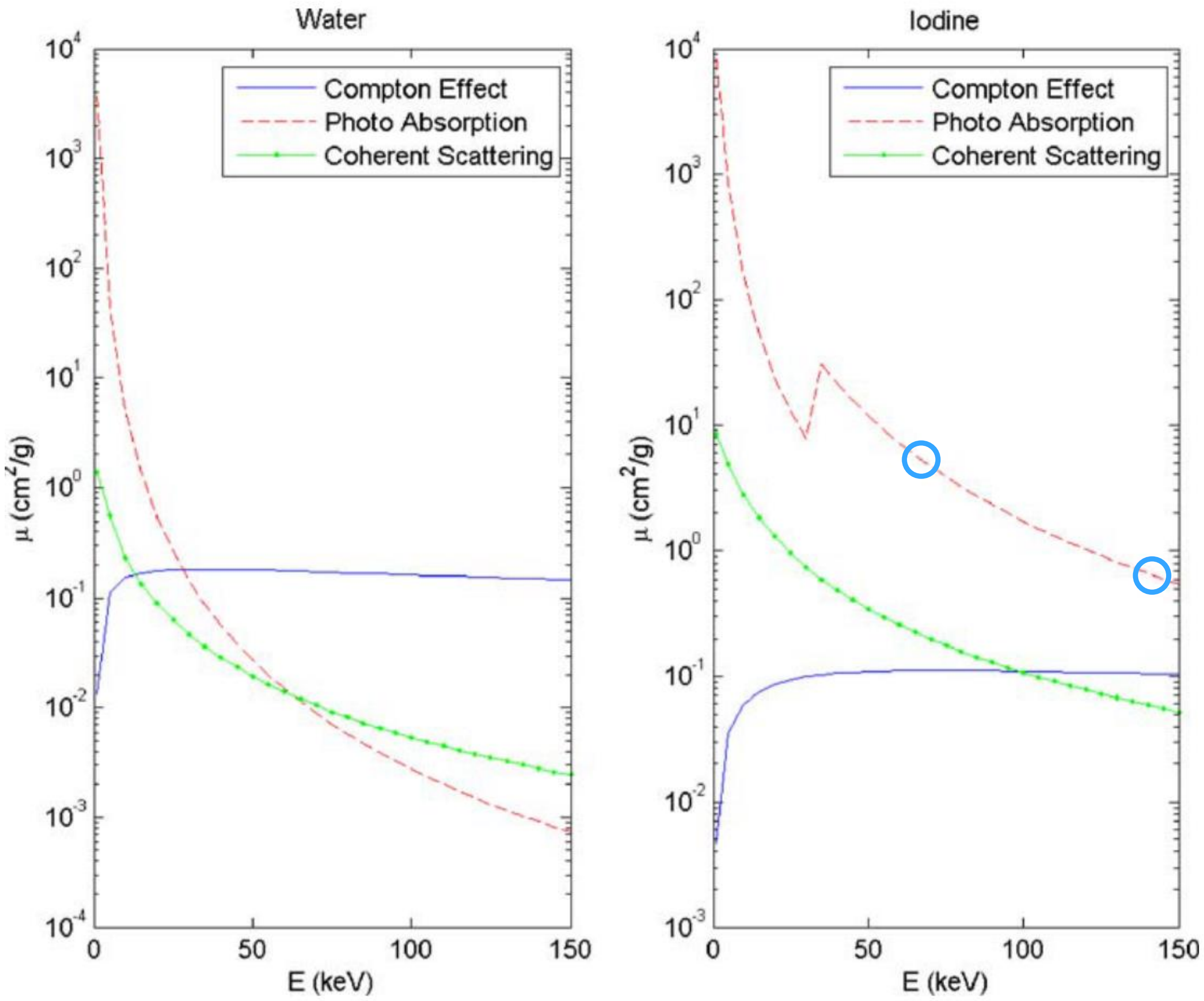
Mariangela Pellegrini[1,3], Aleksandra Larina[1], Evangelos Mourtos[2], Robert Frithiof[1], Miklos Lipcsey[1,3], Michael Hultström[1,4], Monica Segelsjö[2], Tomas Hansen[2] and Gaetano Perchiazzi[1,3*]



Pellegrini et al. Crit Care (2021) 25:276
https://doi.org/10.1186/s13054-021-03685-4

