CHAPTER 2 - MULTI-ORGAN DAMAGE

COVID 19-
RESPIRATORY COMPLICATIONS
PART ONE- Clinical Presentation

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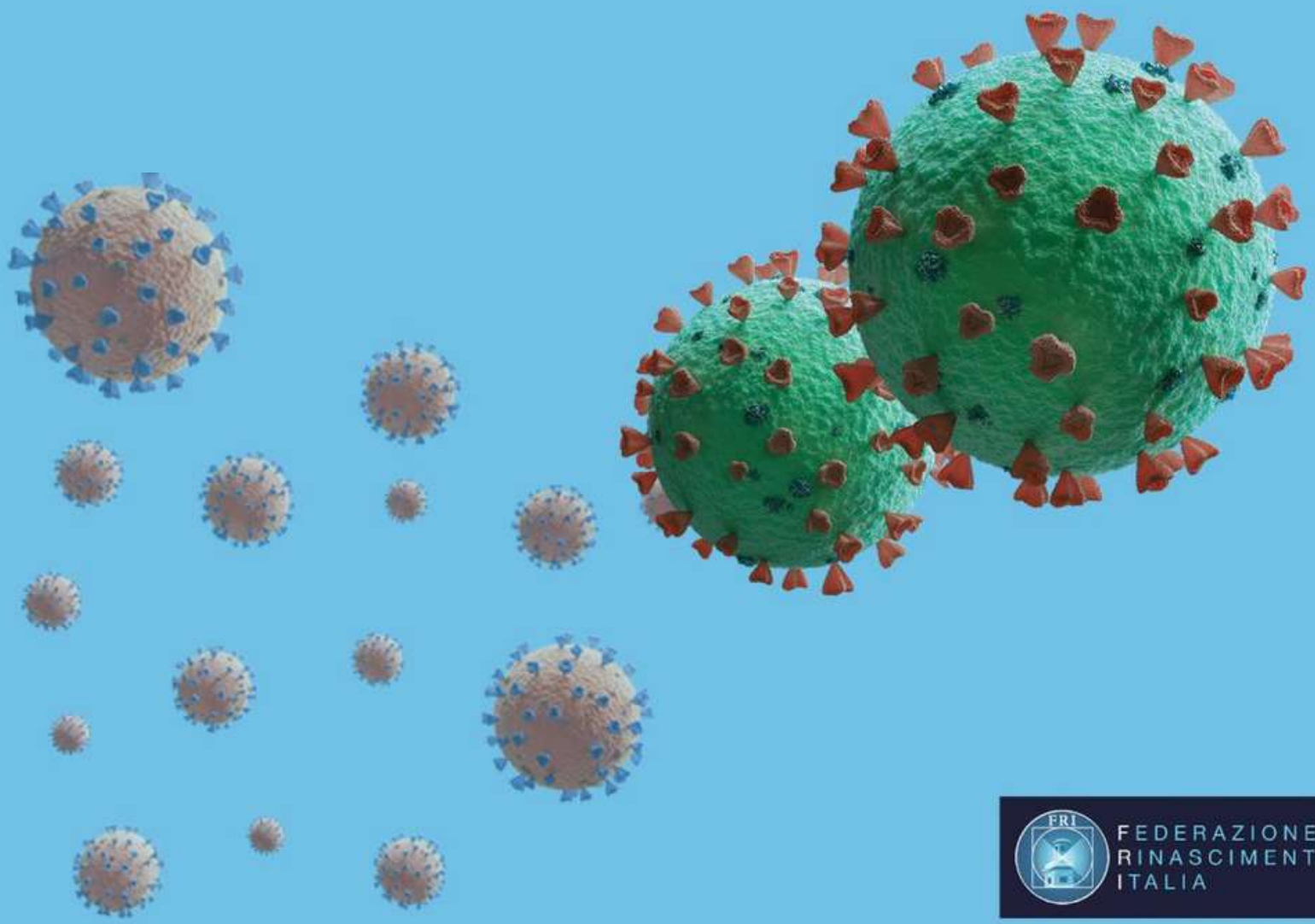

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COVID-19

CHAPTER 2 - MULTI-ORGAN DAMAGE

RESPIRATORY COMPLICATIONS PART ONE - clinical presentation

SUMMARY

INTRODUCTION

In December 2019, in Wuhan, China, an outbreak of viral pneumonia caused by a new coronavirus (from the name SARS-CoV-2: severe acute respiratory syndrome from coronavirus 2). Within months, this disease-now known as coronavirus disease 2019 (COVID-19)-has spread worldwide, causing a global health emergency.

The clinical presentation of COVID-19 ranges from asymptomatic infection to severe respiratory failure, with fever, fatigue and cough occurring in most cases[1] .
However, the pathophysiology of SARS-CoV-2 infection is complex and is now known to involve activation of the immune and hematologic systems with the onset of cytokine storm syndrome and its complications. [2]

Moreover, it is well established that the clinical spectrum of COVID-19 is not limited to local pneumonia, but rather represents a multisystem disease involving multiple organs, with pulmonary, vascular, cardiac, neurological, renal, hepatic, and gastrointestinal manifestations[3] .

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Follow-up studies in COVID-19 recovered patients - is it mandatory?
Sci Total Environ. 2020;729:139021. doi:10.1016/j.scitotenv.2020.139021
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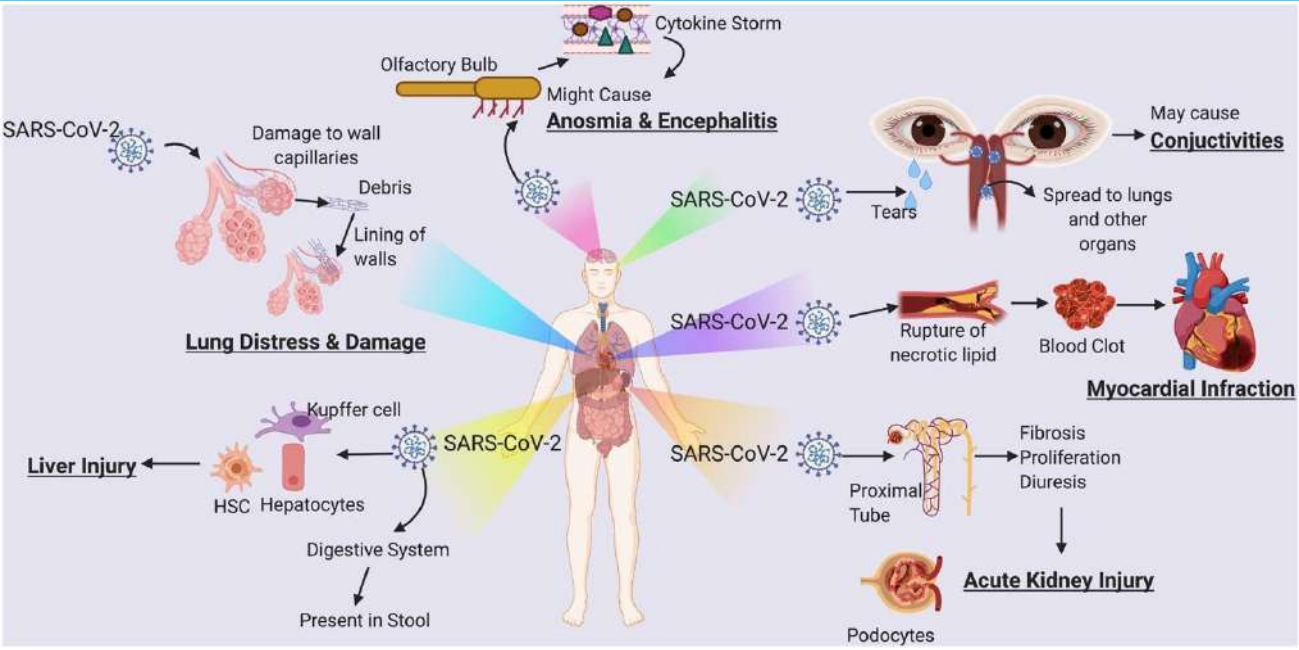
How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes
Meredith Wadman, Jennifer Couzin-Frankel, Jocelyn Kaiser, Catherine Matacic Apr. 17, 2020
10.1126/science.abc3208
https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes



Taken from https://www.sciencedirect.com/science/article/pii/S0048969720325389

Effect of SARS-CoV-2 infection on organs in different parts of the body. (Clockwise) The virus enters through the olfactory bulb causing an inflammatory response that leads to a cytokine storm. This can cause anosmia and encephalitis. Following entry into the eyes, the virus can spread through the tears and mediate spread through the nasolacrimal system to other organs of the body and can cause conjunctivitis in the eyes. As the virus enters the heart through the blood, it can cause necrotic lipid formation. When the lipid breaks down, it can cause blood clots leading to myocardial infarction. In the kidney, the virus enters tubules and proximal podocytes through ACE2 receptors. After entry, it causes deposition of extracellular matrix causing fibrosis, diuresis, and proliferation of renal cells leading to acute kidney injury. In the liver, the virus activates Kupffer cells mediating an inflammatory response. This causes activation of hepatic stellate cells (HSCs) and hepatocytes resulting in pyroptosis and fibrosis injury. In the lungs, the virus causes damage to the alveolar cell walls, resulting in the formation of debris. The debris accumulated in the alveolar cell walls causes thickening and results in lung distress and damage. This causes shortness of breath, the symptom commonly manifested in COVID-19

IN-DEPTH STUDY

Covid-19 and immune response Between weaknesses in defense and errors in offense

STEFANO VOLPI, SAMUELE NAVIGLIO , ALBERTO TOMMASINI

Understanding the pathophysiology of Covid-19 to think about a better therapeutic approach, focusing on the different stages of infection

With special attention to the early stages.

http://www.fimp-pc.it/wp-content/uploads/2020/04/covid19MB.pdf

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SARS, MERS, COVID-19: Clinical Manifestations and Organ-System Complications: A Mini Review
Pathog Dis. 2020;ftaa033. doi:10.1093/femspd/ftaa033
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The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections.
[published online ahead of print, 2020 Jul 21]. J Neuroimmune Pharmacol. 2020;1-28. doi:10.1007/s11481-020-09944-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7373339/

Recently some authors[4] have discussed that the current definition of SARS-CoV-2 (severe acute respiratory syndrome by coronavirus 2) is not quite correct, as the virus does not only cause a respiratory infection.

It has also been suggested to rename COVID-19 to "MicroCLOTS" (MICROvascular Covid-19 Lung vessels obstructive thromboinflammatory **syndrome**) as well. [5], but even this definition is limiting because COVID-19 is not only-or mainly-a vascular disease, and so a new nomenclature has been proposed that takes into account clinical evidence, in which the concept of multi-organ damage is included: "**multi-organ dysfunction by SARS-CoV-2**" (**MODS-CoV-2**).

[4] Robba C, Battaglini D, Pelosi P, Rocco PRM.
Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2.
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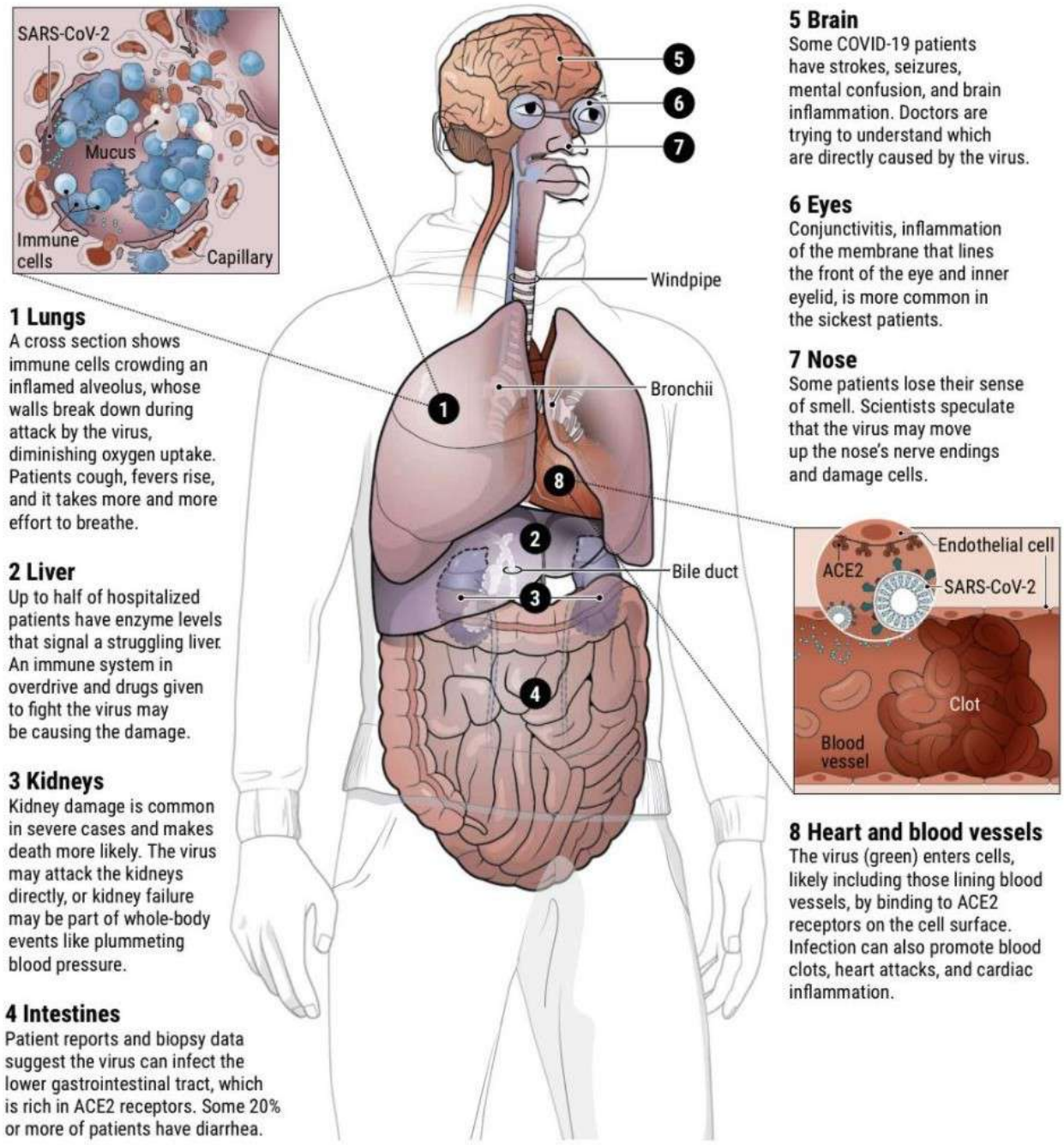
[5] Ciceri F, Beretta L, Scandroglio AM, et al.
Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis [published online ahead of print, 2020 Apr 15]. Crit Care Resusc. 2020;
https://ccr.cicm.org.au/config/cicm-ccr/media/pdf/june-covid-19/ccr_landoni120_june_v6.pdf

Lippi G, Sanchis-Gomar F, Henry BM.
COVID-19: unravelling the clinical progression of nature's virtually perfect biological weapon.
Ann Transl Med. 2020;8(11):693. doi:10.21037/atm-20-3989
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7327324/



Route https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes
INTERACTIVE FIGURE

RESPIRATORY COMPLICATIONS

Critical COVID-19 patients frequently develop a form of ARDS[6] (acute respiratory distress syndrome), in which most of the damage seems to be caused by the release syndrome of cytokines such as IL-1β, IL-18, TNF-α, IL-6, IL-8 and IL-10.

The consequences of this catastrophic inflammation include desquamation of lung epithelial cells, fibrosis, and alterations in the coagulation process. [7]

There is relatively well preserved lung mechanics despite the severity of hypoxemia, characterized by high respiratory compliance and shunt fraction, and increasing recognition of the systemic features of a hypercoagulable state in this disease. *
Therefore, the pathology and pathophysiology of COVID-19 might differ from that of typical acute respiratory distress syndrome [8]

Unfortunately, COVID-19 has the potential to cause severe pulmonary fibrosis and permanent loss of lung function at various levels.[9]

[6] https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/insufficienza-respiratory-acute-hypoxemic-insufficiency,-acute-respiratory-distress-syndrome

[7] Assessment of the pathophysiological properties of COVID-19 as a multi-organ disease
David A. Jamison Jr.
https://docs.google.com/document/d/11JPJI8ae01tcnmRl1DgMAxgKbUbetHLyN5oIXSrlS-4/edit

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Mo X, Jian W, Su Z, et al.
Abnormal pulmonary function in COVID-19 patients at time of hospital discharge.
Eur Respir J. 2020;55(6):2001217. Published 2020 Jun 18. doi:10.1183/13993003.01217-2020
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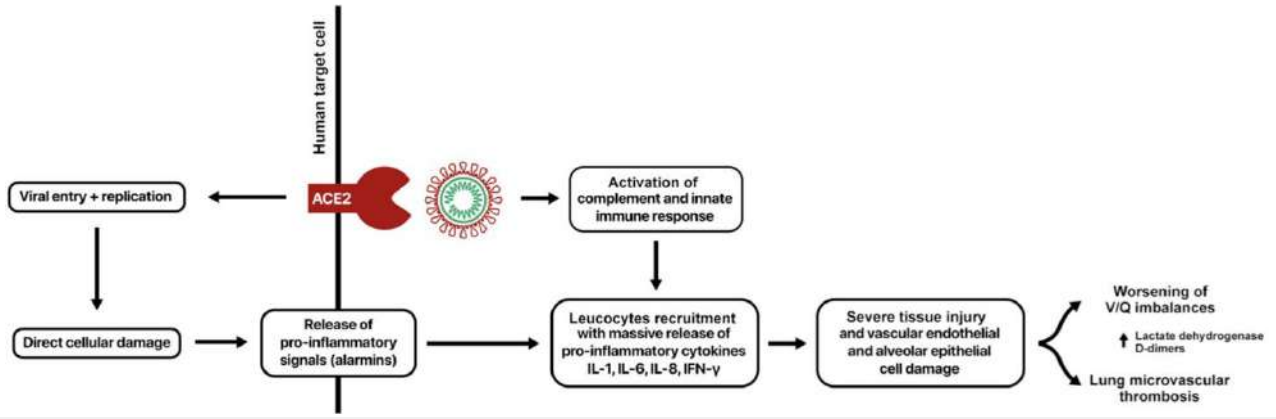

Taken from https://ccr.cicm.org.au/config/cicm-ccr/media/pdf/june-covid-19/ccr_landoni120_june_v6.pdf
Atypical acute respiratory distress syndrome operating hypothesis [MicroCLOTS (COVID-19 thrombo-inflammatory obstructive pulmonary vessel syndrome)]
ACE2 = angiotensin-converting enzyme 2; IFN = interferon; IL = interleukin; V/Q = ventilation/perfusion.