DUAL ENERGY COMPUTED TOMOGRAPHY

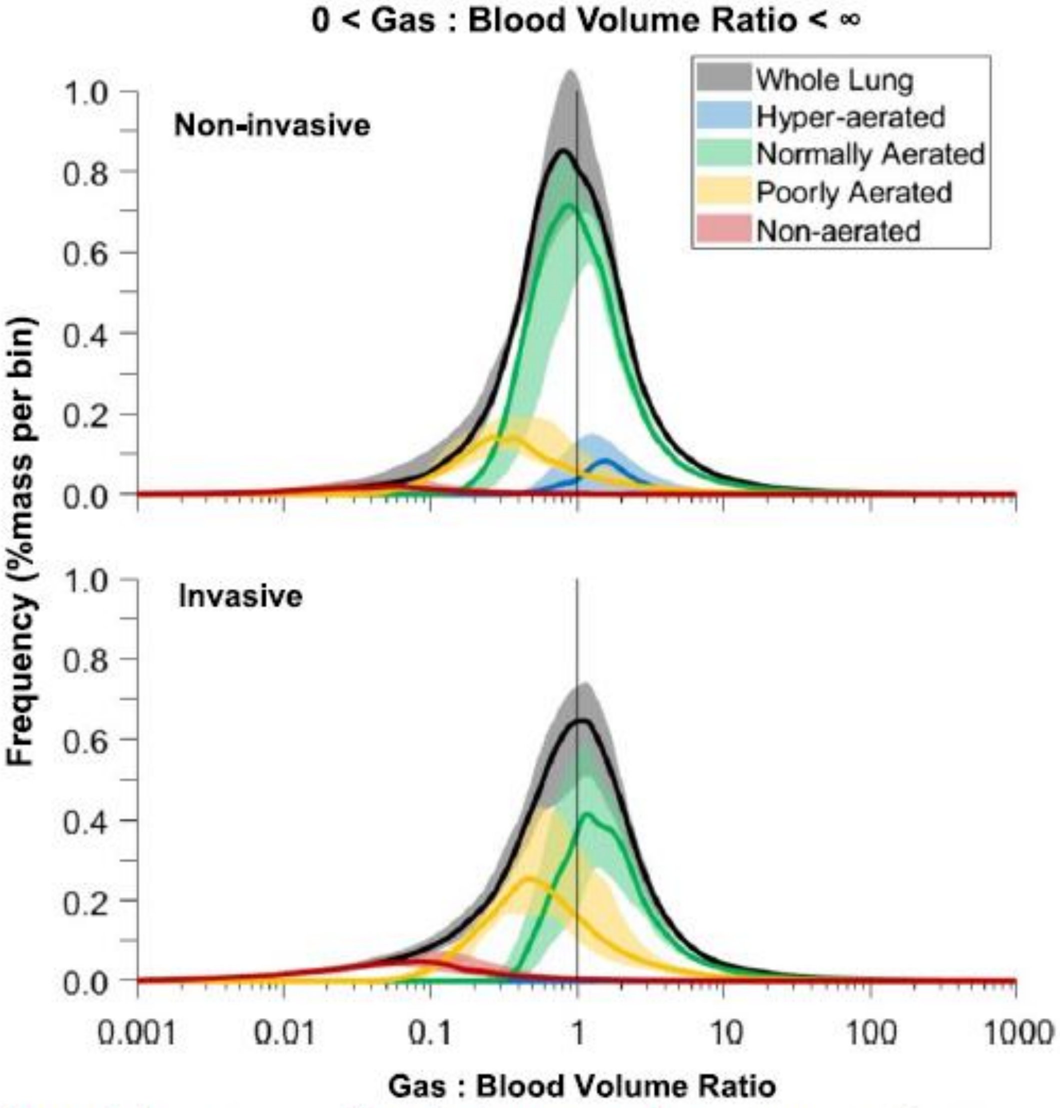




Johnson TRC, et al.: Material differentiation by dual energy CT: initial experience. *Eur Radiol* 2007; 17:1510–1517

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET



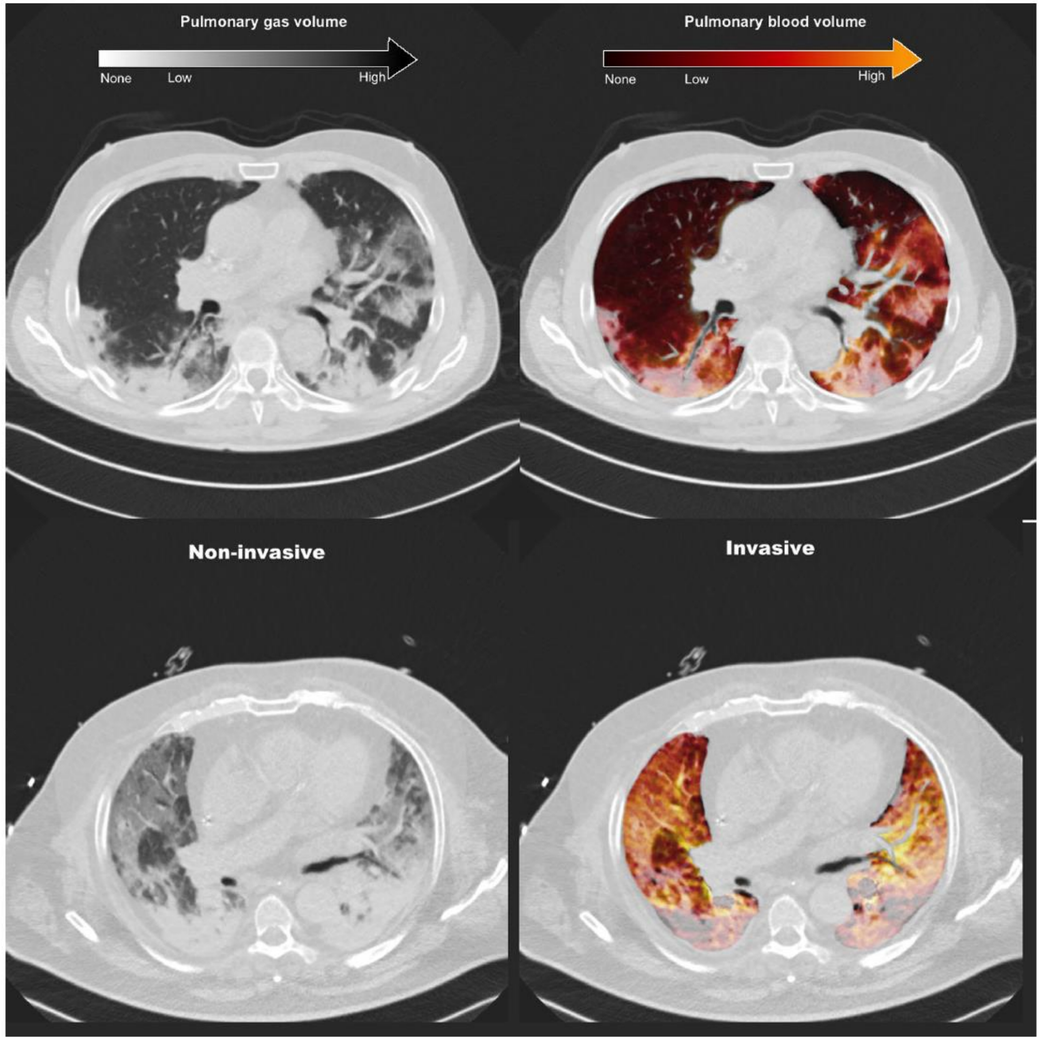
Ball et al. Crit Care (2021) 25:214
https://doi.org/10.1186/s13054-021-03610-9

Critical Care

RESEARCH Open Access

Lung distribution of gas and blood volume in critically ill COVID-19 patients: a quantitative dual-energy computed tomography study

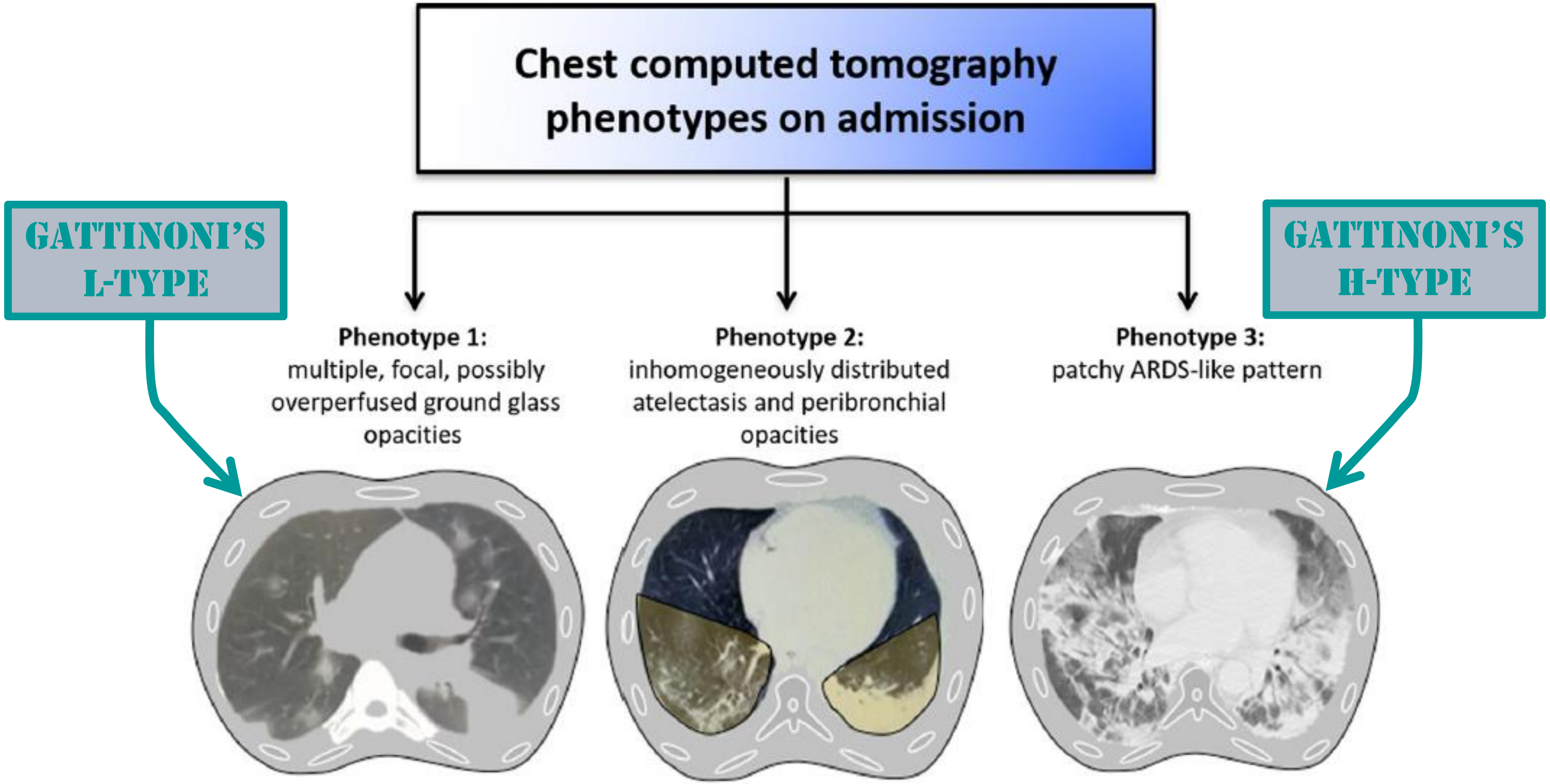
Lorenzo Ball[1,2*], Chiara Robba[1,2], Jacob Herrmann[3], Sarah E. Gerard[4], Yi Xin[5], Maura Mandelli[2], Denise Battaglini[2], Iole Brunetti[2], Giuseppe Minetti[6], Sara Seitun[6], Giulio Bovio[6], Antonio Vena[7], Daniele Roberto Giacobbe[7], Matteo Bassetti[7,8], Patricia R. M. Rocco[9], Maurizio Cereda[10], Rahim R. Rizi[5], Lucio Castellan[11], Nicolò Patroniti[1,2], Paolo Pelosi[1,2] and Collaborators of the GECOVID Group



Kan man ”behandla” V/Q?

(och när?)

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET



Robba C et al. Respir Physiol Neurobiol. 2020 May 10:103455

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Prone in Covid-19
as solution for perfusion mismatch?