*** DEFINITIONS AND FURTHER STUDY:**

BIOLOGY OF THE LUNGS AND AIRWAYS

RESPIRATORY SYSTEM

PATHOPHYSIOLOGY OF RESPIRATORY FAILURE

COMPLIANCE IN COVID-19 PATIENT

Within this massive host immune response, lymphocytes, resident macrophages, monocytes, and neutrophils exert their powerful pro-inflammatory functions, causing massive damage to epithelial and alveolar cells. [10]

Functional implications of this peculiar pathogenesis of ARDS include a progressive worsening of ventilation/perfusion imbalances and a loss of hypoxic vasoconstriction reflexes, with a marked microvascular pulmonary thrombosis component, as suggested by increases in lactate dehydrogenase and D-dimer[11] , [12]

[10] Mastellos DC, Ricklin D, Lambris JD.
Clinical promise of next-generation complement therapeutics.
Nat Rev Drug Discov. 2019;18(9):707-729. doi:10.1038/s41573-019-0031-6
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7340853/

Thompson BT, Chambers RC, Liu KD.
Acute Respiratory Distress Syndrome.
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COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome.
Am J Respir Crit Care Med. 2020;201(10):1299-1300. doi:10.1164/rccm.202003-0817LE
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7233352/

Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ.
Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability.
Am J Hematol. 2020;95(7):E156-E158. doi:10.1002/ajh.25822
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262023/

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Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis
[published online ahead of print, 2020 Apr 15]. Crit Care Resusc. 2020;
https://ccr.cicm.org.au/config/cicm-ccr/media/pdf/june-covid-19/ccr_landoni120_june_v6.pdf

In a recent study[13] lung tissue samples from 38 consecutive patients who died due to COVID-19 between February 29 and March 24, 2020, were histologically analyzed at two reference centers for the management of the COVID-19 outbreak in northern Italy: the Luigi Sacco Hospital in Milan (20 autopsies) and the Papa Giovanni XXIII Hospital in Bergamo (18 autopsies).

All of the patients had SARS-CoV-2 infection confirmed by RT-PCR analysis of oro-pharyngeal swab specimens taken upon admission to the hospital, and all of them underwent molecular testing for common respiratory viruses and bacteria by the microbiology laboratories in their respective hospitals, with negative results.

All cases showed features of the exudative and proliferative phases of diffuse alveolar damage, which included capillary congestion (in all cases), necrosis of pneumocytes (in all cases), hyaline membranes (in 33 cases), interstitial and intra-alveolar edema (in 37 cases), pneumocyte hyperplasia type 2 (in all cases), squamous metaplasia with atypia (in 21 cases), and fibrin-platelet thrombi (in 33 cases).

The inflammatory infiltrate, observed in all cases, was largely composed of macrophages in the alveolar lumen (in 24 cases) and lymphocytes in the interstitium (in 31 cases).
Immunohistochemistry with anti-CD61 antibodies identified increased numbers of megakaryocytes in lung capillaries in 33 (87%) cases.

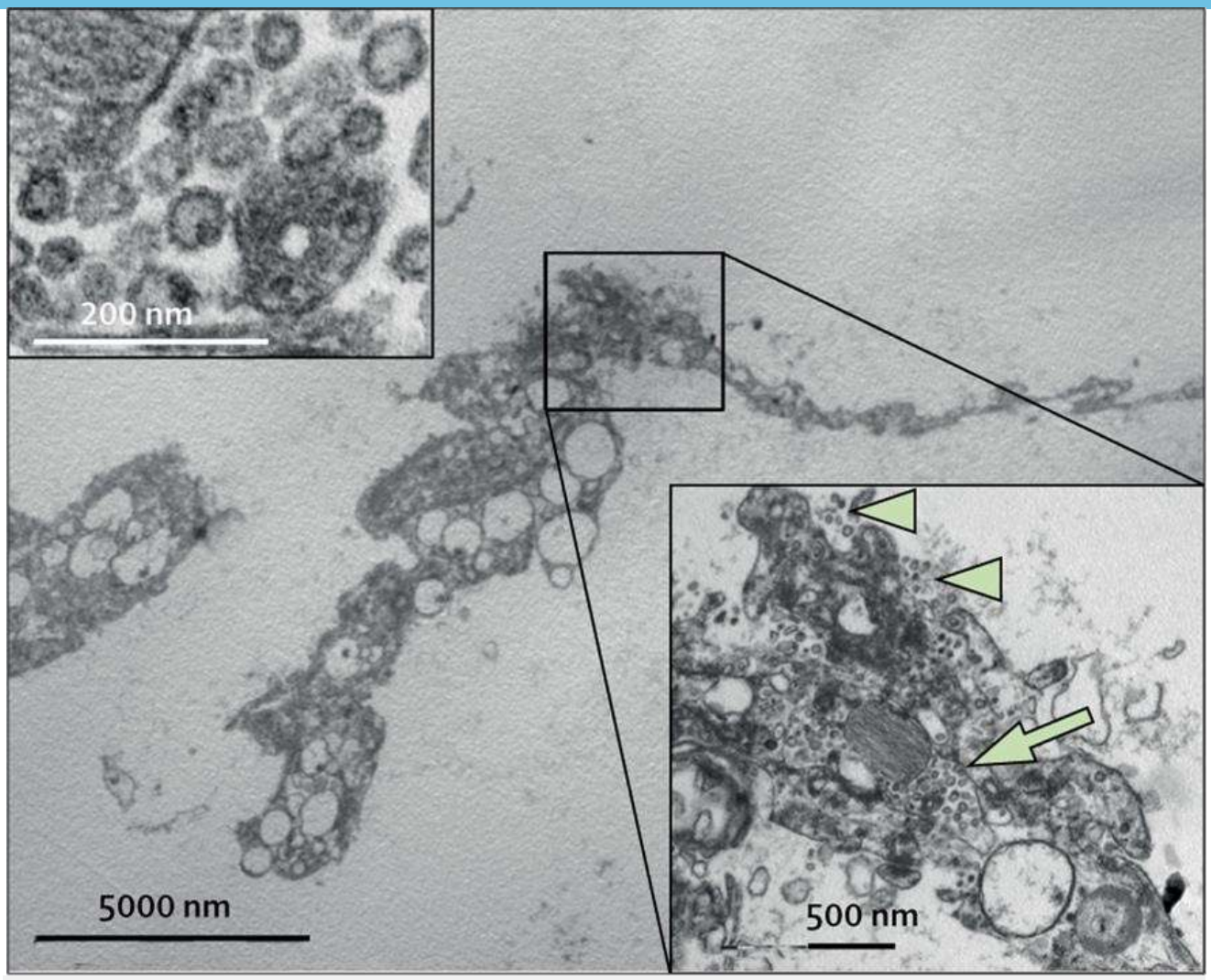
Electron microscopy revealed that the viral particles were localized predominantly in pneumocytes.

Danzi GB, Loffi M, Galeazzi G, Gherbesi E.
Acute pulmonary embolism and COVID-19 pneumonia: a random association?
Eur Heart J. 2020;41(19):1858. doi:10.1093/eurheartj/ehaa254
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184406/

Mariano RZ, Ramos MC, Reis F.
COVID-19 and pulmonary embolism: Do not forget the association!
Rev Soc Bras Med Trop. 2020;53:e20200234. Published 2020 Jun 8. doi:10.1590/0037-8682-0234-2020
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7294956/

Flor N, Tonolini M.
From ground-glass opacities to pulmonary emboli. A snapshot of the evolving role of a radiology unit facing the COVID-19 outbreak.
Clin Radiol. 2020;75(7):556-557. doi:10.1016/j.crad.2020.04.009
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7205649/

[13] Carsana L, Sonzogni A, Nasr A, et al.
Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study
[published online ahead of print, 2020 Jun 8]. Lancet Infect Dis. 2020;S1473-3099(20)30434-5. doi:10.1016/S1473-3099(20)30434-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7279758/



Taken from https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30434-5/fulltext
Ultrastructural examination revealed particles indicative of viral infection in nine (90%) of the ten cases analyzed. The particles had an average diameter of about 82 nm and protuberances of about 13 nm in length. The particles, presumed to be virions, were mainly located along plasmalemma membranes and within cytoplasmic vacuoles, as described for other coronaviruses. [14] The infected cells were type 1 and type 2 pneumocytes; however, in two cases, particles were observed in alveolar macrophages, albeit sparsely. No virus-like particles were observed in multinucleated cells. Ultrastructural analysis of alveolar capillaries frequently showed platelet and fibrin spines within the lumen, but no virion-like particles were detected in endothelial cells.

Electron microscopy studies have been challenged recently by several physicians including Dr. A. Klaufman and Dr. Fabio Franchi, who have questioned the existence of virus particles on the basis of similarity to exosomes produced by cells following the inflammatory process, containing waste toxins. [15]
The implication of exosomes in immunopathology by COVID-19 and the similarity between virus and exosomes will be discussed later.

[14] Stertz S, Reichelt M, Spiegel M, et al. T
The intracellular sites of early replication and budding of SARS-coronavirus.
Virology. 2007;361(2):304-315. doi:10.1016/j.virol.2006.11.027
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7103305/

[15] What I Think COVID-19 Really Is
Andrew Kaufman, M.D.
https://drive.google.com/file/d/1SXe2VcQDYgfyKAdtDaB8jYFdT0emD5pD/view?fbclid=IwAR1uH3EyRML4GZVHGvlqWPjfrNryzWdM_HSc8CwO1cWReOo81FCPlg4J5Fs

COVID-19 pandemic? The tests
By Fabio Franchi (Version 1, April 3, 2020,)
http://www.sspp.it/wp-content/uploads/2020/04/COVID-colpevole-senza-regolare-processo-ff_.pdf

ROLE OF THORACIC TC IN THE MANAGEMENT OF SUSPECTED PATIENTS [16]

Computed tomography plays a key role in the management of COVID-19 pneumonia, particularly for early evaluation, allowing rapid triage of dyspneic patients, and also in case of clinical worsening to detect complications, particularly thromboembolic.

The extent of lesions detected on lung CT is related to clinical severity and should be assessed semiquantitatively by the radiologist.

In the near future, artificial intelligence techniques should make it possible to automate the positive diagnosis and quantitative assessment of lesions and perhaps enable the extraction of biomarkers to predict the outcome of COVID-19 patients.

IN-DEPTH STUDY

"Frosted Glass" Images and the "Beehive Lung" in CT, Explained by the COVID-19 Pneumologist:

what the radiologist needs to know.

Thoracic radiology for beginners

According to the ESR/ESTI advisory document and the recommendations of the French Society of Thoracic Imaging, unmodified chest CT is currently indicated for patients presenting with dyspnea, polypnea, or desaturation in order to refer them to "COVID" or "non-COVID" departments, pending the results of RT-PCR[9] .

The sensitivity of chest CT for the diagnosis of COVID-19 is more than 90%, with false-negative results mainly in patients who have been symptomatic for less than 3 days [5],[10] .
The specificity of CT is more variable. Series from China and Italy reported specificity values between 25% and 5 6 % . [5],[11] .
A meta-analysis, including mainly Asian studies, reported sensitivity and specificity of 94% and 37%, respectively, for the diagnosis of COVID-19 pneumonia [12] .

[16] Bibliography reference article in square brackets Jalaber C, Lapotre T, Morcet-Delattre T, Ribet F, Jouneau S, Lederlin M. Chest CT in COVID-19 pneumonia: A review of current knowledge.
Diagn Interv Imaging. 2020;101(7-8):431-437. doi:10.1016/j.diii.2020.06.001
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/

Carotti M, Salaffi F, Sarzi-Puttini P, et al.
Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists.
Radiol Med. 2020;125(7):636-646. doi:10.1007/s11547-020-01237-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7270744/

Dangis A, De Brucker N, Heremans A, et al.
Impact of gender on extent of lung injury in COVID-19.
Clin Radiol. 2020;75(7):554-556. doi:10.1016/j.crad.2020.04.005
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177134/

Pan F, Ye T, Sun P, et al.
Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19).
Radiology. 2020;295(3):715-721. doi:10.1148/radiol.2020200370
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7233367/

In addition, this meta-analysis reported a high degree of variability in the positive predictive value of chest CT based on prevalence.
Depending on whether the prevalence is 1%, 10% or 39%, the positive predictive value would become 1.5%, 14.2% or 48.8%, respectively.

Therefore, the use of CT as a screening tool in low-prevalence areas would lead to a large number of false positives. [13],[14]

DEFINITIONS: PREVALENCE AND INCIDENCE

In practice, chest CT findings can lead to three scenarios:

• when the chest CT scan is of suspected case of COVID-19, the patient should be admitted to a COVID-19 isolation ward, and RT-PCR tests* generally confirm the diagnosis;

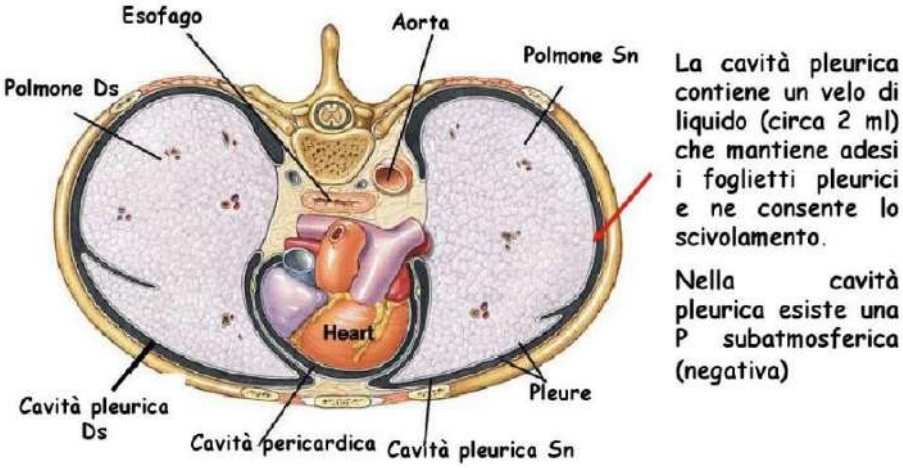
• when chest CT shows an obvious alternative diagnosis (e.g., bacterial lobar pneumonia or left ventricular failure), the patient will be admitted to a "non-COVID-19" ward;

• when chest CT findings are indeterminate, RT-PCR testing along with clinical symptoms will be essential for referral to the most appropriate department.

** The reference method is the laboratory test of nasopharyngeal aspirates for the identification of SARS-CoV-2 by RT-PCR. However, it takes several hours to obtain results, and the sensitivity of the test is only 60 to 70 percent, depending on the quality of the sample and the rate of viral replication in the upper respiratory tract.* [5],[6]
The reliability and use of the RT-PCR test will be discussed in the dedicated chapter, however, it is reiterated that the RT-PCR test is not a diagnostic test for COVID-19.

COMPUTED TOMOGRAPHY PRESENTATION IN COVID-19 PNEUMONIA

Lung presentation



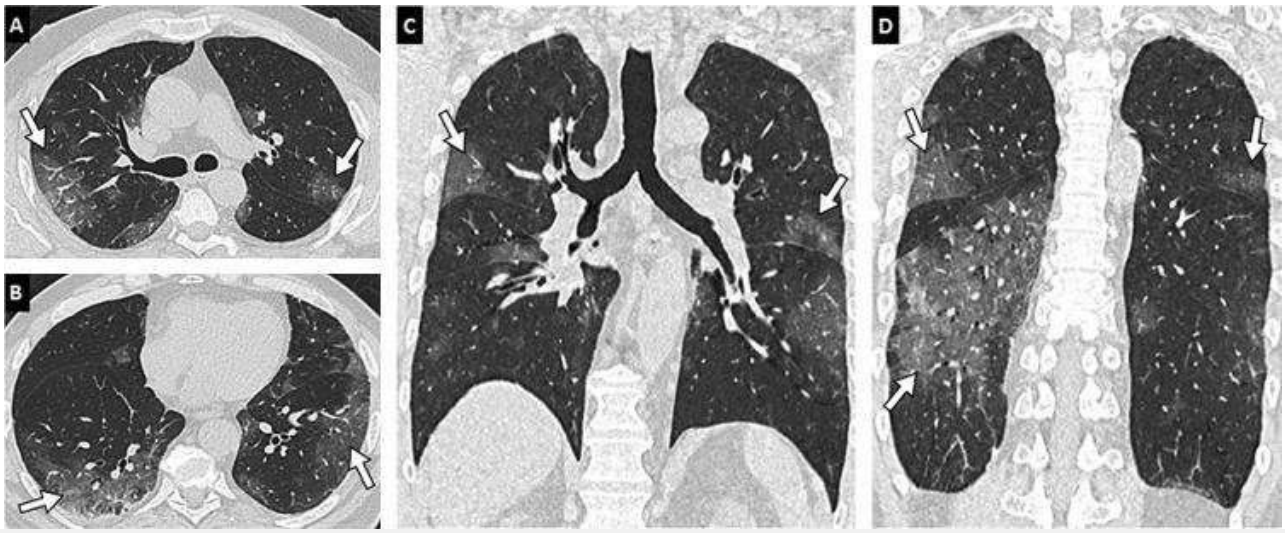
https://www.dbcf.unisi.it/sites/st13/files/allegati/21-01-2016/respiratorio.pdf

Typical computed tomography (CT) presentation

The most typical CT features of COVID-19 pneumonia are **bilateral and multifocal ground-glass opacities**.

Lesions classically predominate in the peripheral, posterior, and basal part of the lungs (Fig. 1)[10] . Other signs such as the presence of **fine reticulations, peribronchovascular thickening, vascular dilatations within the areas of pneumonia or architectural distortion** have been reported[15] .

Usually, there are no micronodules, excavations, septal lines, mediastinal lymph node enlargement, or pleural effusions.
Some infected but asymptomatic patients may present with mild ground-glass opacities, but they are generally not extensive. [16]



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/
Fig.1 64-year-old man with COVID-19 pneumonia. Unchanged CT images of the chest (lung window: W1600 / L-500 HU) in the axial (A, B) and coronal (C, D) planes reveal bilateral multifocal ground-glass opacities (arrows) located predominantly in the peripheral and posterior part of the lungs.

The CT appearance of the chest of COVID-19 pneumonia may be quite similar to that of other viral pneumonias, however, the peripheral location of the lesions, involvement of the five lobes, presence of thin reticulations, and peribroncovascular thickening are more frequently found in COVID-19 pneumonia. [17], [18]

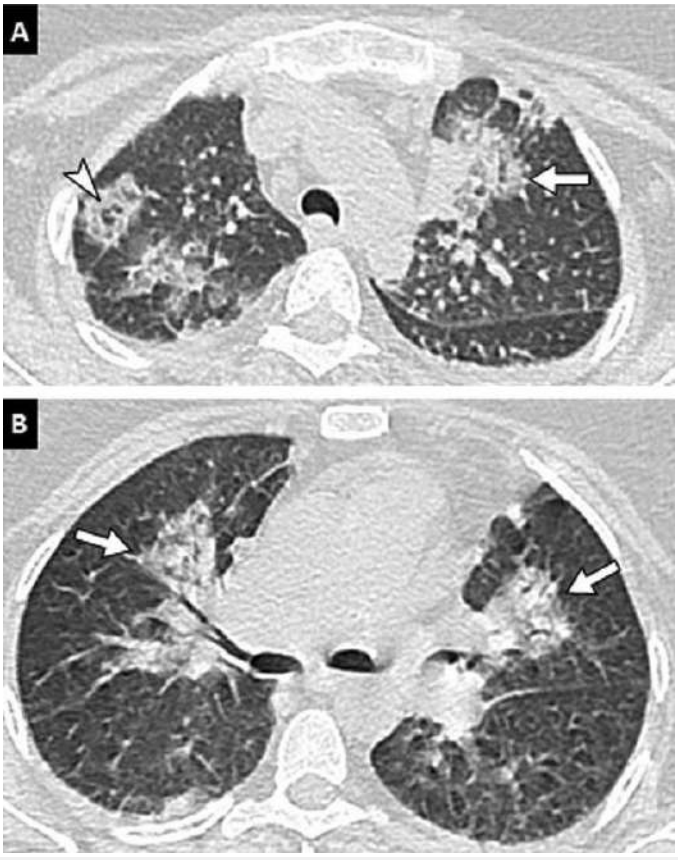
In influenza pneumonia, nodular or micronodular *tree-in-bud* pattern may be more common, as may pleural effusions. [19]

Presentation of atypical CT

In about 10% of patients, pulmonary involvement by COVID-19 may present as an arciform or pseudonodular consolidation suggesting a pattern of organizing pneumonia[20] , sometimes with a "reverse halo sign" similar to that observed in other infectious diseases[21] .