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Langer *et al. Crit Care* (2021) 25:128
https://doi.org/10.1186/s13054-021-03552-2

Critical Care

RESEARCH Open Access

Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients

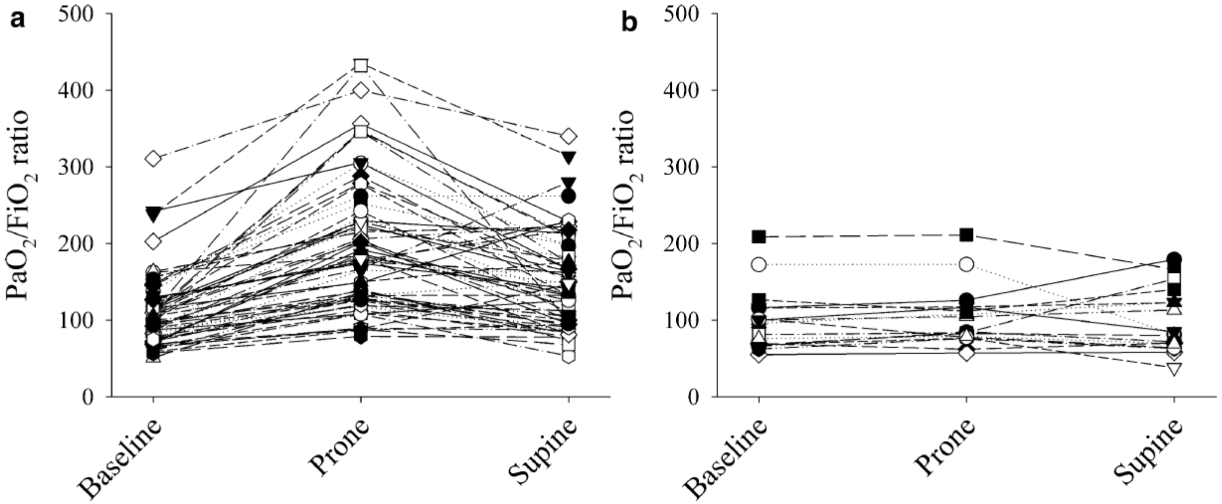
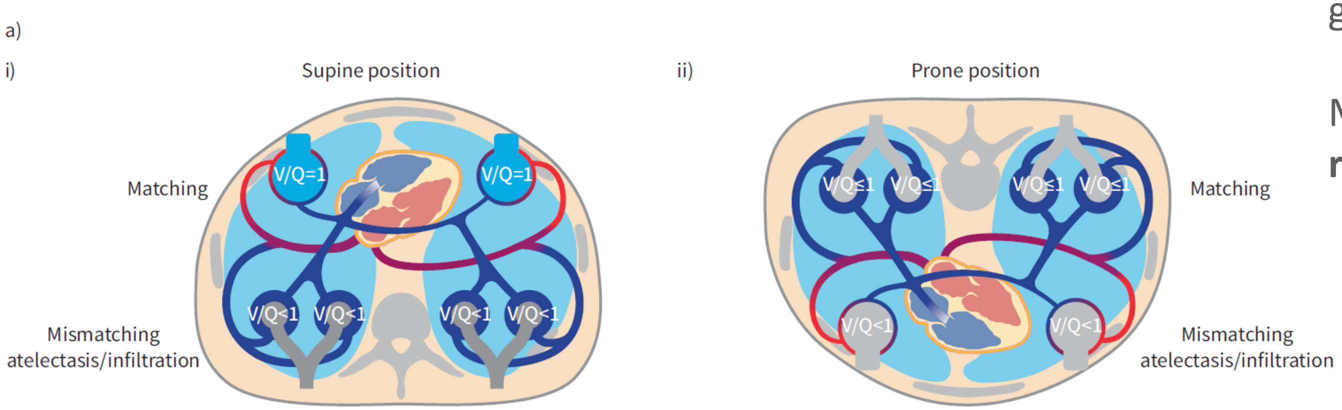


Fig. 2 Individual variations in PaO_2/FiO_2 ratio in Responders and Non-Responders during the first session of prone positioning



Gierhardt M, et al. Eur Respir Rev 2021;30:

Favours the **re-expansion of collapsed lung in dorsal** lung regions & **reduction in aeration in ventral** ones,
leading to lung recruitment and more homogenous lung aeration.

Distribution of ventilation is influenced by the postural change, lung **perfusion is usually considered less dependent** on gravity.

The net effect is usually a better ventilation-perfusion and improved gas exchange.

Moreover the more homogenous distribution of ventilation should **reduce the risk of ventilator-induced lung injury**.

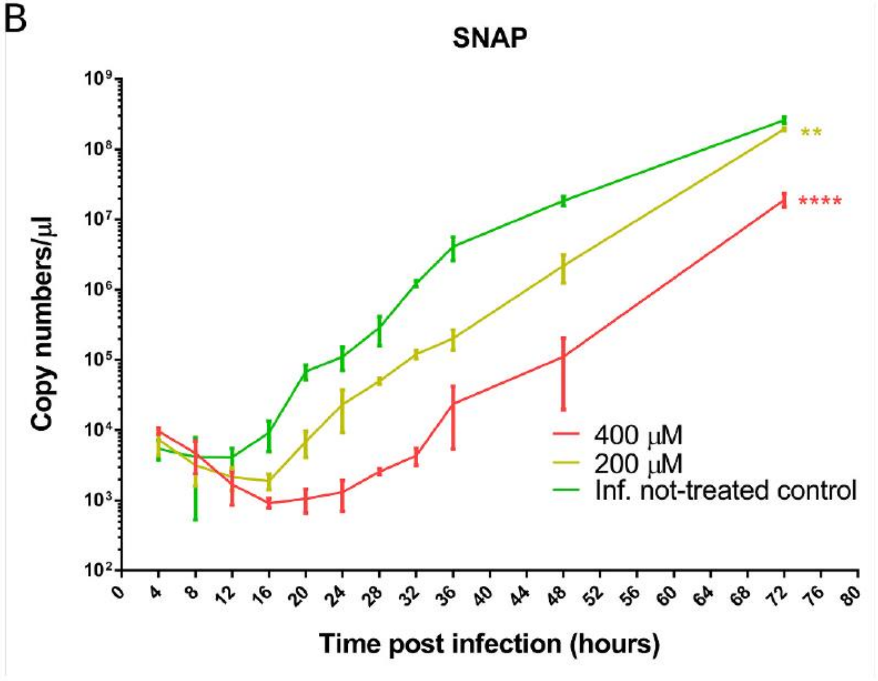
UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Behandling med Kvävemonoxid, NO

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Mitigation of the replication of SARS-CoV-2 by nitric oxide in vitro