Unilateral presentation is possible in about 20-30% of patients, usually at an early stage before bilateralization of lesions [5],[22] . Peribroncovascular or apical predominance is also described (Fig. 2)
[23].

When COVID-19 pneumonia occurs in a previously abnormal lung (e.g., with emphysema or underlying fibrosis), CT presentation becomes less specific, making accurate comparison with previous CT examinations mandatory when available. [24]



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/
Fig. 2 Unenhanced CT examination in a 26-year-old woman with COVID-19 pneumonia. Unenhanced CT image of the chest (lung window: W1600 / L-500 HU) in the axial plane reveals predominant apical and peri-ilar lung lesions (arrows) with a "reverse halo sign" (arrowhead).

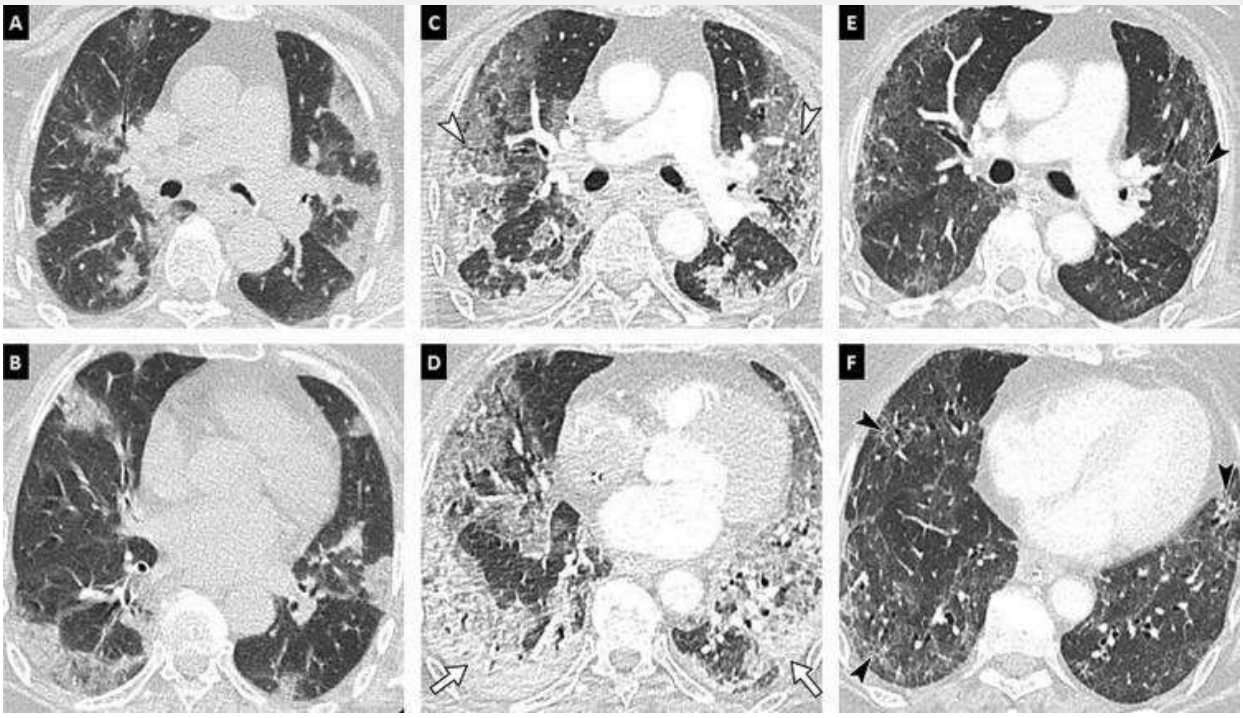
Evolution of CT results

Ground-glass opacities tend to progress over time, both in extent and attenuation value, and evolve toward areas of coiling (*crazy-paving* pattern-that is, overlapping ground-glass and intra-lobular gratings) or toward areas of linear and retractile consolidation (Fig. 4). [10], [25], [26], [27]

Lung damage is maximal around day 10 and then generally progressively decreases in size and attenuation value. [28] However, available data on the late evolution of lung parenchyma are still scarce.

While complete resolution seems to be common in patients with mild pneumonia, many patients, particularly those with early severe disease, still show a reticular pattern of fibrotic stripes after more than one month of evolution (Fig. 4).
According to a recent study, lung abnormalities could persist for more than a month in 98% of patients. [29]
There is therefore some concern about a significant number of pulmonary fibrotic sequelae[17] , although the proportion is not yet known.[15], [26]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/
Fig. 4 78-year-old woman with COVID-19 pneumonia. (A, B) The initial unmodified CT image of the chest in the axial plane (lung window: W1600 / L-500 HU) shows bilateral and peripheral ground-glass areas and consolidation. (C, D) Follow-up contrast-enhanced CT images performed 13 days later to rule out pulmonary embolism reveal the progression in extent and density of lung lesions with a coiled (crazy-paving pattern) (white arrowheads) and areas of consolidation (arrows). (E, F) Contrast-enhanced CT images obtained 28 days after symptom onset show partial regression of areas of consolidation but persistence of fibrotic stripes (black arrowheads) with architectural distortion.



Signs of severity

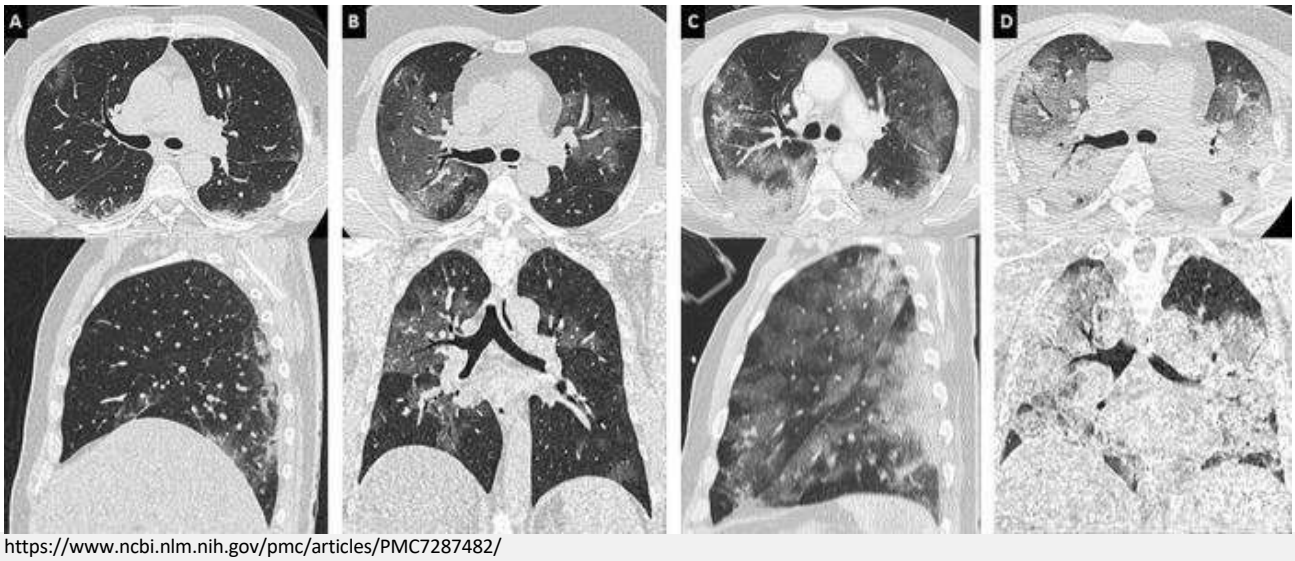
The total extent of lung involvement at the first CT examination correlates with clinical severity. [13], [25], [30]

[17] https://www.empillsblog.com/fibrosi-polmonare-post-covid-19/?cli_action=1597515706.465

The French Society of Thoracic Imaging (SIT) recommends classifying pulmonary involvement as absent or minimal (<10%), moderate (10-25%), extensive (25-50%), severe (50-75%) or critical (>75%) (Fig. 5).

Lung lesion density is also an indicator of severity, as areas of lung consolidation appear more extensive than ground-glass opacities in critically ill patients.
Equally, pleural effusion and early architectural distortion with traction bronchiectasis on initial chest CT would indicate a poor prognosis[15] .

A Chinese series suggests that consolidation in the upper lobes in early CT is also associated with adverse outcomes[31] .



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/
Fig.5 Various degrees of lung involvement in COVID-19 pneumonia in four different patients. Unchanged CT images of the chest (lung window: W 1600 / L - 500 HU) in the axial (up) and coronal (down) planes show typical examples of moderate (<25%), extensive (25-50%), severe (50-75%) and critical (>75%) lung involvement (A, B, C, D, respectively). The latter images are (D) characteristic of acute respiratory distress syndrome with a gravitationally dependent gradient.

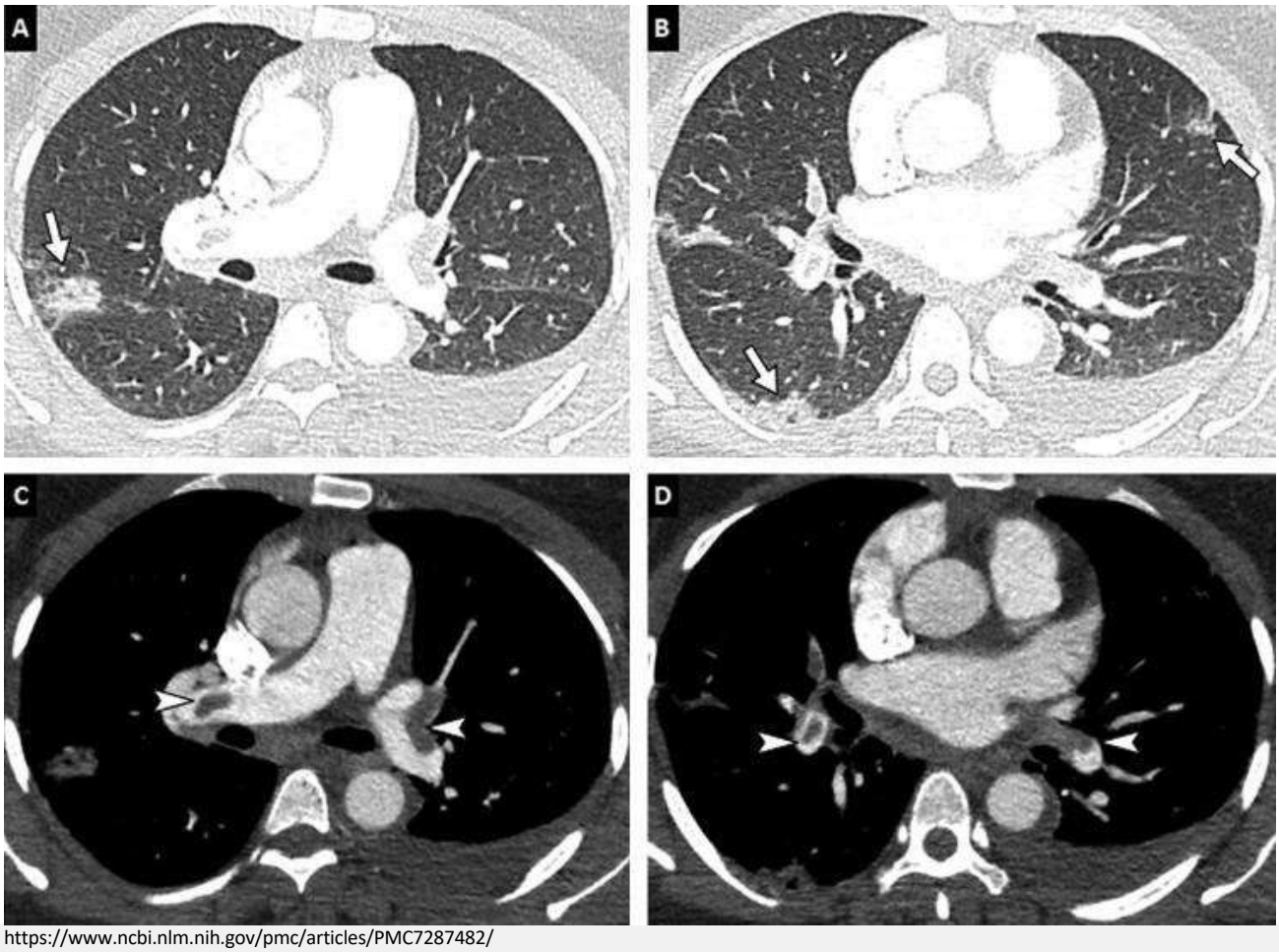
Complications

Between 15 and 30 percent of hospitalized patients progress to acute respiratory distress syndrome (ARDS), the leading cause of mortality for COVID-19.

ARDS is characterized in CT by extensive bilateral lung consolidation with a predominance in dependent areas (Fig. 5) [4],[32] . In addition, various complications may occur in the clinical course of these patients.

Bacterial pulmonary superinfection is suspected if there are additional areas of alveolar consolidation with pleural effusion and/or enlarged lymph nodes[15] .

In a recent study, COVID-19-associated pulmonary aspergillosis was reported in 5 out of 19 consecutive patients with ARDS[33] , however, the distinction between COVID-19 and pulmonary aspergillosis lesions with CT remains difficult[34] .
Pulmonary embolism has also been reported in COVID-19 patients (Fig. 7) [35], [36], [37],[38] .



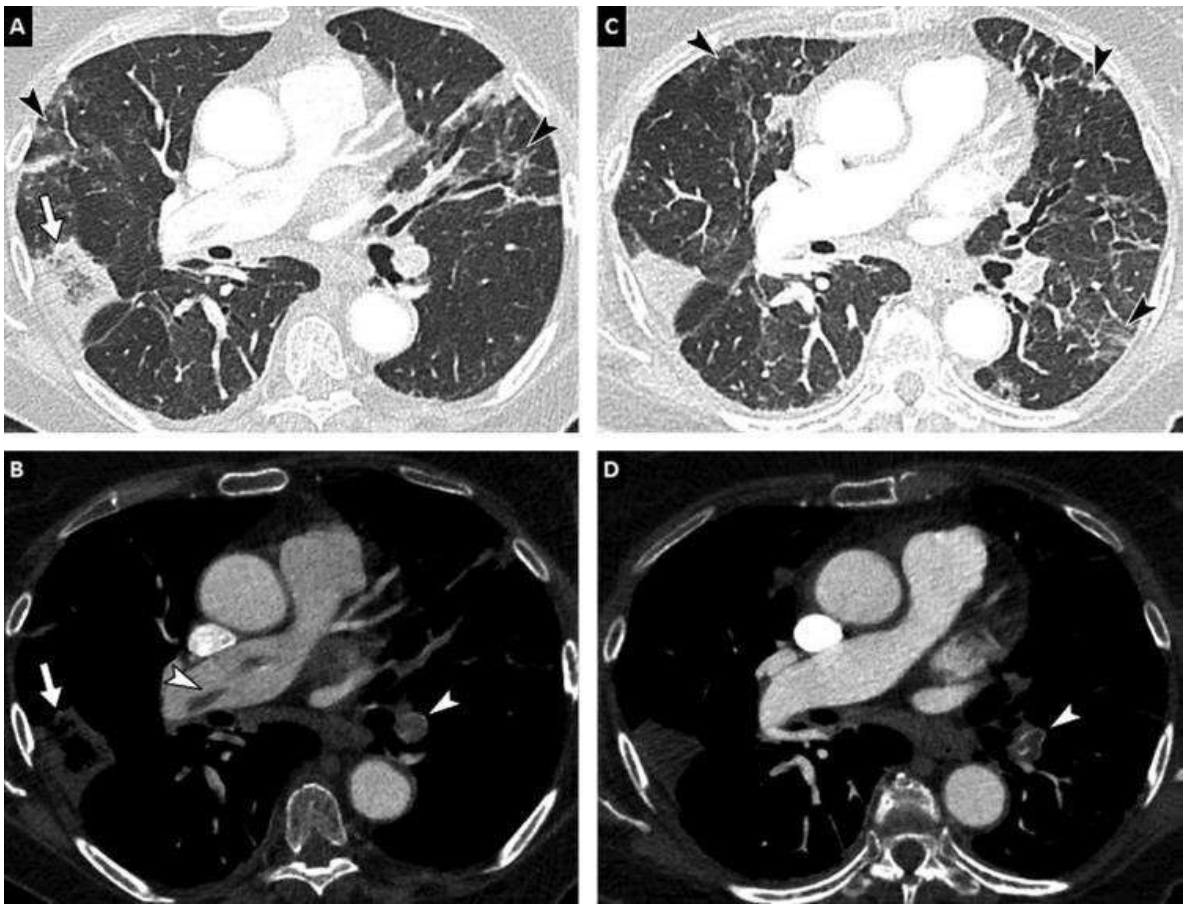
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/

Fig. 7 A 36-year-old woman positive for COVID-19 and pulmonary embolism. CT pulmonary angiography images in the axial (A, B) and coronal (C, D) planes show typical peripheral ground-glass areas related to COVID-19 pneumonia (arrows) and bilateral proximal pulmonary embolism (arrowheads).

In critically ill patients, there is an exacerbated systemic inflammatory response leading to a hypercoagulable state, detected by the marked increase in serum D-dimer level in these patients[39] .
The presence of pulmonary embolism is mainly reported in ICU patients, based on retrospective studies. The exact prevalence of pulmonary embolism in COVID-19 remains unknown and would require prospective evaluation, with systematic assessment of clinical symptoms, CT features and D-dimers.

CT with routine pulmonary angiography to check for pulmonary embolism is so far not indicated as a first-line diagnostic tool.
However, clinical-radiological discordance (dyspnea and hypoxemia without pulmonary abnormality) or respiratory worsening in a known COVID-19 patient should prompt the use of contrast medium.

It would be worth evaluating the value of CT with routine pulmonary angiography in patients with very high D- dimer levels.
Finally, radiologists should be aware that pulmonary infarction secondary to pulmonary embolism can be quite similar in appearance to COVID-19 pneumonia (Fig. 8).



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287482/

Fig.8 74-year-old woman with COVID-19 pneumonia. (A, B) Basal CT images obtained after intravenous administration of contrast material show peripheral ground-glass opacities (black arrowheads), bilateral proximal pulmonary embolism (white arrowheads) and a well-demarcated quadrangular subpleural consolidation containing central radiolucencies corresponding to a pulmonary infarction (arrow).
(C, D) Follow-up CT images obtained 7 days later show progression of COVID-19 lung lesions with reticulations, fibrotic streaks and architectural distortion (black arrowheads) and persistent thrombi (white arrowhead).

Key computed tomography and chest X-ray features of COVID-19 infection

Finding	Computed tomography (%)	Chest radiography (%)
Multifocal lung lesions with peripheral distribution	>50	41
Ground-glass opacities	40.3-100	33
Consolidation	13-72	47
"Crazy paving" pattern	12-39	-
Interlobular thickening	13-37	-
Linear opacities combined	27-61	-
"Airway abnormalities"	17.7-27	
Pleural thickening	48.4	
Pleural effusion	3-9.7	3
Pericardial effusion	5	-
Lymphadenopathy	58	-
Normal	23 (initially, especially in asymptomatic patients, but many progress)	21

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335247/

Pulmonary thromboembolism in COVID-19: venous thromboembolism or arterial thrombosis?