Dario Akaberi [a], Janina Krambrich [a], Jiaxin Ling [a], Chen Luni [b], Göran Hedenstierna [c], Josef D. Järhult [d], Johan Lennerstrand [e], Åke Lundkvist [a,*]



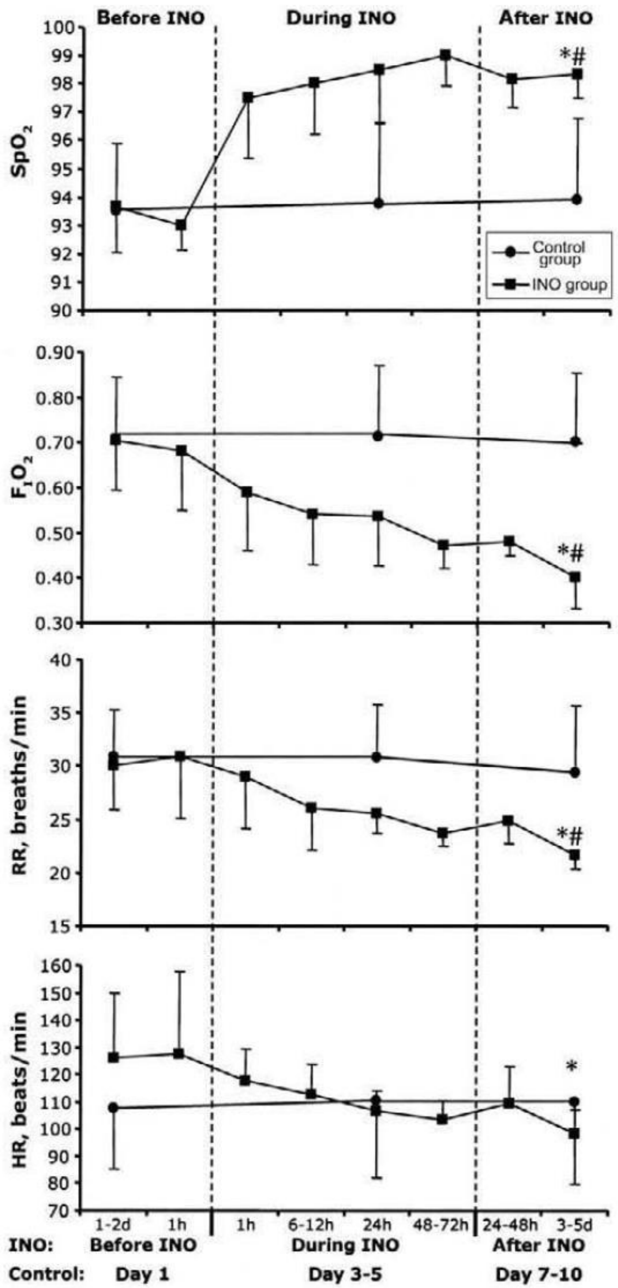
The NO-donor S-nitroso-N-acetylpenicillamine (SNAP) had a dose dependent inhibitory effect on SARS-CoV-2 replication,

Redox Biology 37 (2020) 101734

Inhalation of Nitric Oxide in the Treatment of Severe Acute Respiratory Syndrome: A Rescue Trial in Beijing

Luni Chen,[1,2] Peng Liu,[3] He Gao,[2] Bing Sun,[4] Desheng Chao,[3] Fei Wang,[3] Yuanjue Zhu,[5] Göran Hedenstierna,[1] and Chen G. Wang[4]

Clinical Infectious Diseases 2004;39:1531–5



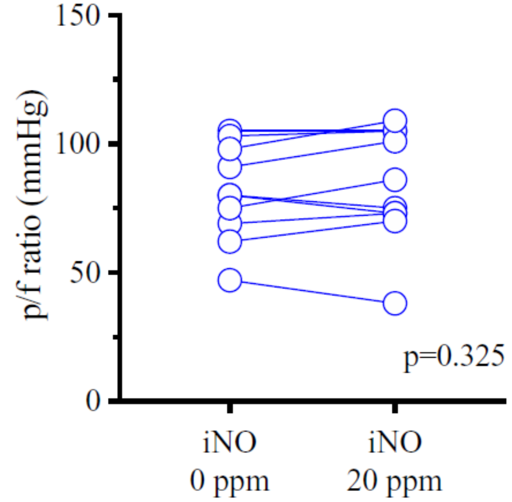
UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Abou-Arab O et al. Inhaled nitric oxide for critically ill Covid-19 patients: a prospective study. *Crit Care* 2020;24:1–3.

We administered 10 ppm of iNO through the inspiratory limb of the ventilator tubing when PaO2/FiO2 ratio was under 150