Pulmonary thromboembolism (PTE) is frequently observed in patients with COVID-19 (40.6%), and mainly involves segmental (90.2%) and sub-segmental (61.0%) arteries of lung segments affected by a consolidation pattern (67.6%).

Patients with more severe COVID-19 lung disease (higher CT injury score, D-dimer, LDH and CRP) tend to be more affected by TEP.

Rceently, some authors[18] hypothesized that the development of TEP in COVID-19 could probably be associated with pulmonary artery thrombosis due to severe pulmonary inflammation and a hypercoagulation state rather than common thromboembolism.

As will be seen below, pulmonary thromboembolism is closely associated with the use of ventilation Invasive and the development of lung damage from vortex ventilation

Specificity in children, pregnant women, and gender difference

In the **pediatric population**, lung involvement in CT is often less extensive than in adults, and there are no abnormalities on CT. [40]
In case of pulmonary involvement, ground-glass pattern is the predominant sign [40],[41] . The "halo sign" is found more frequently than in adults [39],[41] . Infections, especially viral, are also more frequent[42] .

In **pregnant women, there** is no evidence of maternal-fetal transmission of SARS-CoV-2 or specific pre- or postnatal complications [43] and it still seems confirmed that there is no increase in COVID-19-related mortality in pregnant women[45] .
Consolidation may be more common than in the general population. [44]

Regarding **gender difference,** more extensive lung disease was found in male patients with COVID-19, despite similar age and time from symptom onset for both gender groups. Male vulnerability to COVID-19 may, in part, be explained by a gender disparity in the behavior more likely in men than women to engage in unhealthy habits such as smoking and to seek medical advice more infrequently and in a less timely manner.[19]
In addition, biological differences in immune response may result in differential susceptibility in males and females to infectious diseases (e.g., animal studies have suggested a protective effect of estrogen against severe acute respiratory syndrome coronavirus [SARS-CoV]).[20]

[18] Cavagna E, Muratore F, Ferrari F.
Pulmonary Thromboembolism in COVID-19: Venous Thromboembolism or Arterial Thrombosis?
Radiol Cardiothorac Imaging. 2020;2(4):e200289. Published 2020 Jul 9. doi:10.1148/ryct.2020200289
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Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection.
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5450662/

Artificial intelligence (AI) in the imaging of COVID-19

Machine learning techniques have t h e potential to drastically transform medical imaging [46], [47], [48].

Several deep learning and radiomics tools are currently under development for automated diagnosis, quantification of lesion extent, and prognostic estimation of COVID-19 pneumonia.

In a study from Wuhan City, China, conducted on a database of 4356 CT examinations (30% with COVID- 19, 40% with community-acquired pneumonia, and 30% with non-infectious pneumonia), a deep learning model diagnosed COVID- 19 pneumonia with a sensitivity of 90% and a specificity of 96%, allowing reliable differential diagnosis with community-acquired pneumonia[49] .

Huang et al. applied a deep learning algorithm to a database of 842 COVID-19 patients and tested it on an independent series of 126 patients. Lung involvement rates were significantly different for mild, moderate and severe clinical conditions, and automatic quantification also allowed longitudinal follow-up of patients [50].

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IN-DEPTH STUDY

Treatment of respiratory distress syndrome by assisted ventilation

The only strategy with significant impact in ARDS is mechanical ventilation.
Most patients with ARDS will require ventilatory support to restore gas exchange and decrease respiratory work, thus improving the probability of survival.

However, mechanical ventilation is not free from serious iatrogenic reactions. Among these, the potential of positive pressure ventilation to damage the lungs, including ventilator-induced or ventilator-associated lung damage (VILI / VALI, referred to experimental models and patients, respectively), is currently considered one of the key mechanisms responsible for adverse disease outcome.

VALI is a molecular response to the application of abnormal forces within the lungs that can lead to inflammation, edema, and remodeling of the extracellular matrix. [21]

A large number of molecular signal pathways are altered during mechanical ventilation, with
The involvement of almost all processes related to cellular homeostasis. [22]

Inflammatory responses, changes in cell survival signals, and processing of extracellular matrix components have been described after mechanical ventilation.
The spread of this mechanism beyond the lungs has been linked to the development of multiorgan failure.

Overall, VALI has been correlated with clinical outcome, so its avoidance is a key goal in the ventilated patient.

Operating Procedures

Care pathway for the patient with COVID-19 Section 1 - Critical area procedures.
Care pathway for the patient with COVID-19 Section 2 Recommendations for local management of the critical patient
SIIARTI- Published on 03/14/2020

Interim directions for carrying out isolation and home health care in the current COVID-19 context.
July 24, 2020 version. ISS Working Group Infection Prevention and Control 2020, ii, 8 p. ISS COVID-19 Report No. 1/2020 Rev.

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[22] Ngiam N, Kavanagh BP.
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IN-DEPTH LINKS
Mechanical ventilation

The respiratory system oxygenates and removes carbon dioxide from venous blood.

Thus, a useful classification of respiratory failure is based on whether the main alteration is inadequate oxygenation or inadequate carbon dioxide elimination (this means there is inadequate ventilation); many of the conditions involve both.

Although there are measures to stall, respiratory failure frequently requires invasive or noninvasive mechanical ventilation. [23]

Acute hypoxemic respiratory failure (acute hypoxemic respiratory failure, acute respiratory distress syndrome
https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/insufficienza-respiratory-acute-hypoxemic-insufficiency,-acute-respiratory-distress-syndrome

Overview of mechanical ventilation
https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/panoramica- on-ventilation-mechanics

Suspension of mechanical ventilation
https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/sospensione- of-ventilation-mechanics

Tracheal intubation
https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/arresto-respiratorio/intubazione-tracheale

Non-invasive ventilation, alveolar recruitment, and pronation: the experience in patients with COVID-19.
http://www.ventilab.org/2020/05/10/ventilazione-non-invasiva-reclutamento-alveolare-e-pronazione-lesperienza-nei-pazienti-con-covid-19/

A unified approach to ARDS: ventilating functional capacity
http://www.ventilab.org/2020/05/02/un-approccio-unitario-alla-ards-la-ventilazione-della-capacita-funzionale/

The key to all forms of ARDS: residual functional capacity and its effect on compliance.
http://www.ventilab.org/2020/04/28/la-chiave-di-accesso-a-tutte-le-forme-di-ards-la-capacita-funzionale-residua-e-il-suo-effetto-sulla-compliance/

Sedation and tracheal intubation: breaking out of clichés
http://www.ventilab.org/2018/07/29/sedazione-ed-intubazione-tracheale-evadere-dai-luoghi-comuni/

[23] https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/panoramica-on-respiratory-insufficiency.

The characteristics of mechanical ventilation [24]

Mechanical ventilation is responsible for ensuring an adequate supply of O_2 and CO_2 by administering an adequate and controlled amount of O_2 to the patient and eliminating the CO_2 produced.

To best understand how it works, some basics need to be known.

The basis of mechanical ventilation

Mechanical ventilation is a form of instrumental therapy in which through a mechanical ventilator (MV), it supports the patient with severe respiratory failure, enabling them to ventilate adequately and maintain normal gas exchanges between the lungs and the environment.

When discussing mechanical ventilation, the concepts of:

- **Respiratory rate**: is the number of respiratory acts a person performs every minute. The value changes with age; in an adult it is between 12 and 20 acts/min. As the respiratory rate increases, it is normally associated with ineffective ventilation, as the lungs fail to empty completely;
- F_{iO_2}: is the inhaled fraction of oxygen, or even the amount of O_2 inhaled by a patient and is expressed as a percentage. The ambient F_{iO_2} is 21%.

[24] The paragraph is excerpted from:
https://www.nurse24.it/studenti/risorse-studenti/le-caratteristiche-della-ventilazione-meccanica.html
Published on 11/28/16 by Chiara Vannini Updated on 06/15/18

https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-critical-care-and-airway-management-issues

Overview of mechanical ventilation
https://www.msdmanuals.com/it-it/professionale/medicina-di-terapia-intensiva/insufficienza-respiratoria-e-ventilazione-meccanica/panoramica- on-mechanical-ventilation?query=ventilation%20protective#v926982_en

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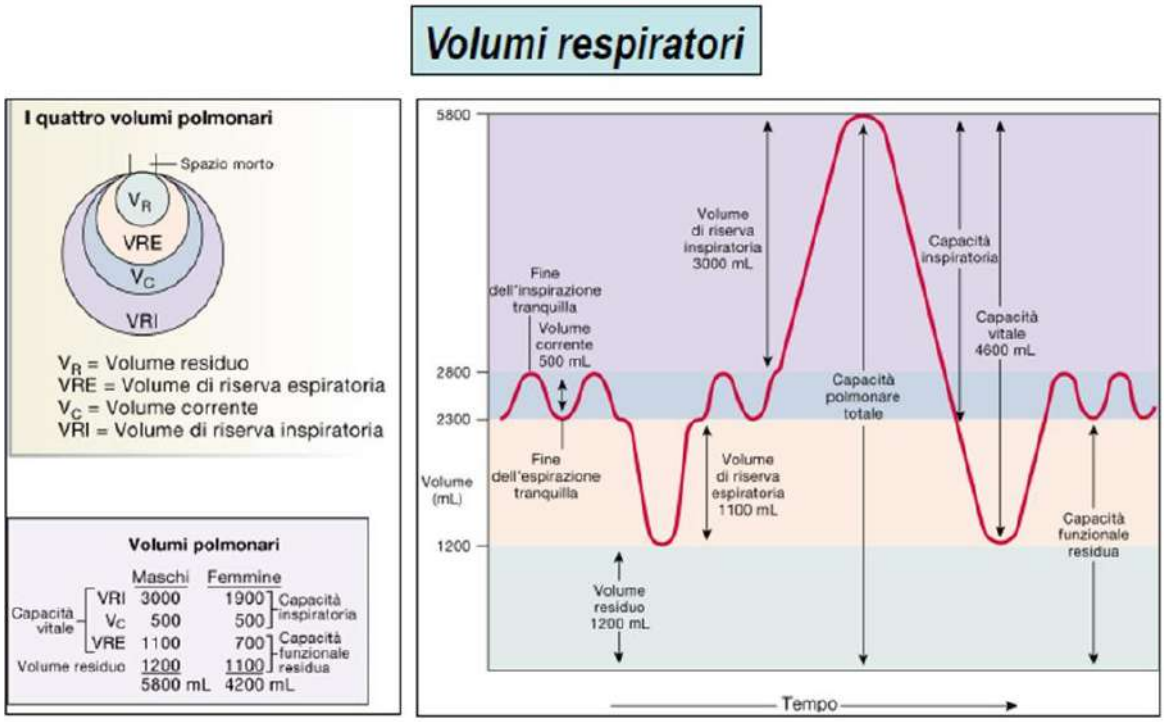
https://www.monaldi-archives.org/index.php/macd/article/view/1085/1033

Winck JC, Ambrosino N.
COVID-19 pandemic and noninvasive respiratory management: Every Goliath needs a David. An evidence-based evaluation of problems.
Pulmonology. 2020;26(4):213-220. doi:10.1016/j.pulmoe.2020.04.013
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7183996/

- **tidal/tidal volume**: amount of air that enters and leaves the lungs with each respiratory act. It is normally estimated to be between 7-8 mL/kg body weight and approximately 500 mL per inspiration.
- **PIP (peak inspiratory pressure)**: is the highest pressure generated by the ventilator to deliver the predetermined tidal volume. It varies with airway resistance and lung compliance. The optimal PIP in an adult is less than 40 $_{cmH2O}$;
- **PEEP (positive end-expiratory pressure)**: is a pressure that the ventilator applies during pauses between the end of expiration and the beginning of the next inspiration, preventing the pressure from returning to atmospheric level. PEEP is used to improve oxygenation of patients who do not respond to increases in $_{FiO2}$ and to prevent lung atelectasis (i.e., collapse of the alveoli);
- volume/minute: is the amount of gas inhaled and exhaled each minute. It is calculated by multiplying the respiratory rate and the tidal volume;
- **Inspiratory trigger**: this is a mechanical ventilator (MV) feature used when the ventilator is in assisted mode: it allows the patient to initiate an inspiratory act that is then supported by the machine, improving synchronization between machine and patient.



●Tabella semplificativa dei principali parametri respiratori●

SEALS of respiratory parameters measured during m e c h a n i c a l ventilation [25]

VC = Tidal volume, Volume inhaled and exhaled under normal conditions (500 ml)
VCE = Current Exhaled Volume, displays the current volume measured at patient connection. Current Volume is updated at the end of each exhalation.
VRI = Inspiratory reserve volume, maximum volume that can be inhaled beyond a normal inhalation (3000 ml) **VRE = Expiratory reserve** volume, maximum volume that can be exhaled beyond a normal exhalation (1100 ml) **VR = Residual** volume, volume that remains in the lung at the end of a maximum exhalation (1200 ml)
CFR = Functional residual capacity, volume present in the lungs at the end of a normal exhalation (VRE+VR)
CI = Inspiratory capacity, maximum volume that can be inhaled from the end of a normal exhalation (VC+VRI)
CPT = Total lung capacity, volume present in the lungs at the end of a maximum inhalation
CV = Vital capacity, maximum volume that can be inhaled and exhaled (VC+VRI+VRE)

[25] PULMONARY AND ALVEOLAR VENTILATION
http://anemosformazione.it/onewebmedia/03_Ventilazione_e_scambi_gassosi.pdf

PIP = Peak Inspiratory Pressure, displays the highest pressure measured during the inhalation phase. PIP is not updated in spontaneous and pressure-supported breaths. PIP is updated at the end of the inspiration phase.
MAP = Average Airway Pressure, continuously displays the average airway pressure over the past 60 seconds. This value is updated every 10 seconds.
PEEP = Positive end-expiratory pressure, displays the pressure in the airway circuit at the end
Of the exhalation. PEEP is updated at the end of each exhalation.
VVE/M = Ventilatory Volume per Minute, displays the current volume exhaled in the last 60 seconds, calculated from the last 8 breaths. The Ventilatory Volume per Minute is recalculated and updated at the end of each exhalation or every 20 seconds.
FR = Respiratory Rate, displays breaths per minute based on the last 8 breaths, takes into account all breath types. Respiratory Rate is recalculated and updated at the end of each exhalation phase or every 20 seconds.

Ventilation modes

The fan can be set:

- In **volumetric mode**: aims to have the patient maintain an established constant tidal volume by the operator;
- in the **pressometric mode**: the VM always delivers the same positive pressures chosen by the operator, regardless of the current volume that will then be developed by the patient.

The type of ventilation is chosen on the basis of how ventilator-autonomous the patient is, the degree of sedation, and on the basis of how much the ventilator needs to replace the patient's muscle effort.

Ventilation begins at the moment when the patient is in the **critical phase**, that is, when vital functions are compromised. Once the patient has passed the critical phase, the goal is to "wean" the patient, that is, to move from a phase in which the ventilator totally replaces the patient, to a phase in which the patient becomes autonomous again.

This weaning **phase**, called **weaning**, is the longer the longer the patient remains ventilated. For example, in a patient ventilated during surgery, with no lung disease and no complications during surgery, the weaning phase will be very short. It will be sufficient to support the patient from the ventilatory point of view until fully awakened and then administer oxygen as supportive therapy if necessary.

In contrast, a patient who has come out of a long period of coma, even a pharmacological one, needs a longer time before becoming fully respiratory autonomous again. This transition must be done gradually, constantly evaluating the patient's condition, vital parameters, respiratory dynamics, and blood gas values.

Ventilation is controlled, when the ventilator works independently of the patient's respiratory activity; the patient makes no respiratory effort, and the ventilator fully replaces itself by delivering respiratory acts according to a predetermined rate per minute. It is a ventilation mode used, for example, in a **patient in deep coma due to brain injury**, or in the case of paralysis of respiratory muscles (also secondary to the use of curare).

Ventilation is assisted when the ventilator synchronously adjusts to the patient's autonomic ventilation. The choice obviously depends on the patient's condition, degree of sedation, and stage of illness.

Volumetric modes

- **Volume-controlled ventilation (VC)**: the ventilator does not detect the patient's respiratory efforts and delivers respiratory acts at an established rate per minute. A tidal volume is established for each respiratory act, and the ventilator continues to insufflate air until that value is reached, after which insufflation is stopped and the valve is opened to allow air to escape, i.e., the expiratory act;
- **Volume-assisted ventilation-Controlled/Assist Control (AC)**: the ventilator delivers a respiratory act each time the patient starts breathing. In fact, the ventilator senses a negative pressure given by inspiratory effort and delivers a respiratory act according to the current set volume;
- **Synchronized Intermittent Mandatory Ventilation/Synchronized Intermittent Mandatory Ventilation (SIMV)**: is the mode of ventilation used during weaning from the ventilator. The acts delivered by the ventilator synchronize with the patient's inspiration. If the patient does not initiate a spontaneous respiratory act, the ventilator intervenes

by delivering one respiratory act. The tidal volume varies according to the patient's efforts, but the ventilator ensures that the patient performs a predetermined minimum number of acts per minute.

Pressometric modes

- **Pressure-controlled ventilation** (**PCV**): it is the ventilator that determines the time of inspiration, without patient participation. A peak inspiratory pressure (PIP) is programmed, and the ventilator insufflates air until the set pressure value is reached. When the limit is reached, the ventilator stops insufflation and opens the valve that allows air to escape and then the expiratory phase;
- **Pressure Support Ventilation/Pressure Support Ventilation** (**PSV**): is the mode of ventilation used when the patient is breathing spontaneously but is not yet ready to be extubated. Each respiratory act is initiated and sustained by the patient. The ventilator applies a constant pressure in the airway throughout inspiration, which is synchronized with the patient's inspiratory effort;
- **Continuous Positive Airway Pressure/Continuous Positive Airway Pressure** (**CPAP) Mechanical Ventilation**: the ventilator administers continuous high pressure to the patient that overlaps with the patient's spontaneous ventilation, improving oxygenation and reducing ventilatory effort and cardiac work.

Mechanical ventilation and monitoring in the intensive care unit

Goals of mechanical ventilation

As already seen, it has the task of **ensuring an adequate supply of o_2 and co_2** by administering an adequate and controlled amount of o_2 to the patient and eliminating the co_2 produced. It also aims to reduce the respiratory effort of a patient who has exhausted, or is exhausting, his or her energy reserves due to an excessive increase in lung work.

First, **mechanical ventilation** can be of two types:

- **Invasive**: necessarily involves the patient having an oro-tracheal tube, naso-tracheal tube, or tracheostomy cannula in place;
- **Non-invasive ventilation (NIV)**: is done through a face mask, mouthpiece or helmet.

Mechanical ventilation can be performed either in the intensive care setting or at home with the help of portable home ventilators. It can also be performed continuously or intermittently.

Indications for mechanical ventilation

Mechanical ventilation is indicated, **under anesthesia**, during surgery in which it is necessary to sedate the patient while continuously monitoring his ventilation and gas exchange.

It is indicated, in **intensive care**, in severe respiratory failure that threatens to compromise the patient's vital functions; in the early stages after cardiac arrest, in order to ensure adequate lung oxygenation; and whenever the patient has brain injury such that the brain is unable to ensure adequate respiratory function.

In addition, it can be used **at home** in all those patients who are no longer able to breathe on their own: for example, patients with diseases such as **end-stage ALS** who require constant and controlled ventilatory support via tracheostomy cannula.

At home, NIV is also frequently used by patients with, for example, **sleep apnea,** as it ensures **proper oxygenation even during sleep**.

The mechanical fan

The mechanical ventilator used in intensive care is a piece of equipment that, through a circuit, is connected to the patient's tracheal tube or tracheostomy cannula. The circuit commonly consists of **two tubes**: a tube that carries the gases produced by the ventilator to the patient through an **inspiratory valve,** and a tube that is responsible instead for carrying the patient's waste gases through an **expiratory valve**.

Each ventilator has a monitor and controls to choose the most suitable type of ventilation, set volume values, respiratory rate, PEEP, etc.

In general, it is first of all essential to remember that **a mechanical ventilatory act includes**:

- **The inspiratory phase**, in which the ventilator insufflates air into the patient's airway;
- **The transition from inspiratory to expiratory phase;**
- **The expiratory phase, in which the ventilator collects the patient's waste gases;**
- **The return to the inspiratory phase.**

Fans can be divided into two broad categories:

- **Negative-pressure ventilators**: they work by applying sub-atmospheric pressure to the chest of a patient who is enclosed in an airtight suit; the ventilator creates a pressure gradient such that it passively forces air into the lungs. The **steel lung**, much used in past decades, is an example of a negative-pressure ventilator. Even today, there are less bulky and less common systems that use the same mechanism of action. **The advantage** of negative pressure ventilators is that they do **not require the patient to have any artificial airway**, keeping the patient autonomous in communicating or eating;
- **Positive pressure ventilators**: use an artificial airway (oro-tracheal tube (TOT), naso-tracheal tube or tracheostomy cannula) to push air into the lungs. Exhalation occurs passively due to elastic recovery of the lungs and chest wall.

Patient monitoring

In the ventilated patient, **constant monitoring** is essential. This is because, especially in the first few days of being on mechanical ventilation, the patient is not respiratory autonomous and needs prompt intervention as the condition and signs and symptoms change.

Through clinical observation of the patient and monitoring of gases (**with hemogasanalysis**) and capnometry (exhaled CO_2), early intervention is possible if conditions change or worsen.

It is essential to frequently check the correct positioning of the TOT, as dislocation may not ensure adequate ventilation for the patient.

Signs and symptoms

A patient who is breathing adequately with the VM is usually calm; the saturation and respiratory rate are good. The skin is pink, he is not sweating, and there is no noise coming from the tube.

If the patient presents agitated, sweaty, or tachypnoid; if he presents coughing, **if there is a major change in vital parameters** such as BP, HR, SO2, it is necessary to go to see how he ventilates the patient.

This is often associated with the fact that the ventilator, in which "normal" and physiological parameters are set within which the patient must adhere to, sounds.

Clogging of **secretions in the bronchial tree** also results in discomfort for the patient, who may present agitated and with altered ventilatory parameters resulting in ventilator alarm. It is also crucial to remember how the presence of the oro- or naso-tracheal tube is not physiological and that this often results in discomfort or discomfort in the awake patient.

Maladaptation occurs when the patient fails to ventilate synchronously with the VM, a situation that results in ineffective exchanges and inadequate ventilation.

The Risks of Mechanical Ventilation

VM, like all therapeutic procedures, can pose risks to the patient. The most common are:

- **barotrauma**: manifested by PNX (pneumothorax), pneumomediastinum, or subcutaneous emphysema. The patients most likely to develop this complication are those with COPD, ARDS (acute respiratory distress syndrome) and acute asthma;

- **infections**: we talk about **VAP**, or ventilation associated pneumonia, an event directly proportional to the duration of mechanical ventilation;
- **Hemodynamic alterations**: at the onset of ventilation, it is possible to reduce cardiac output. This results in reduced venous return, increased pulmonary vascular resistance, and related worsening of left ventricular function

Pneumonia associated with mechanical ventilation

The acronym **VAP** refers to mechanical ventilation-associated pneumonia, the onset of which occurs at least 48 hours after the start of **Mechanical Assisted Ventilation** (MVA) in patients admitted to the Intensive Care Unit (ICU).

In the pathogenetic mechanism of VAP, the presence of the respiratory "prosthesis" (e.g., endotracheal tube) is the **main risk factor**, as it promotes microinhalation of the oro-pharyngeal contents, reduction of upper airway defenses, and formation of a bio-film with consequent increase in bacterial load.

As a result, colonization of the aero-digestive tract and contamination of circuit devices connected to the artificial airway become the perfect humus for which microorganisms in the oro-pharyngeal cavity can reach the lung parenchyma, overcome the body's defenses and cause the **local inflammatory reaction** resulting in pneumonia.

In **patients undergoing mechanical ventilation,** the incidence of VAP is about **22 percent**.

The mortality attributable to VAP is 27%, a rate that increases **to 43%** in the case where the agent That the cause turns out to be antibiotic resistant.

The microorganisms causing VAP are in 56.5% of cases Gram-negative, especially **Escherichia coli**, **Klebsiella spp**, **Haemophilus Influenzae**. In 42% of cases, the pathogens are Gram-positive cocci such as **Staphylococcus aureus**. [26]

[26] https://www.nurse24.it/studenti/procedure/l-infermiere-nella-polmonite-associata-a-ventilazione-vap.html

Papazian L, Klompas M, Luyt CE.
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Intensive Care Med. 2020;46(5):888-906. doi:10.1007/s00134-020-05980-0
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Update on ventilator-associated pneumonia.
F1000Res. 2017;6:2061. Published 2017 Nov 29. doi:10.12688/f1000research.12222.1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5710313/

Agente patogeno	Frequenza %
Pseudomonas aeruginosa	24,4
Staphylococcus aureus*	20,4
Enterobacteriaeceae**	14,1
Haemophilus	9,8
Streptococcus	8,0
Acinetobacter	7,9
Streptococcus pneumoniae	4,1
Altri	11,3
*MRSA 55,7%, MSSA 44,3% **Klebsiella 15,6%, Escherichia coli 24,1%, Proteus 22,3%, Enterobacter 18,8%, Serratia 12,1%, Altri 7,1%	

Nursing care in the prevention of VAP
Interventions for the prevention of VAP should begin just before the patient is intubated and continue throughout the management phase of the patient connected to the circuit for assisted mechanical ventilation.

The endotracheal tube is the gateway for possible bacterial colonization of the respiratory tract; in fact, microorganisms can spread through the oropharynx, sinuses, dental plates, nostrils, gastrointestinal tract, ventilatory circuits, and patient-patient contact.

For a good preventive strategy, it is necessary to know **the risk factors for developing VAP**.

Fattori di rischio legati alla presenza del tubo endotracheale	Fattori di rischio legati al paziente
› alterazione della clearance muco-ciliare › accumulo di secrezioni sotto-glottiche › formazione di uno strato di materiale biologico endoluminale	› patologie croniche respiratorie › età > 70 anni › alterazione dello stato di coscienza › aspirazione del contenuto gastrico › pH gastrico elevato › pregressa terapia antibiotica

Respiratory intensive care and nursing (excerpt)

Care of patients with respiratory failure

The **UTIR is** defined as a specialized pulmonary area of monitoring and treatment of **patients with Acute Respiratory Insufficiency** (ARI) from a primarily respiratory cause and/or chronic respiratory failure (CRI) flare-ups, where predominantly noninvasive monitoring techniques are commonly employed and where noninvasive mechanical ventilation is preferentially, but not exclusively, employed.

Patients undergoing prolonged and/or difficult weaning from conventional NICUs and patients who have already been weaned but **have an endotracheal cannula** whose removal should be considered and who still need monitoring and/or intensive interventions will also be accommodated in the NICU.

Because of the high intensity and complexity of care, the nurse relies on the use of electromedical devices that allow monitoring and support of vital functions, as well as the management of drug therapy.

The inpatient unit, as in all intensive care **units**, together with the preparation of the medical staff and excellent clinical observation, is an indispensable resource for meticulous care.

It sees the presence of a **multi-parameter monitor** on which it is possible to appreciate:

- Heart rate and morphology of electrical activity;
- NIBP (noninvasive blood pressure) blood pressure;
- satururimetry;
- respiratory rate;
- body temperature;

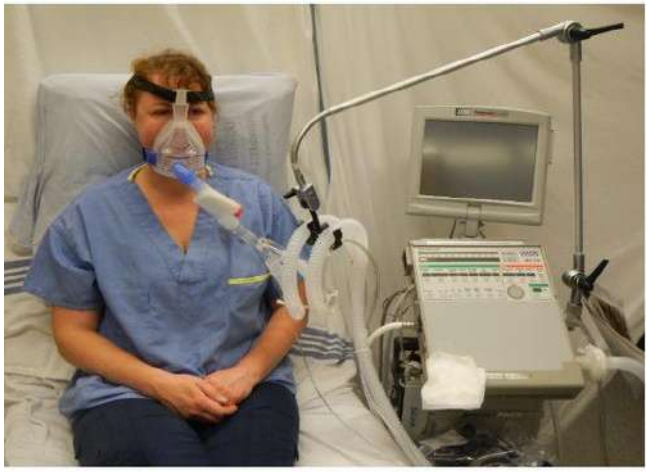
of a **mechanical ventilator, which provides the** patient with ventilatory support in different modes and ensures the possibility of observing, on the display of the ventilator, the waves of the inhalation and exhalation phases and thus carry out respiratory monitoring; of a **bronchoaspirator** that ensures, if necessary, effective tracheobronchial suction and thus optimal airway patency; of **infusion pumps** for the administration of drug therapy "continuously."

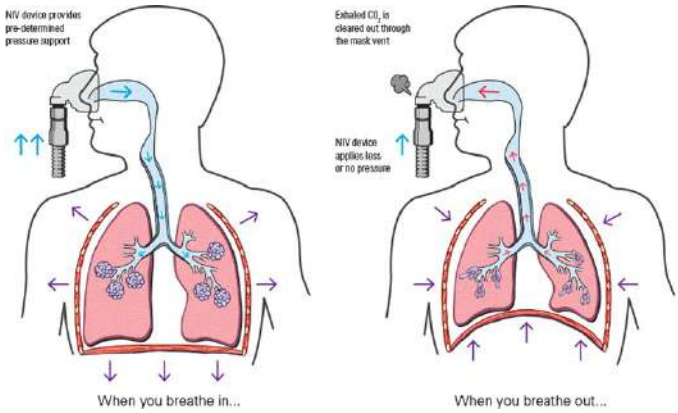
Another peculiarity peculiar to the UTIR is the presence of a **blood gas analyzer** and a **fibroscope**, which when needed allow diagnostic tests necessary for the proper management of the patient.

NIV (Non Invasive Ventilation) nursing management, monitoring and indications

NIV is a ventilatory system of a positive-pressure mechanical nature that replaces the user in the various phases of respiratory acts; it can be nasal, facial, total-face, or scaph, depending on need and tolerability. The nurse's role in the management of Non Invasive Ventilation is crucial, especially in the early recognition phase of any impairment of gas exchange (due to disease acuity or machine malfunction).

Monitoring and practical guidance





Non-Invasive Mechanical Ventilation (**NIMV**), otherwise referred to as **NIV** (Non Invasive **Ventilation**) or **NPPV** (**Non Invasive Positive Pressure Ventilation**) provides positive pressure mechanical ventilatory support using different ventilatory strategies.

It requires a ventilator-patient interface consisting of different types of devices, which include:

- nasal mask;
- FACE MASK;
- total-face mask;
- helmet[27] or diving suit.

The effectiveness of NIV depends largely on the **skills of nurses** well trained in the use of these ventilatory techniques and with firm experience in relation to these kinds of patients.

When properly applied, it reduces oro-tracheal intubation and the need for tracheostomy. It also facilitates weaning (weaning) from invasive mechanical ventilation.

Non-invasive mechanical ventilation also ensures a similar degree of effectiveness as invasive ventilation, but was developed with the aim of avoiding the complications associated with the use of the latter.

Another important benefit is that **patients can avoid endotracheal tube discomfort and its associated risks**, such as increased incidence of ventilator-associated pneumonia (VAP), prolonged ICU and hospital stay, or increased intrahospital mortality.

Potential disadvantages of NIV, on the other hand, include discomfort caused by the interface (some masks misplaced or left in place too long can create injury) or the possibility that ventilatory support may not be sufficient to achieve an adequate result.

Hence the need to consider the effectiveness of NIV depending on the operational context in which it is applied.
An appropriate setting must possess organizational requirements to ensure a good outcome as well as quality of care.

Non-invasive ventilation, when to use it

Essential requirements for the use of NIV may be the possibility of adequate monitoring, the presence of trained and motivated personnel, the availability of h24 staff, and, finally, the possibility of rapid recourse to intubation and invasive ventilation.

The nurse in charge must know how to recognize the basic signs of worsening **Acute Respiratory Insufficiency (IRA)**, be familiar with the operation, use, and possible drawbacks of NIV devices, and have the ability to interpret the data collected from monitoring as well as be able to act appropriately in case of failure. Close physician-nurse collaboration, early identification of signs and symptoms, and recognition of the patient's evolving clinical status all contribute to improving the quality of care provided.

Indications for the use of NIV

Indications for NIV reported in the literature include conditions such as:

- **IRA secondary to COPD exacerbation**: in the guidelines of the major societies (ATS, ERS, BTS, GOLD), NIV is listed as the gold-standard for the treatment of IRA secondary to COPD exacerbation;
- **IRA secondary to acute cardiogenic pulmonary edema (EPAC)**: some studies have shown that the use of continuous positive pressure (C-pap) is able to reduce the need for intubation and, therefore, the patient's stay in the ICU;
- **Hypoxemic, noncardiogenic IRA**: In this case, the recommendation of the major societies in the field is to use NIV with a strictly individualized approach and in a setting that allows rapid transition to invasive ventilation if improvement fails;
- other indications may include the **polytrauma patient**, **hypoventilation syndrome of the obese**, **respiratory failure in patients with neuromuscular diseases**.

[27] https://www.medimagazine.it/caschi-respiratori-cpap-per-far-fronte-allemergenza-covid-19-cosa-sono-e-come-funzionano/

Contraindications to the use of NIV

Noninvasive ventilation, however, is contraindicated in the following cases:

- Coma or severely impaired neurological state;
- Uncooperative, agitated and confused patient;
- need to protect the airway, upper airway obstruction, major bronchial secretions, inability to clear secretions;
- PNX, if not drained;
- Hemodynamic instability and severe arrhythmias;
- Facial anatomical abnormalities congenital or following trauma, recent craniofacial trauma;
- Recent surgery of the upper airway or gastrointestinal tract;
- vomiting;
- nosebleed;
- severe comorbidities.

Over the years, NIV has become a therapeutic device that is widely accessible to ordinary inpatient wards to ensure developments from the point of view of responding to the person's needs, but it becomes crucial to have the ability to identify a priori those individuals in whom NIV is highly likely to fail, so that decisions can be made to manage these patients in equipped wards (such as ICUs) where invasive mechanical ventilation is quickly and easily available.

Positive prognostic factors for the use of NIV

- Elevated $_{PaCO2}$ in the presence of moderate hypoxemia;
- pH 7.25-7.35;
- improvement of pH, $_{PaO2/FiO2}$, $_{PaCO2}$ and respiratory rate in one hour and preserved sensory.

Negative prognostic factors to the use of NIV

- high physiological score (APACHE II, SAPS II);
- Presence of pneumonia;
- copious secretions;
- edentulous (nasal breathing);
- Poor nutritional status;
- compromised sensorium.

Among the ventilatory modalities, the ones that have most established themselves for noninvasive use are **Continuous Positive Airway Pressure** (**C-PAP**) and **Pressure Support Ventilation** (**PSV**) possibly associated with application of **Positive External End Expiratory Pressure** (**PEEP**).

C-PAP consists of the delivery of a constant positive pressure during the respiratory cycle, while **PSV** consists of the delivery of a pressure above the end-expiratory pressure, which is selected by the operator in order to support the patient's muscles during inspiration.

Damage caused by invasive mechanical ventilation [28]

In 1967, the term " pulmonary respirator syndrome " was coined to describe the diffuse alveolar damage and hyaline membranes found in post-mortem studies of patients undergoing positive pressure ventilation. [29]

During the following decades, studies with experimental models showed the deleterious effects of high positive pressure ventilation and the benefit obtained from the application of positive end-expiratory pressure (PEEP).

These pioneering studies made it possible to introduce the experimental concept of

- ventilator-induced lung injury (**VILI**) and, later, its clinical counterpart of the
- ventilator-associated lung injury (**VALI**). [30]

[28] Antonelli M, Azoulay E, Bonten M, et al.
Year in review in Intensive Care Medicine, 2008: II. Experimental, acute respiratory failure and ARDS, mechanical ventilation and endotracheal intubation.
Intensive Care Med. 2009;35(2):215-231. doi:10.1007/s00134-008-1380-5
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Ventilator management strategies for adults with acute respiratory distress syndrome
https://www.uptodate.com/contents/ventilator-management-strategies-for-adults-with-acute-respiratory-distress-syndrome

[29] Respiratory lung syndrome.
Minn Med. 1967;50(11):1693-1705.

[30] Webb HH, Tierney DF.
Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure.
Am Rev Respir Dis. 1974;110(5):556-565. doi:10.1164/arrd.1974.110.5.556
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Akoumianaki E, Vaporidi K, Georgopoulos D.
The Injurious Effects of Elevated or Non-elevated Respiratory Rate during Mechanical Ventilation.
Am J Respir Crit Care Med. 2019;199(2):149-157. doi:10.1164/rccm.201804-0726CI
https://www.atsjournals.org/doi/pdf/10.1164/rccm.201804-0726CI

The primary conditions that influence the onset of VILI are the:

- "baby lung" [in most patients with acute lung injury/respiratory distress syndrome, normally aerated tissue is the size of a 5-6 year old child's lung (300-500 g of aerated tissue)] [31],
- parenchymal recruitability (or recruitment) [32]
- The degree of lung inhomogeneity. [33]

The three classical mechanisms responsible for VALI are:

- biotrauma,
- the barotrauma/volutrauma
- atelectrauma [34]

It is important to point out that in biomechanical terms, lung strain is measured in terms of "**strain**" (strain or tension), defined as the relative change in volume normalized by a reference volume. This biomechanical property can be defined for the entire lung (global strain) as the ratio of Vt (Tital volume) to a reference volume, usually the volume of air at the end of passive exhalation, and the functional residual capacity (FRC).

Ventilator Induced Lung Injury (VILI)
https://academy.esicm.org/mod/emodulepage/view.php?id=7977

Ventilator Induced Lung Injury: an update
http://www.attidellaaccademialancisiana.it/76/19/articolo/Ventilator-Induced-Lung-Injury-an-update

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Physical and biological triggers of ventilator-induced lung injury (VILI) and its prevention
http://www.sidamgroup.com/wp-content/uploads/2020/05/Gattinoni-2.pdf

[31] L. Gattinoni A. Pesenti
The concept of "baby lung"
Intensive Care Med (2005) 31:776-784 Intensive Care Med (2006) 3:205-213 Italian ed.
http://www.timeoutintensiva.it/tecne_data/88_7_Il_Concetto_di_Baby_Lung-1550.pdf

Marini, John J. MD1; Gattinoni, Luciano MD2
Time Course of Evolving Ventilator-Induced Lung Injury: The "Shrinking Baby Lung."
Critical Care Medicine: August 2020 - Volume 48 - Issue 8 - p 1203-1209 doi: 10.1097/CCM.0000000000004416
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[32] Lung Recruitment during Positive Pressure Mechanical Ventilation in the ICU: what can we learn from the literature?
http://www.anestesiarianimazione.com/2006/04f.asp

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[published correction appears in N Engl J Med. 2014 Apr 24;370(17):1668-9]. N Engl J Med. 2013;369(22):2126-2136. doi:10.1056/NEJMra1208707
https://pubmed.ncbi.nlm.nih.gov/24283226/

Similarly, the force acting on a surface unit, producing its deformation, is the "**stress**" (solicitation).
Transpulmonary pressure corresponds to stress in the lung. Strain and stress in lung tissue are closely related to each other through the relationship *stress = tissue elasticity x strain*.