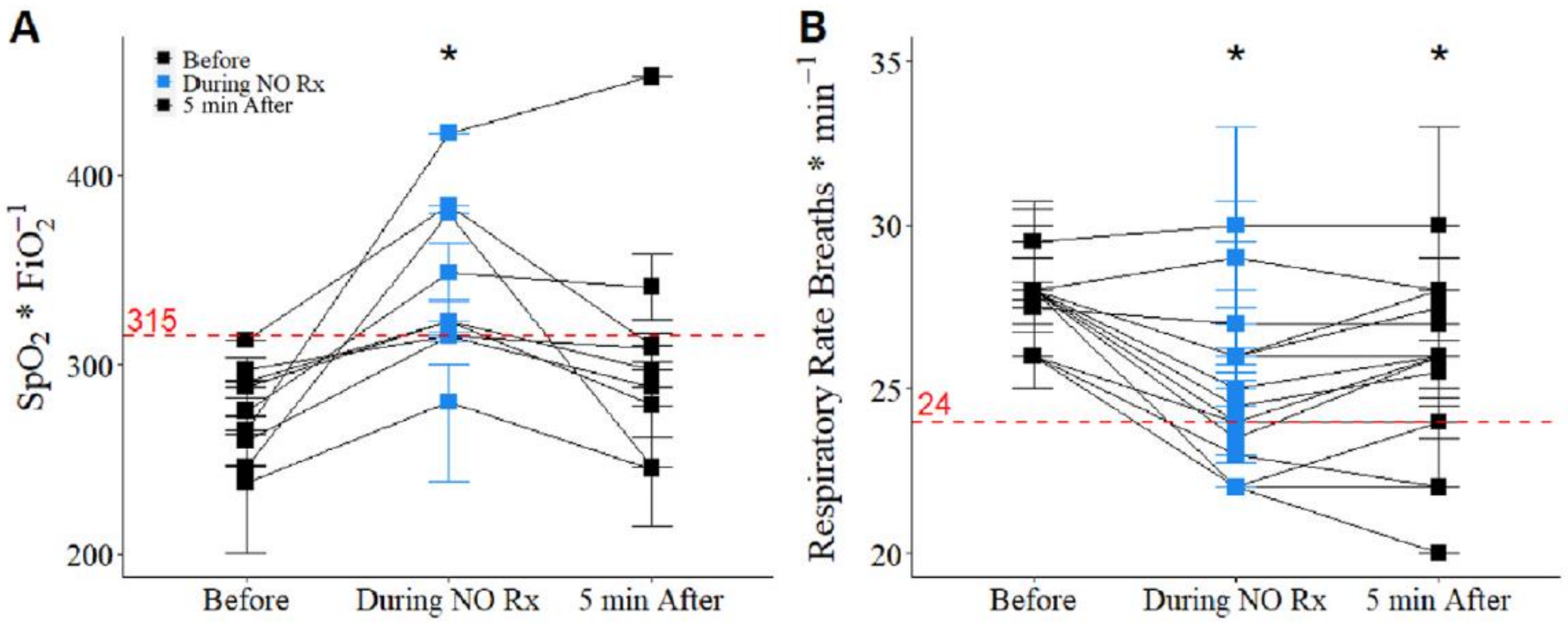
We found a response rate of 65% to iNO administration.

Ferrari M et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. *J Crit Care* 2020;60:159–160.



However, in this small series of patients with severe hypoxemia due to COVID-19, it did not significantly improve arterial oxygenation.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET



Twenty-nine COVID-19 patients received intermittent inhaled NO treatments for 30 min at **160 ppm**

Breathing NO acutely **decreased the respiratory rate** of tachypneic patients and **improved oxygenation** in hypoxemic patients.

The maximum level of nitrogen dioxide delivered was 1.5 ppm.

The maximum level of methemoglobin (MetHb) during the treatments was 4.7%.

Safaee Fakhr B, et al. Inhaled high dose nitric oxide is a safe and effective respiratory treatment in spontaneous breathing hospitalized patients with COVID-19 pneumonia. Nitric Oxide - Biol Chem 2021;116:7–13.

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

PRONMED & Respiration fokusgrupp (AnOpIVA, UU):

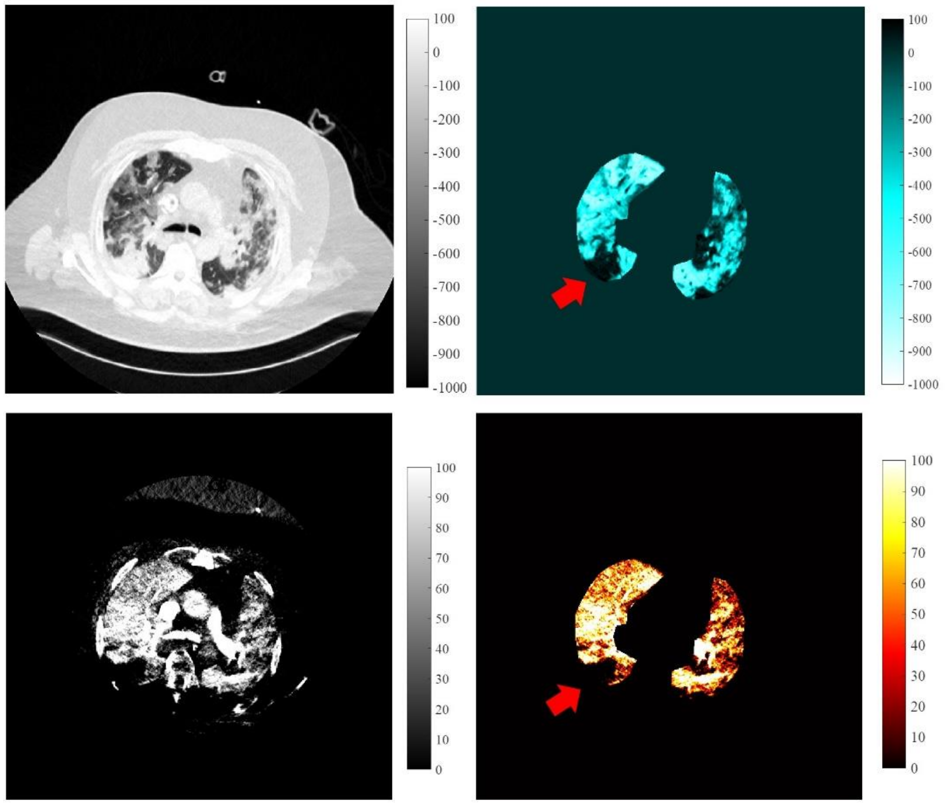
Steroids affect the distribution of lung perfusion in COVID-19 ARDS. Evidences from a dual-energy computed tomography study