Both are thought to play an important role in the onset and development of ventilator-induced lung injury (VILI). It is known that high (nonphysiological) values of strain, measured as lung tissue deformation versus volume change, are harmful to the lung and increase mortality in patients with ARDS in MV [35]

Biotrauma [36]
It is caused by the mechanical stimulus involving the application of positive pressure during mechanical ventilation triggers, through a process of mechanotransduction, and induces a biological response characterized by the secretion of proinflammatory cytokines and the emergence of a neutrophilic infiltrate.
As a result, there is a release of inflammatory mediators from the ventilated lung that can lead to systemic spread, contributing to the development of multiple organ dysfunction syndrome. [37]

Biotrauma contributes to the persistence of the inflammatory process and is associated with worse prognosis in patients with ARDS. [38]
In particular, among the most frequently reported mediators are[39] :
Cytokines: TNF-alpha, IL-1, IL-6, MIP-2 and pre-B-cell colony enhancing factor are among the primary mediators of inflammation thought to contribute to VILI

[35] Davide Chiumello et al.
Stress and lung strain during mechanical ventilation for acute respiratory distress syndrome
http://www.nutrivent.eu/pdf/Chiumello-2.pdf

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https://journal.chestnet.org/article/S0012-3692(16)35708-7/fulltext

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Intensive Care Med. 2010;36(5):750-757. doi:10.1007/s00134-010-1850-4
https://link.springer.com/content/pdf/10.1007/s00134-010-1850-4.pdf

Coagulation factors: Intra-alveolar fibrin is common in damaged lungs[40] .
Proinflammatory mediators can stimulate expression of tissue factor that activates coagulation[41] , suppress activation of protein C (APC), and promote secretion of both thrombomodulin and plasminogen activator inhibitor 1 (PAI-1)[42] .

Increased levels of the latter are detectable in ARDS and correlate with disease outcome. Consistent with these effects, ventilation injury causes similar alterations in coagulation[43] and protective ventilation attenuates these effects. [44]

Hormones: a prototypical hormone related to lung injury is angiotensin II, which stimulates the expression of proinflammatory mediators such as cytokine-induced interleukin-8/Neutrophil Chemoattractant (CINC)-3 and interleukin-6 through angiotensin II type 1 and type 2 receptors. [45]

Mechanical ventilation upregulates the renin-angiotensin system (RAS)[46] and angiotensin-converting enzyme (ACE) activity, increasing the conversion of Angiotensin-I to Angiotensin-II [47]

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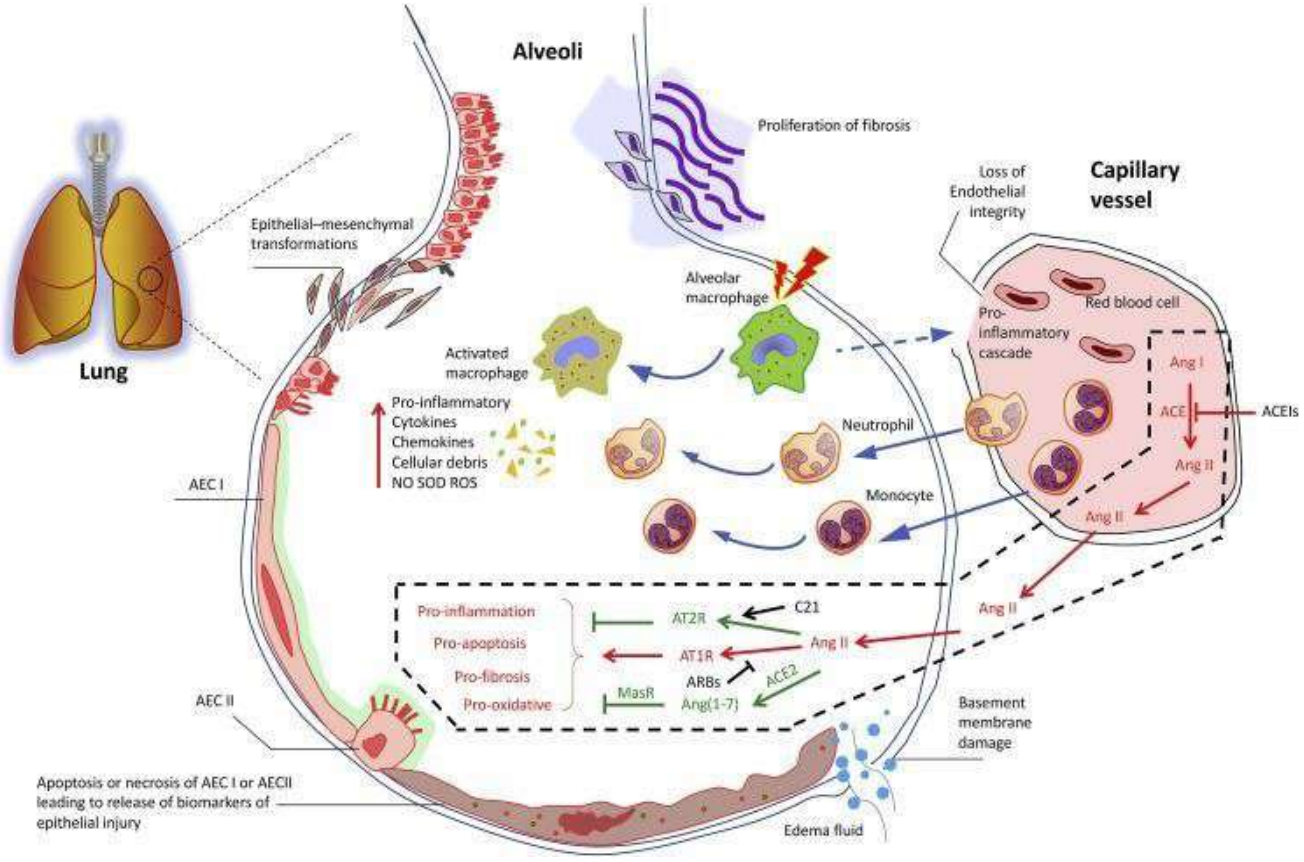

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7110665/

Overview of RAS components within ARDS. Pathologically, ARDS is characterized by inflammatory cell infiltration into the lungs, loss of epithelial and endothelial integrity, increased capillary permeability, interstitial pulmonary edema, and fibrosis. Ang-II, which is centrally located in RAS, originates from Ang-I upstream of ACE. Because ACE is abundantly expressed in the entire pulmonary capillary network, a considerable amount of Ang-II enters the pulmonary alveoli when ARDS occurs. Ang-II combines with AT1R or AT2R, both expressed in AEC and inflammatory cells in the alveoli, exerting opposite effects. Overall, Ang-II / AT1R promotes activation and recruitment of inflammatory cells, induces pulmonary AECs and apoptosis of PVMECs, leading to increased microvascular permeability and loss of epithelial and endothelial integrity. In contrast, activation of AT2R functionally attenuates inflammation, improves survival of AECs and PVMECs, and reduces lung fibrosis and collagen accumulation, resulting in improved lung function and oxygenation. In addition, Ang-II is further metabolized to Ang- (1-7) downstream by ACE2. Angiotensin- (1-7) combines with MasR to antagonize the Ang-II / AT1R effect, thus functionally similar to AT2R.

Abbreviations: renin-angiotensin system (RAS), acute respiratory distress syndrome (ARDS), angiotensin-converting enzyme (ACE), angiotensin-converting enzyme 2 (ACE2), angiotensin- (1-7) [Ang- (1-7)], AT1R blockers (ARB), compound 21 (C21), angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R), alveolar epithelial cells (AEC), pulmonary microvascular endothelial cells (PVMEC), Mas receptor (MasR), nitric oxide (NO), superoxide dismutase (SOD), reactive oxygen species (ROS)

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Lipid-derived mediators: eicosanoids[48] , platelet activation factors[49] and sphingolipids[50] have been proposed as mediators of lung damage. [51]

Importantly, these mediators are also implicated in the onset of the severe-fatal complications of COVID-19, particularly overexpression of proinflammatory cytokines, activation of coagulation mediators, underregulation of ACE2 receptors, and overexpression of angiotensin II [COVID-19-associated lung injury (CALI) *][52]

Specifically, the lung loses protection of the non-canonical RAS system as a result of the Underregulation of ACE2 after SARS-CoV-2-induced endocytosis.

As a result, the canonical ACE/Ang II/AT1R pathway becomes dominant and Ang II levels increase resulting in the promotion of fibrosis, myocardial hypertrophy, increased ROS, vasoconstriction, inflammation, endothelial dysfunction, and hypercoagulation. [53]

Therefore, it can be argued that **COVID-19 patients with pulmonary complications are more likely to manifest mechanical ventilation-induced lung damage**.

***Pulmonary damage associated with COVID-19 (CALI).**

SARS-CoV-2 appears to induce acute lung damage in a similar manner to other respiratory viruses, but with additional symptoms derived from alterations in the inflammatory resolution phase and in the RAS-KKS

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Cytosolic phospholipase A2 and arachidonic acid metabolites modulate ventilator-induced permeability increases in isolated mouse lungs.
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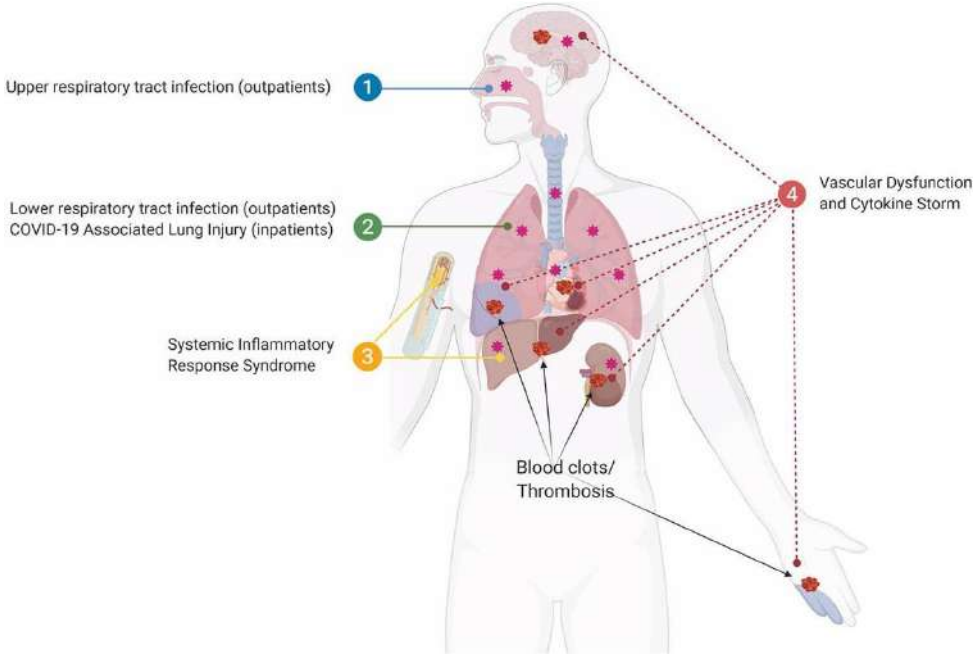
probably due to underregulation of ACE2 and/or elimination of type II pneumocytes[55] . The elimination of type II pneumocytes could explain the slow tissue recovery in patients with severe COVID- 19.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7344249/

*** KKS indicates the kinin-kallikrein system (Kinin-Kallikrein, or kinin system); RAS, renin-angiotensin system**

The four stages of SARS-CoV-2 infection.
(1) Upper and lower respiratory tract infection (outpatients);
(2) COVID-19-associated lung injury (CALI), in which some patients will be hospitalized (inpatients);
(3) systemic inflammatory response syndrome (SIRS), in which the bone marrow and acute phase response of the liver accumulate pro-thrombotic factors resulting in blood clot formation/thrombosis; **(4**) Prolonged recirculation between pulmonary and systemic inflammation results in multiorgan vascular dysfunction and cytokine storm syndrome.

Patterns of systemic inflammatory response induced by lung injury strongly suggest that lung inflammation is a "two-hit" model.
This means that underlying inflammation caused in the lung or from another site (e.g., cardiovascular disease, obesity, diabetes, and liver disease) can return to the lung following a new infection such as SARS-CoV-2, resulting in exacerbation of local and systemic inflammation.
The RAS-KKS system is also already affected in all risk conditions, including aging.

[55] Sungnak W, Huang N, Bécavin C, et al.
SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes.
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Barotrauma/volutrauma

Keep in mind that the term " barotrauma "[56] is to refer to excessive pressure-induced "stress" (this includes pneumothorax, pneumomediastinum, subcutaneous emphysema and gas embolism), while "volutrauma "[57] to excessive "strain."

Experimental studies presented on rats at high ventilatory pressures have shown alveolar damage by overstretching, consisting of perivascular and alveolar edema. [58] It is known that the use of high volumes can cause alveolar wall rupture.

Excessive lung elongation is increased due to the coexistence of healthy alveoli and collapsed un-aerated areas. This regional heterogeneity may exacerbate lung damage in previously healthy aerated alveoli and areas at the aerated/un-aerated interface, even when low volumes are used for ventilation.

Recent research confirming lung damage from invasive ventilation was published by Georgeann McGuinness et in the article "*High Incidence of Barotrauma in Patients with COVID-19 Infection on Invasive Mechanical Ventilation*"[59] in which it is reported that barotrauma is an independent risk factor for death in COVID-19 (OR = 2.2, p = .03) and is associated with longer hospital stay (OR = .92, p <.001). It follows that patients with COVID-19 infection undergoing invasive mechanical ventilation manifested a higher rate of barotrauma than patients with ARDS and patients without COVID-19 infection.

Atelectrauma

Mechanical ventilation can cause cyclic variations in alveoli aeration, leading to epithelium damage due to the emergence of shear forces at the air-fluid interfaces in the damaged lung and the generation of open collapse alveoli phenomena.[60]

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[59] McGuinness G, Zhan C, Rosenberg N, et al.
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Volutrauma and atelectrauma: which is
worse?
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6203268/

Cipulli F, Vasques F, Duscio E, Romitti F, Quintel M, Gattinoni L.
Atelectrauma or volutrauma: the dilemma.

The application of PEEP minimizes the closing and reopening stress in the alveolar spaces, thus reducing lung damage.

Types of ventilator induced lung injury (VILI) [24].

Injury	Mechanism	Minimization Strategy
Atelectrauma (Recruitment/derecruitment injury)	Lung injury caused by cyclic opening and collapse of atelectatic, but recruitable lung units.	Ensure appropriate PEEP and tidal volumes.
Barotrauma	Lung injury (e.g. pneumothorax, pneumomediastinum, etc.) caused by high transpulmonary pressure disrupting the alveolar structures.	Minimize excessive airway pressure and tidal volumes.
Biotrauma	Mechanical lung injury causes up-regulation and release of cytokines with a subsequent pulmonary and systemic inflammatory response causing multi-organ dysfunction.	Lung protective strategy while treating the underlying cause. Consider immunomodulating therapies (e.g. corticosteroids).
Oxygen toxicity	Injury caused by the inability of cells to overcome oxygen free radicals, and absorption atelectasis.	Turn down FiO_2 as soon as possible to target an oxygen saturation of 92–96%.
Patient self-inflicted lung injury (P-SILI)	Intense inspiratory force by the patient causing high transpulmonary pressure swings.	Increase sedation with or without neuromuscular blockade if persistent, excessive, spontaneous respiratory effort is present.
Shearing injury	High shear forces at the junction of the collapsed and open lung units causing lung injury.	Use appropriate PEEP to maintain recruitment and low tidal volumes. Modes like airway pressure release ventilation (APRV) may reduce shear stress.
Volutrauma	Non-homogenous lung injury caused by alveolar overdistension.	Ensure a low tidal volume of 4–8 mL/kg PBW.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335247/

Added to the overexposed biomechanical mechanisms are **ergotrauma** (i.e., energy diffusion from the dynamics of high-stress breathing cycles), **vascular** injury (endothelial injury due to alveolar expansion), and **hemodynamic** injury (endothelial injury due to increased capillary hydrostatic pressures or shear forces). [61]

Mechanical power and ergotrauma

Regarding ergotrauma specifically, it is important to cite what is reported in the article "*Static and Dynamic Contributors to Ventilator-induced Lung Injury in Clinical Practice. Pressure, Energy, and Power*" by Marini et al:[62] although most guidelines and clinical practices are certainly defensible

J Thorac Dis. 2018;10(3):1258-1264. doi:10.21037/jtd.2018.02.71
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5906244/

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Alveolar dynamics during mechanical ventilation in the healthy and injured lung.
Intensive Care Med Exp. 2019;7(Suppl 1):34. Published 2019 Jul 25. doi:10.1186/s40635-019-0226-5
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Static and Dynamic Contributors to Ventilator-induced Lung Injury in Clinical Practice. Pressure, Energy, and Power.
Am J Respir Crit Care Med. 2020;201(7):767-774. doi:10.1164/rccm.201908-1545CI
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7124710/

Marini JJ.

based on experimental models, it should be emphasized that no clinical study has yet directly demonstrated that VILI itself is the causal link between ventilation strategy and mortality risk, and we do not know what percentage of any mortality risk is directly attributable to mechanical ventilation itself. Moreover, ventilation is inherently a dynamic process, not a static one.

Although there is general agreement that intolerable tidal stresses and strains applied repeatedly to sensitive lung tissues are capable of initiating the VILI process, questions persist about how exactly these forces develop and damage.

Thus, the authors hypothesize that ventilator-related causes of lung damage can be unified into a single variable: **mechanical power**. [63]
In fact, energy must be expended to cause injury, and the product of the applied stress and the resulting tension determines the energy delivered to the lungs for each respiratory cycle.

It follows that the injury potential of the inflation pattern depends on the vulnerability of the tissues, the number of intolerable high-energy cycles applied in the unit of time (mechanical power), and the duration of that exposure.

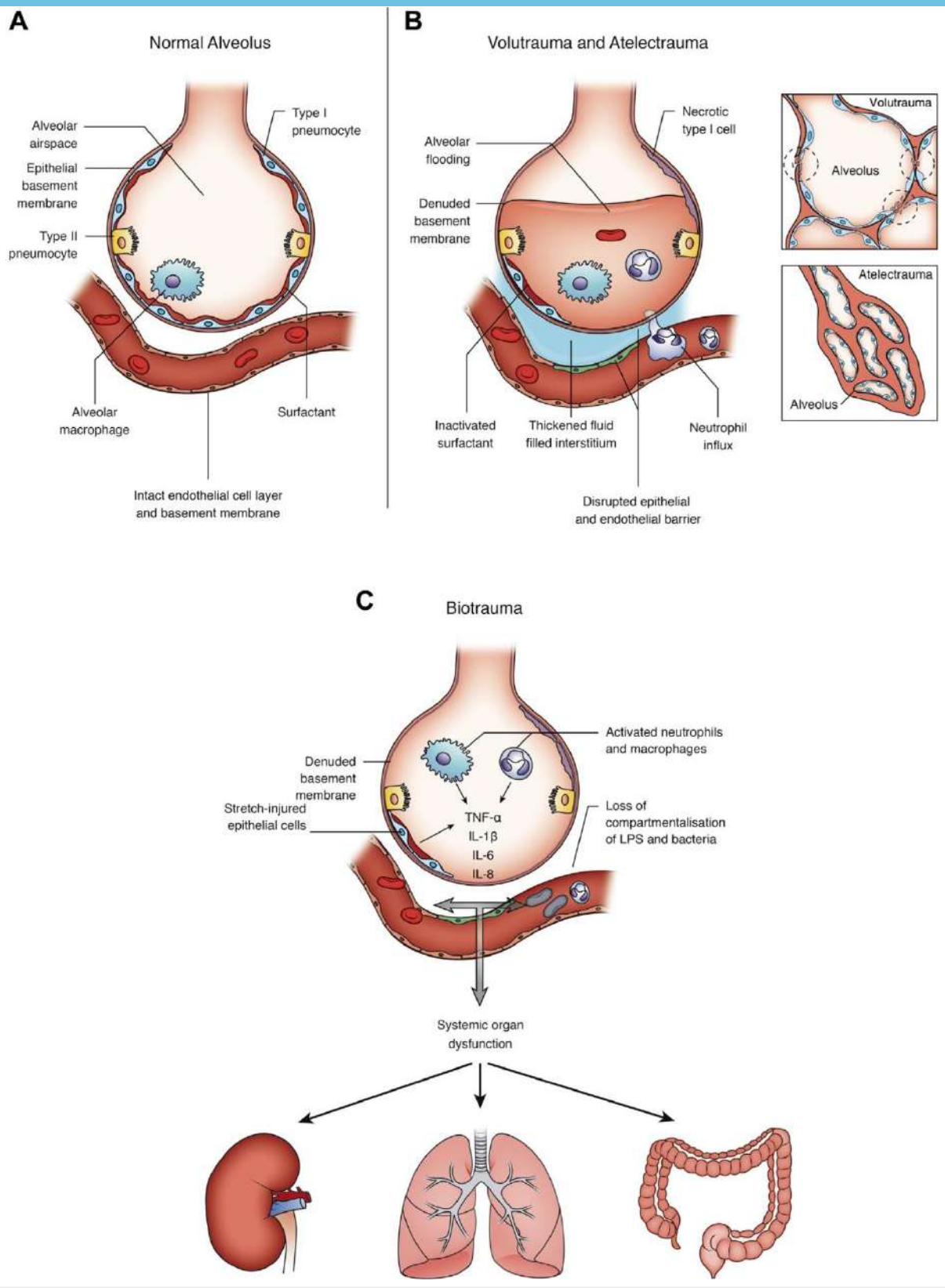
Definitions of Ventilator-induced Lung Injury Energetics

Stress	Forces tending to cause (and oppose) extension from resting state
Strain	Amount of elongation in the direction of applied force, relative to initial length
Energy per cycle	The entity that performs work of inflation
	Integral of pressure and inspiratory flow: $\int P\Delta V dt$
	Force × length product:
	pressure (force/area) × volume (area × length)
Power	Energy expended per unit time
	Product of inflation energy × ventilating frequency
Threshold	Stress–strain level at which tidal damage is initiated
Cumulative energy load and cumulative strain	Total number of energy or strain cycles delivered over a given period
Specific power	Power/volume on which it acts
Unaccounted (absorbed) energy	Inflation energy that is neither stored as potential energy nor dissipated in driving airflow

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7124710/

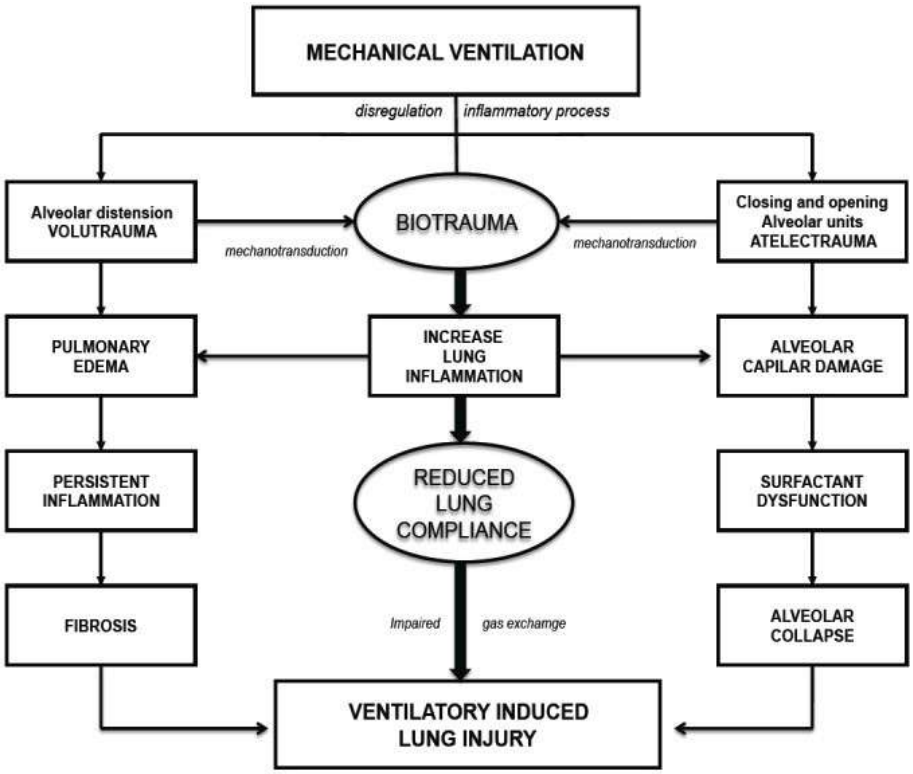
Dissipation of energy during the respiratory cycle: conditional importance of ergotrauma to structural lung damage.
Curr Opin Crit Care. 2018;24(1):16-22. doi:10.1097/MCC.0000000000000470
https://pubmed.ncbi.nlm.nih.gov/29176330/

[63] Tonetti T, Vasques F, Rapetti F, et al.
Driving pressure and mechanical power: new targets for VILI prevention.
Ann Transl Med. 2017;5(14):286. doi:10.21037/atm.2017.07.08
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537108/

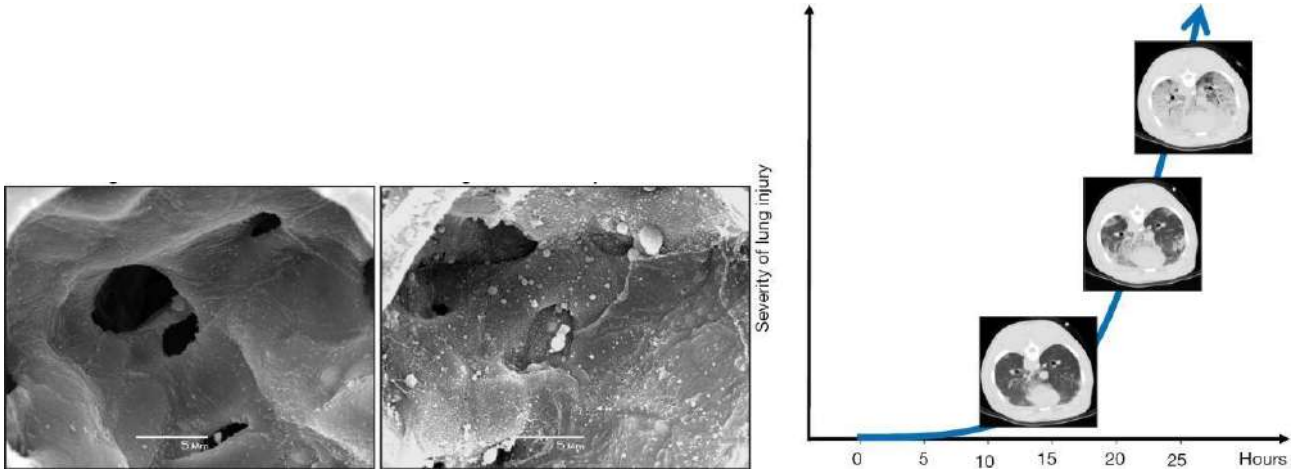


https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2816%2952763-9

A, **The normal alveolus**. **B**, **The ventilation-damaged alveolus,** resulting in pulmonary endothelial and epithelial injury, airspace flooding with protein-rich pulmonary edema and activated macrophages and neutrophils. **Volutrauma and atelectrauma (B)** during mechanical ventilation cause further disruption of the alveoli-capillary barrier and increased permeability, a hallmark of experimental VILI. **C,** Mechanical forces also induce increased concentrations of proinflammatory mediators (including IL-1b, tumor necrosis factor-alpha, IL-8 and IL-6) in the distal airspaces of the lung. Loss of compartmentalization in the lung results in the release of these mediators into the systemic circulation where they may play a role in end-organ dysfunction. I L . interleukin; LPS. lipopolysaccharide; TNF-a. tumor necrosis factor alpha.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4541417/
The term mechanotransduction refers to the conversion of mechanical stimuli into a biochemical response when the alveolar epithelium or vascular endothelium is stretched during mechanical ventilation



A B

A) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6212358/
Scanning electron micrograph depicting an undamaged alveolar surface (right panel) and fragmented alveolar epithelium (left panel) caused by two hours of ventilation at high tidal volumes and zero end expiratory pressure. Reproduced with permission from Hamlington et al. [64]

B) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537108/
The diagram represents the time course of experimentally ventilator-induced lung injury. As shown, the first lesions appear after 10-15 he are mainly represented by small CT opacities at the interface between the visceral and parietal pleura.
After 15 h the process becomes exponential and after 25 h the opacities affect the whole lung parenchyma .[65]

[64] Hamlington KL, Smith BJ, Dunn CM, Charlebois CM, Roy GS, Bates JHT.
Linking lung function to structural damage of alveolar epithelium in ventilator-induced lung injury.
Respir Physiol Neurobiol. 2018;255:22-29. doi:10.1016/j.resp.2018.05.004
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5986619/

[65] Cressoni M, Chiurazzi C, Gotti M, et al.
Lung inhomogeneities and time course of ventilator-induced mechanical injuries.
Anesthesiology 2015;123:618-27. 10.1097/ALN.0000000000000727
https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2323182

Ventilator-induced diaphragmatic dysfunction (VIDD)

Further experimental evidence suggests that controlled mechanical ventilation (CMV) may induce diaphragm dysfunction, resulting in an early onset and progressive decrease in diaphragmatic force generation capacity, called **ventilator-induced diaphragmatic dysfunction (VIDD)**.

Mechanisms of VIDD include muscle atrophy (resulting from lysosomal, calpain, caspase, and proteasome activation), oxidative stress, structural injury (altered myofibrils, increased numbers of lipid vacuoles, and abnormally small and disrupted mitochondria), myofiber remodeling, and mitochondrial dysfunction.
[66]

Lung protective ventilation

Protective ventilation aims to prevent ventilation-induced lung damage, particularly in patients without pulmonary problems who need to undergo anesthesia.

However, the potential is emerging for mechanical ventilation to worsen outcomes in patients with previously healthy lungs.
Normal lungs are probably no longer "healthy" during and after prolonged general anesthesia.

Atelectasis (collapse of lung tissue with volume loss) develops in about **90% of** anesthetized patients, regardless of ventilatory control (spontaneous or mechanically supported) and type of anesthesia. [67]

Excessive use of crystalloids increases capillary hydrostatic pressure and promotes interstitial/alveolar edema,[68] particularly when the lymphatic system is disrupted. In addition, tissue trauma, reperfusion from ischemia, blood transfusion, and exposure to extracorporeal devices may combine to cause regional heterogeneity that makes the lung more vulnerable to VILI.

There are three tools of protective ventilation:

1) **low volume**: a tidal volume can be considered low (hence protective) up to 7-8 mL/kg of ideal weight. In an average adult individual we can estimate an ideal weight of about 70 kg.
   Thus, protective ventilation would require a tidal volume of about 500 mL, which corresponds to that of a normal person.

[66] Vassilakopoulos T.
Ventilator-induced diaphragm dysfunction: the clinical relevance of animal models.
Intensive Care Med. 2008;34(1):7-16. doi:10.1007/s00134-007-0866-x
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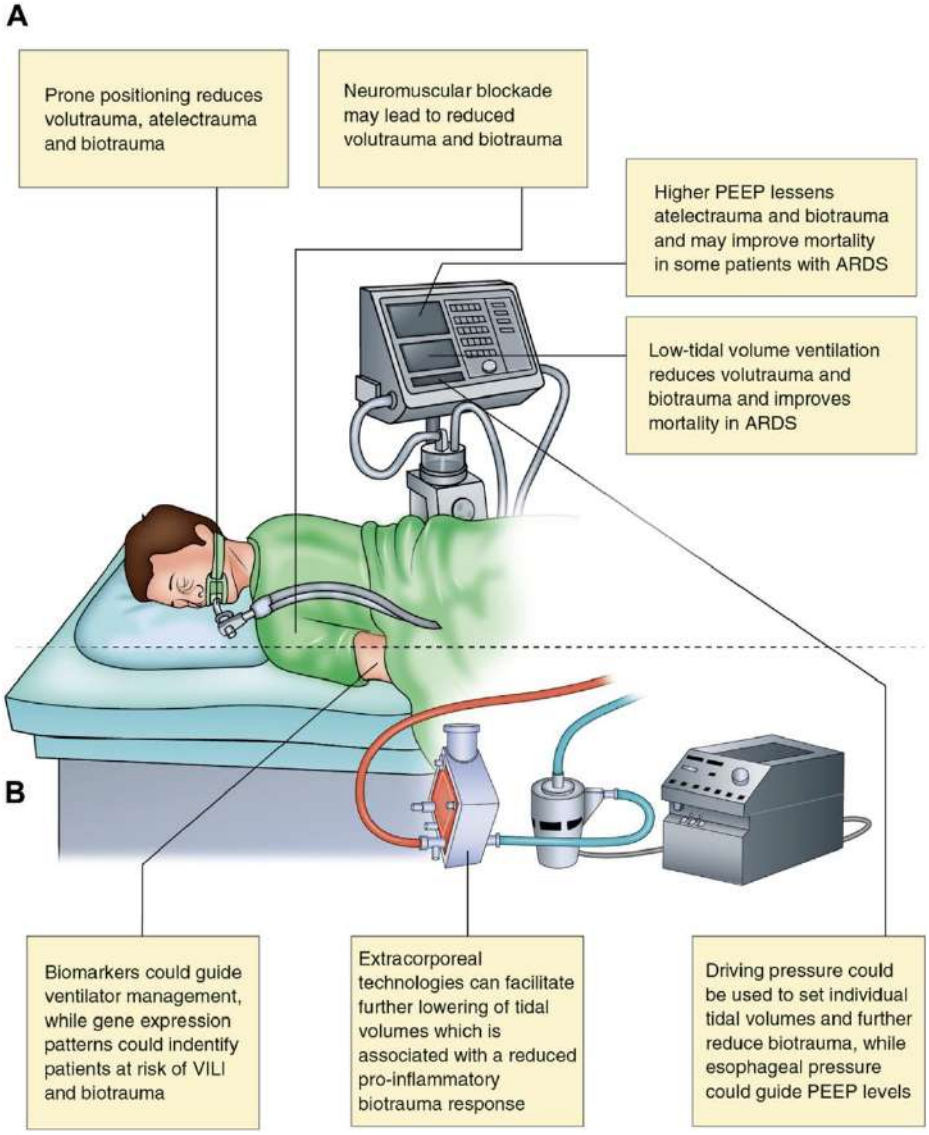
Peñuelas O, Keough E, López-Rodríguez L, et al.
Ventilator-induced diaphragm dysfunction: translational mechanisms lead to therapeutic alternatives in the critically ill.
Intensive Care Med Exp. 2019;7(Suppl 1):48. Published 2019 Jul 25. doi:10.1186/s40635-019-0259-9
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6658639/

[67] Hedenstierna G.
Airway closure, atelectasis and gas exchange during anesthesia.
Minerva Anesthesiol. 2002;68(5):332-336.
https://www.minervamedica.it/it/riviste/minerva-anestesiologica/articolo.php?cod=R02Y2002N05A0332

[68] Bihari S, Wiersema UF, Schembri D, et al.
Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes interstitial pulmonary edema in healthy subjects.
J Appl Physiol (1985). 2015;119(7):783-792. doi:10.1152/japplphysiol.00356.2015
https://journals.physiology.org/doi/pdf/10.1152/japplphysiol.00356.2015

2) **Plateau pressure less than 30 cmH2O**: In a healthy subject under general anesthesia, the elastance of the respiratory system is about 20 $_{cmH2O/L}$. This means that with one liter of tidal volume we get 20 $_{cmH2O\ of\ plateau}$ pressure.

3) **PEEP**: Healthy lungs when ventilated under anesthesia show early onset of basal atelectasis. These atelectasis are reversible with the application of PEEP. In other words, PEEP eliminates a side effect of controlled ventilation. [69]



https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2816%2952763-9
A, A protective ventilatory strategy using low tidal volume ventilation, prone positioning, neuromuscular blockade, and PEEP has been shown to reduce biotrauma and improve outcomes in patients with ARDS**. B,** In the future, a more individualized approach could see current volumes and PEEP adjusted using guiding pressures or esophageal pressures. Extracorporeal technologies could facilitate ultra-low tidal volumes and reduced biotrauma, while biomarkers or gene expression patterns could identify patients at high risk for VILI, biotrauma, and multiorgan failure before intubation and mechanical ventilation.
ARDS . acute respiratory distress syndrome; PEEP. positive end-expiratory pressure; VILI. ventilator-induced lung damage e.