Preliminary data

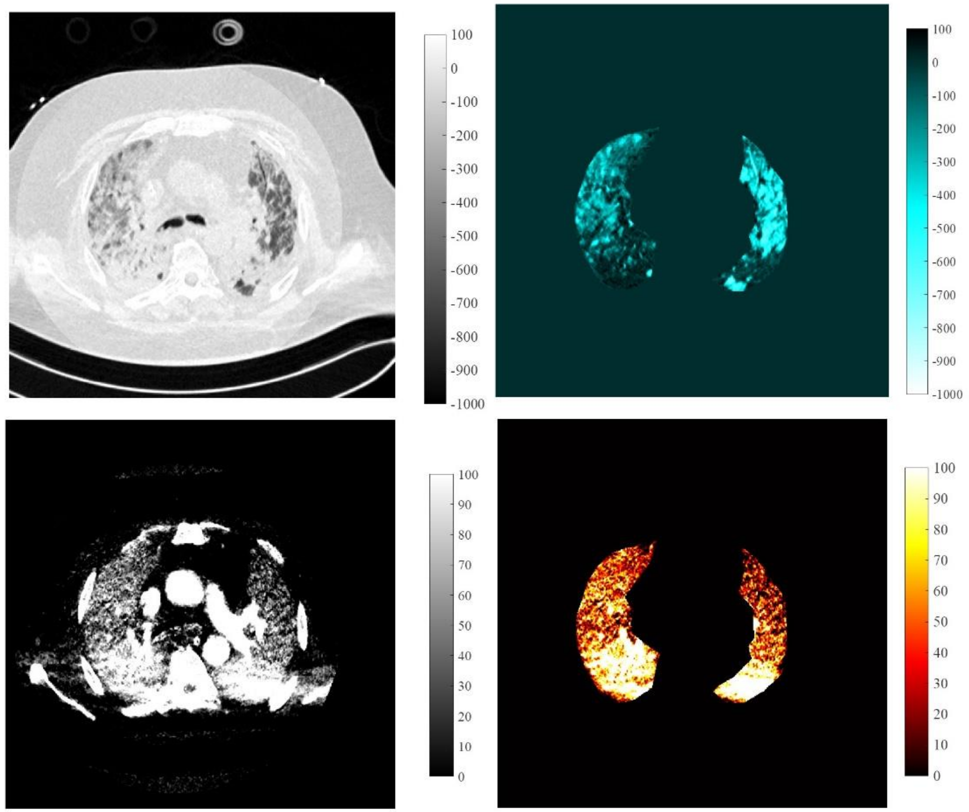
UPPSALA
UNIVERSIT

AKADEMISKA

N-Steroids Group



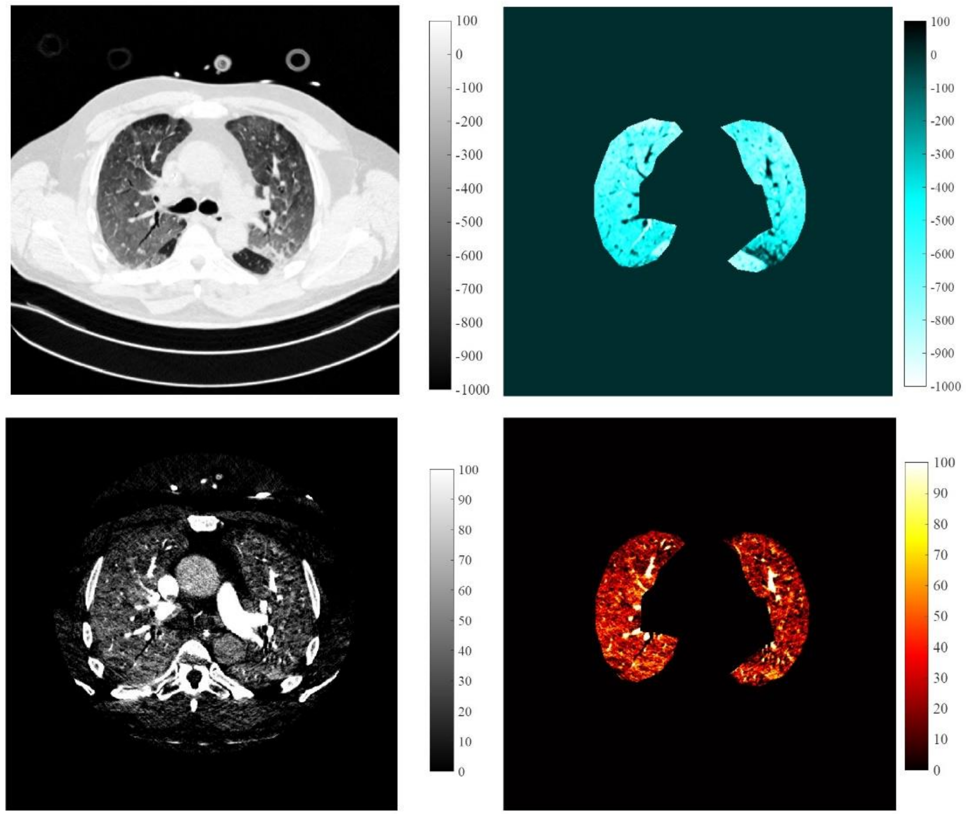
4 (pat 43_0420), 14 days from onset of symptoms, 7 days of mechanical ventilation before CT, level 12



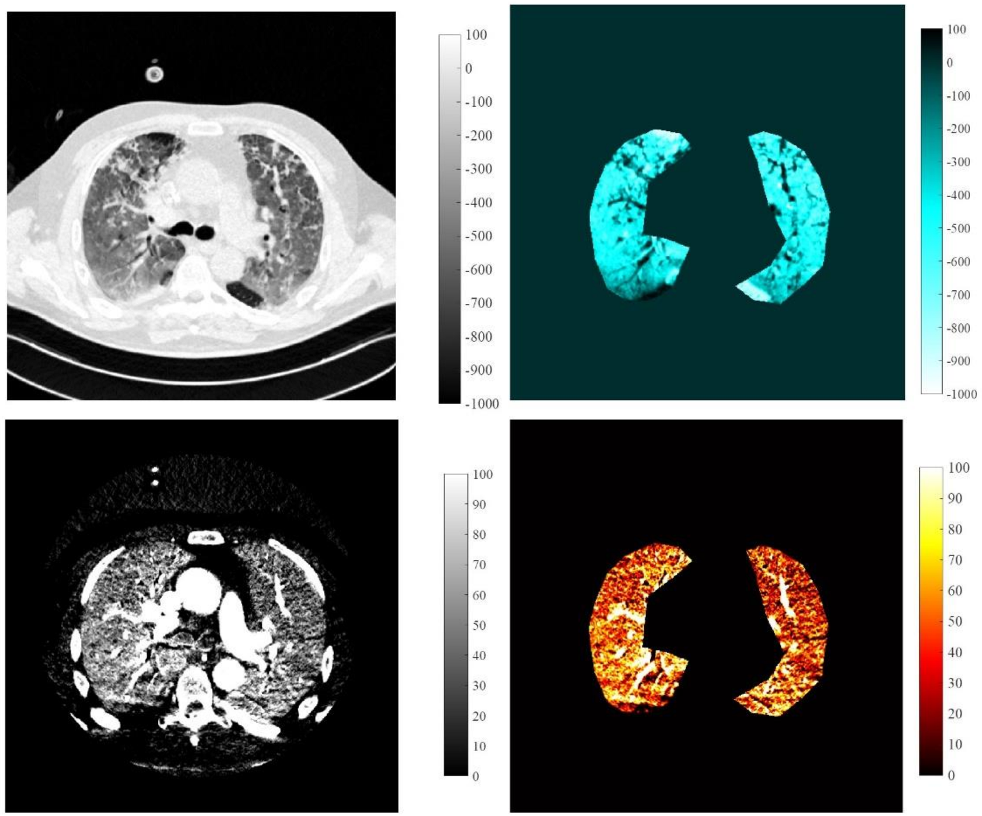
5 (pat 43_0506), 30 days from onset of symptoms, 23 days of mechanical ventilation before CT, level 11

UPPSALA UNIVERSITET | AKADEMISKA SJUKHUSET

Steroids Group



37 (pat 178_1207), 7 days from onset of symptoms, 1 days of mechanical ventilation before CT, level 11



38 (pat 178_1221), 21 days from onset of symptoms, 15 days of mechanical ventilation before CT, level 11

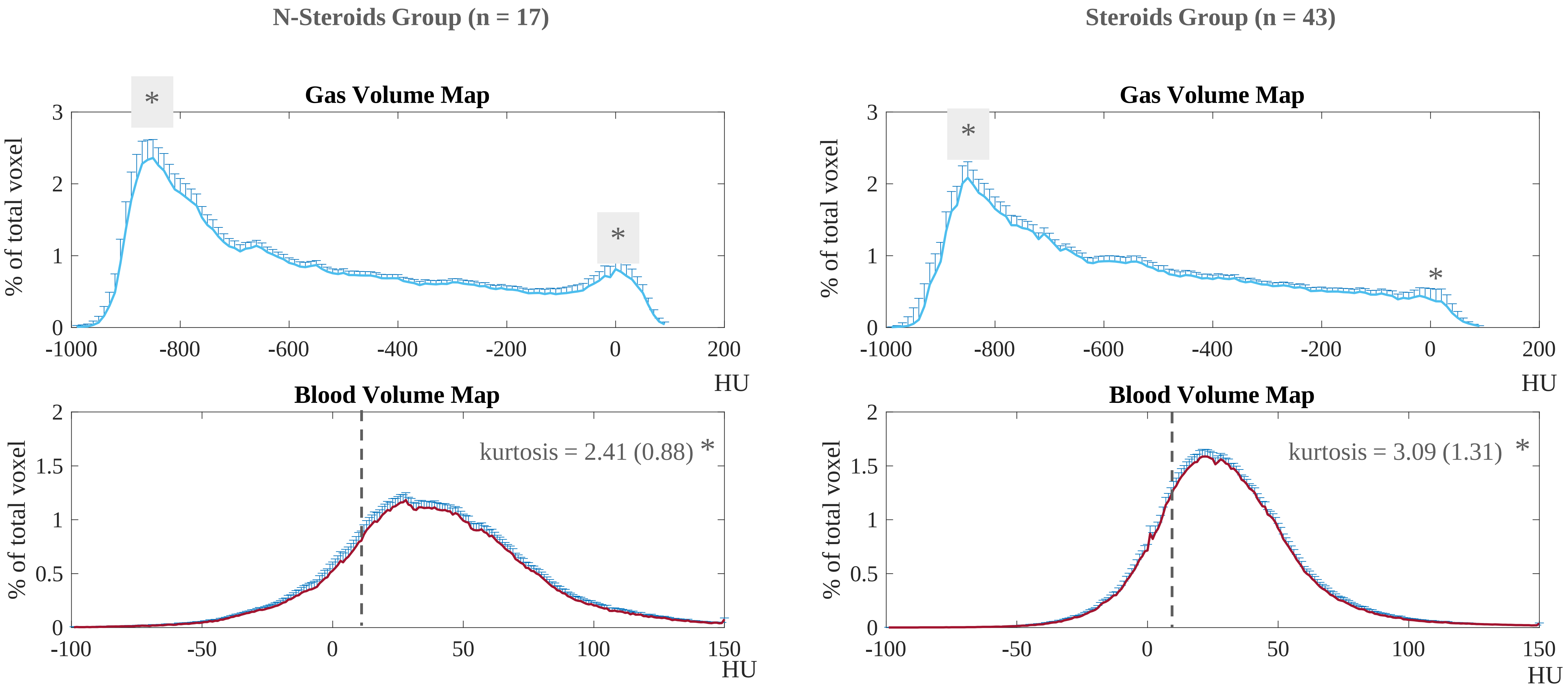


Figure 2. HU distribution for Gas Volume (above) and Blood Volume (below) maps, **in the whole lung parenchyma**, for two gropus of patiens: 1) patients not exposed to steroids (Left, n = 17) and 2) patients exposed to steroids treatment (Right, n = 43). x-axis: HU values. y-axis: percent of total voxel. (median ± SEM); kurtosis indicated as median (IQR). * to mark significant differences between the N-Steroids and the Steroids groups.


Thank you!