The respiratory unit

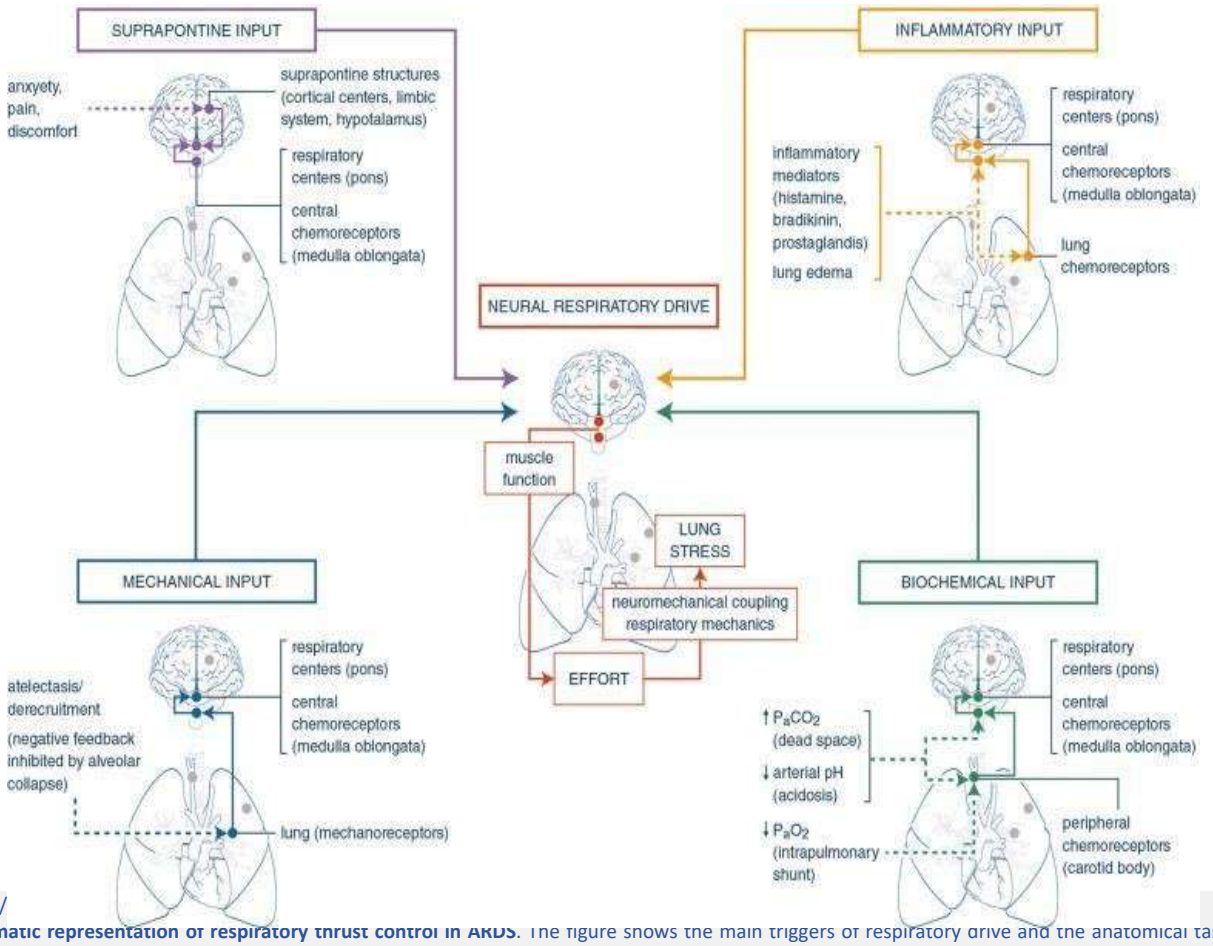
The respiratory drive (respiratory drive: intensity of the signal output from the respiratory center), determines the effort exerted in each breath: high respiratory drive (cough) can induce labored breathing and dyspnea, while weak breathing can lead to poor inspiratory effort and apnea.

Excessive respiratory effort could not only be related to the severity of ARDS but, if not carefully managed, could contribute to lung and diaphragm injury.

[69] http://www.ventilab.org/2011/12/26/ventilazione-protettiva-per-i-polmoni-sani-seconda-parte/

Therefore, monitoring of the respiratory system and interventions that can limit its effects within physiological limits should be the top priorities for the ICU physician caring for individuals with ARDS.

Critical conditions can affect patients' respiratory drive through multiple pathways, operating mainly **through** three **feedback systems: cortical, metabolic and chemical**.
The chemical feedback system, defined as the outgoing response from the respiratory center to changes in arterial blood gases and pH, is one of the most important determinants of the respiratory system. [70]



https:/
Schematic representation of respiratory thrust control in ARDS. The figure shows the main triggers of respiratory drive and the anatomical targets where these triggers exert their effects. In the center is depicted the descending cascade from neural respiratory drive to respiratory effort and pulmonary stress, along with the main factors that can cause a dissociation between drive and effort (i.e., muscle function) and between drive, effort, and pulmonary stress (e.g. , neuromechanical coupling and respiratory mechanics)

[70] Spinelli E, Mauri T, Beitler JR, Pesenti A, Brodie D.
Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions.
Intensive Care Med. 2020;46(4):606-618. doi:10.1007/s00134-020-05942-6
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7224136/

Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D.
Respiratory Drive in Critically Ill Patients. Pathophysiology and Clinical Implications.
Am J Respir Crit Care Med. 2020;201(1):20-32. doi:10.1164/rccm.201903-0596SO
https://pubmed.ncbi.nlm.nih.gov/31437406/

Jonkman AH, de Vries HJ, Heunks LMA.
Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment.
Crit Care. 2020;24(1):104. Published 2020 Mar 24. doi:10.1186/s13054-020-2776-z
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7092542/

Damage caused by noninvasive ventilation

When evaluating the benefit/risk ratio of noninvasive ventilation, it should be kept in mind that while avoidance of intubation with noninvasive ventilation (NIV) or high-flow nasal cannula improves clinical outcome, treatment failure worsens mortality.

Recent data suggest **self-inflicted lung injury (P-SILI)** as a possible mechanism that aggravates lung damage in these patients.
P-SILI is generated by intense inspiratory effort that produces:

(A) fluctuations in transpulmonary pressure (i.e., lung stress) that cause inflation of large volumes in an aerated compartment markedly reduced by disease-induced loss of aeration;

(B) Abnormal increases in transvascular pressure, promoting negative pressure pulmonary edema;

(C) An intra-tidal displacement of gas between different lung zones, generated by different muscle force transmission;

(D) Injury to the diaphragm.

Experimental data suggest that among patients with mild oxygenation impairment ($_{PaO2}$ / FiO2> 200 mmHg), maintenance of spontaneous breathing may be safe and effective, and all noninvasive strategies (i.e., low-flow oxygen, CPAP, NIV, and HFNC) may be essentially equivalent.

In contrast, in patients with $_{PaO2}$ / $_{FiO2}$ ≤200 mmHg, the clinical evidence appears controversial.
This is consistent with pathophysiological data indicating that the detrimental effects of spontaneous breathing may be amplified in the most severe patients and that patients with a $_{PaO2}$ / $_{FiO2}$ ratio below 200 mmHg may represent the population most at risk.

The optimal initial noninvasive treatment of hypoxemic respiratory failure/ARDS, however, remains uncertain; high-flow nasal cannula and high-VEP NIV helmet are promising tools to improve the success of the approach, but the best balance between these techniques has yet to be identified.

During noninvasive support, close clinical monitoring is necessary for prompt detection of treatment failure so as not to delay intubation and protective ventilation. [71]

GUIDELINES FOR THE CLINICAL MANAGEMENT OF THE COVID-19 PATIENT

The guidelines proposed by the experts provide an understanding of why mechanical ventilation was proposed and how it was and is currently adopted.

In the *"Position Paper on the Practical Implementation of Differential Therapy for Acute Respiratory Failure [ARI] in COVID-19" (German Society of Pulmonology and Respiratory Medicine eV (DGP) Position Paper for*

[71] Grieco DL, Menga LS, Eleuteri D, Antonelli M.
Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support.
Minerva Anesthesiol. 2019;85(9):1014-1023. doi:10.23736/S0375-9393.19.13418-9
https://www.minervamedica.it/it/riviste/minerva-anestesiologica/articolo.php?cod=R02Y2019N09A1014

Arnal JM, Chatburn R.
Paying attention to patient self-inflicted lung injury.
Minerva Anesthesiol. 2019;85(9):940-942. doi:10.23736/S0375-9393.19.13778-9
https://www.minervamedica.it/it/riviste/minerva-anestesiologica/articolo.php?cod=R02Y2019N09A0940

the cutting-edge application of respiratory support in patients with COVID-19)[72] the following five topic areas were discussed by a team of experts*:*

1. Pathophysiology of acute respiratory failure in patients without immunity infected with SARS-CoV-2.
2. Time course and prognosis of acute respiratory failure during the course of the disease.
3. Oxygen insufflation, high-flow oxygen, noninvasive ventilation, and invasive ventilation with emphasis on infectious aerosol formation.
4. Noninvasive ventilation in ARI.
5. Providing a continuum for the treatment of ARI.

The significant results described are as follows:
Regarding the pathophysiological aspects of acute respiratory failure (ARI), lung infection with SARS-CoV-2 COVID-19 goes through three stages: early infection, pulmonary manifestation, and severe hyperinflammatory phase.
The severity of respiratory failure is determined by an interaction between 3 factors:
1) severity of infection, immune response, functionality, and comorbidities,
2) The patient's ventilatory response to hypoxemia (respiratory drive) and
3) The interval between first symptoms and initiation of clinical treatment.

There are differences between COVID-19-induced advanced lung damage and the changes observed in acute respiratory distress syndromes (ARDS) as defined by the Berlin criteria*.
In a pathophysiologically plausible, but currently not yet histopathologically proven, pattern, two types (type L and type H) are distinguished, corresponding to early and late stage.
This distinction can be taken into account for the differential treatment of ARI.

**Berlin definition*[73] *of acute respiratory distress syndrome.*

The term acute lung injury (ALI) was previously used to describe mild forms of ARDS, but the definition currently has been dropped and replaced by assigning ARDS a severity scale

[72] Pfeifer M, Ewig S, Voshaar T, et al.
Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19.
Respiration. 2020;99(6):521-542. doi:10.1159/000509104
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7360514/

Pfeifer M, Ewig S, Voshaar T, et al.
Positionspapier zur praktischen Umsetzung der apparativen Differenzialtherapie der akuten respiratorischen Insuffizienz bei COVID-19 [Position Paper for the State of the Art Application of Respiratory Support in Patients with COVID-19 - German Respiratory Society].
Pneumologie. 2020;74(6):337-357. doi:10.1055/a-1157-9976
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7378547/Positionspapier zur praktischen Umsetzung der apparativen Differenzialtherapie der akuten respiratorischen Insuffizienz bei COVID-19

[73] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al.
Acute respiratory distress syndrome: the Berlin Definition.
JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669
https://med.uth.edu/internalmedicine/wp-content/uploads/sites/65/2014/07/ARDS-Berlin-definition1.pdf

Acute respiratory distress syndrome
https://www.erswhitebook.org/files/public/Italian%20PDFs/20.Sindrome%20del%20Distrss.....
pdf

The Berlin definition of the acute respiratory distress syndrome [11].

Clinical Feature	Definition
Timing	Develops within one week of clinical insult
Chest Imaging	Bilateral opacities not otherwise explained by pleural effusions, lobar collapse or nodules
Origin of Edema	Non-cardiogenic edema; edema not suspected to be from an elevated left atrial pressure causing hydrostatic edema; an echocardiogram may be needed in unclear cases
Oxygenation	Mild: PaO_2/FiO_2 of >200 mm Hg to ≤ 300 mm Hg with PEEP or CPAP ≥5 cmH_2O Moderate: PaO_2/FiO_2 of >100 mm Hg to ≤ 200 mm Hg with PEEP ≥5 cmH_2O Severe: PaO_2/FiO_2≤ 100 mm Hg with PEEP ≥5 cmH_2O

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335247/ [74]

COVID-19 type L pneumonia

This early stage, which can be compensated by the patient with oxygen support, is described by Gattinoni et al.[75] and is called COVID-19 type L pneumonia.
L stands for:

• **Low elasticity**. Compliance and amount of gas in the lung is almost normal [76]

*Lung elasticity has two components: **Parenchymal**: elastic components of lung tissue formed by elastin fibers (easily distensible) and collagen (less distensible). **Alveolar**: surface tension (Ts), generated in the alveolus by the existence of the air/liquid interface.*

• **Low ventilation-to-perfusion ratio** (VA/Q): hypoxemia can be best explained by loss of perfusion regulation and loss of hypoxic vasoconstriction. Consequently, at this stage, pulmonary artery pressure should be nearly normal.

The ventilation/perfusion ratio is the ratio of alveolar ventilation ($_{VA}$) to cardiac output (Q)

• **Low lung weight**: Only ground-glass densities are present on the CT scan, located mainly subpleurally and along the lung fissures. As a result, the lung weight is only moderately increased.

• **Low pulmonary recruitability**: the amount of nonaerated tissue and recruitability are very low.[77]

[74] Lentz S, Roginski MA, Montrief T, Ramzy M, Gottlieb M, Long B.
Initial emergency department mechanical ventilation strategies for COVID-19 hypoxemic respiratory failure and ARDS [published online ahead of print, 2020 Jul 4]. Am J Emerg Med. 2020;doi:10.1016/j.ajem.2020.06.082
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335247/

[75] Gattinoni, L., Chiumello, D., Caironi, P. et al.
COVID-19 pneumonia: different respiratory treatments for different phenotypes?
Intensive Care Med 46, 1099-1102 (2020). https://doi.org/10.1007/s00134-020-06033-2
https://rdcu.be/b5Q4S

[76] Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M.
Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis. 1987;136(3):730-736. doi:10.1164/ajrccm/136.3.730
https://doi.org/10.1164/ajrccm/136.3.730

[77] Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G.

Alveolar recruitment is a dynamic process that aims to reopen atelectatic alveolar units, and is achieved by an increase in trans-pulmonary pressure. This increase is necessary to overcome the pressure critical opening of collapsed alveoli. Recruitment leads to an increase in the total number of alveoli available for ventilation and this results in increased lung and thoracic compliance, increased functional residual capacity (which we recall is the sum of residual volume and expiratory reserve volume), reduced small airway resistance, reduced oxygen consumption of respiratory muscles and reduced shunt.

To conceptualize these phenomena, we hypothesize the following sequence of events: viral infection leads to modest local subpleural interstitial edema (ground-glass lesions) located particularly at the interfaces between lung structures with different elastic properties, where stress and strain are concentrated. [78]

Vasoplegia represents severe hypoxemia. The normal response to hypoxemia is to increase minute ventilation, mainly by increasing tidal volume[79] (up to 15-20 mL/kg), associated with a more negative inspiratory intrathoracic pressure.

Indeterminate factors other than hypoxemia markedly stimulate breathing in these patients. Near-normal compliance, however, explains why some of the patients present without dyspnea while the patient inhales the expected volume.
This increase in minute ventilation leads to a decrease in $_{PaCO2}$.

Disease evolution: the transition between phenotypes.
Type L patients may remain unchanged for a period and then either improve or worsen.
The possible key feature that determines the evolution of the disease, in addition to the severity of the disease itself, is the depth of negative intrathoracic pressure associated with increased tidal volume in spontaneous breathing.

Indeed, the combination of negative inspiratory intrathoracic pressure and increased lung permeability due to inflammation results in interstitial pulmonary edema.
This phenomenon, initially described by Barach in[80] and Mascheroni in[81] both in an experimental setting, has recently been recognized as the major cause of self-inflicted lung injury (P- SILI). [82]

Lung recruitment in patients with the acute respiratory distress syndrome.
N Engl J Med. 2006;354:1775-1786. doi: 10.1056/NEJMoa052052.
https://www.nejm.org/doi/pdf/10.1056/NEJMoa052052?articleTools=true

A.N. Cracchiolo, D.M. Palma
ALI/ARDS alveolar recruitment maneuvers: what real utility?
http://www.timeoutintensiva.it/studentcorner/25_Le%20manovre%20di%20reclutamento%20alveolare.pdf

[78] Cressoni M, Cadringher P, Chiurazzi C, et al.
Lung inhomogeneity in patients with acute respiratory distress syndrome.
Am J Respir Crit Care Med. 2014;189(2):149-158. doi:10.1164/rccm.201308-1567OC
https://www.atsjournals.org/doi/abs/10.1164/rccm.201308-1567OC
[79] Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D.
Respiratory drive in critically ill patients. Pathophysiology and clinical implications. Am J Respir Crit Care Med. 2020;201:20–32. doi: 10.1164/rccm.201903-0596SO
https://www.atsjournals.org/doi/abs/10.1164/rccm.201903-0596SO

[80] Al B, Martin J, Eckman M.
Positive pressure respiration and its application to the treatment of acute pulmonary edema.
Ann Intern Med. 1938;12:754-795. doi: 10.7326/0003-4819-12-6-754
https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-12-6-754

[81] Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D.
Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study.
Intensive Care Med. 1988;15(1):8-14. doi:10.1007/BF00255628
https://link.springer.com/content/pdf/10.1007/BF00255628.pdf

[82] Brochard L, Slutsky A, Pesenti A.
Mechanical ventilation to minimize progression of lung injury in acute respiratory failure.
Am J Respir Crit Care Med. 2017;195:438–442. doi: 10.1164/rccm.201605-1081CP.
https://www.atsjournals.org/doi/pdf/10.1164/rccm.201605-1081CP

Over time, increasing edema increases lung weight, superimposed pressure, and dependent atelectasis. When pulmonary edema reaches a certain amplitude, the volume of gas in the lung decreases and the tidal volumes (tidal volume) generated for a given inspiratory pressure decrease. [83]
At this stage, dyspnea develops, which in turn leads to worsening P-SILI.

The transition from Type L to Type H may be due to the evolution of COVID-19 pneumonia on the one hand and injury attributable to high-stress ventilation on the other.

COVID-19 type H pneumonia

According to current studies, about 15-20% of patients treated in the hospital develop severe lung damage.

The progressive critical state is described by Gattinoni et al. as type H-COVID-19 pneumonia:
The type H patient presents:

- **High elasticity**. The decrease in gas volume due to increased edema explains the increase in lung elasticity.

- **High right-to-left shunt**. This is due to the fraction of cardiac output that perfuses the nonaerated tissue that develops in dependent lung regions due to increased edema and superimposed pressure.

- **Elevated lung weight**. Quantitative CT analysis shows a significant increase in lung weight (> 1.5 kg), in the range of severe ARDS. [84]

- **High pulmonary recruitability**. The increased amount of nonaerated tissue is associated, as in severe ARDS cases, with increased recruitability. [85]

In the type H model, 20-30% of patients examined, fully meet the criteria of severe ARDS: hypoxemia, bilateral infiltrates, reduced respiratory system compliance, increased lung weight and recruitment potential.

If not expertly and individually managed with consideration of vasocentric features, a COVID-19 patient with ARDS ("**CARDS**" COVID-19 patient with ARDS)[86] may eventually develop multiorgan failure, even when not of advanced age or predisposed by preexisting comorbidities.

The figure below summarizes the described course.

[83] Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L.
Vertical gradient of regional lung inflation in adult respiratory distress syndrome.
Am J Respir Crit Care Med. 1994;149(1):8-13. doi:10.1164/ajrccm.149.1.8111603
https://www.atsjournals.org/doi/abs/10.1164/ajrccm.149.1.8111603

[84] Maiolo G, Collino F, Vasques F, Rapetti F, Tonetti T, Romitti F, Cressoni M, Chiumello D, Moerer O, Herrmann P, Friede T, Quintel M, Gattinoni L.
Reclassifying acute respiratory distress syndrome.
Am J Respir Crit Care Med. 2018;197:1586–1595. doi: 10.1164/rccm.201709-1804OC.
https://www.atsjournals.org/doi/pdf/10.1164/rccm.201709-1804OC

[85] Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G.
Lung recruitment in patients with the acute respiratory distress syndrome.
N Engl J Med. 2006;354:1775-1786. doi: 10.1056/NEJMoa052052.
https://www.nejm.org/doi/pdf/10.1056/NEJMoa052052?articleTools=true

[86] Marini JJ, Gattinoni L.
Management of COVID-19 Respiratory Distress
[published online ahead of print, 2020 Apr 24]. JAMA. 2020;10.1001/jama.2020.6825. doi:10.1001/jama.2020.6825
https://www.sicp.it/wp-content/uploads/2020/03/JAMA_Marini_management-respiratory-distress-april-2020.pdf

In panel a, CT is shown in the spontaneous breathing of a type L patient on admission and in panel b, his transition to type H after 7 days of noninvasive support. As shown, a similar degree of hypoxemia was associated with different profiles in lung imaging.

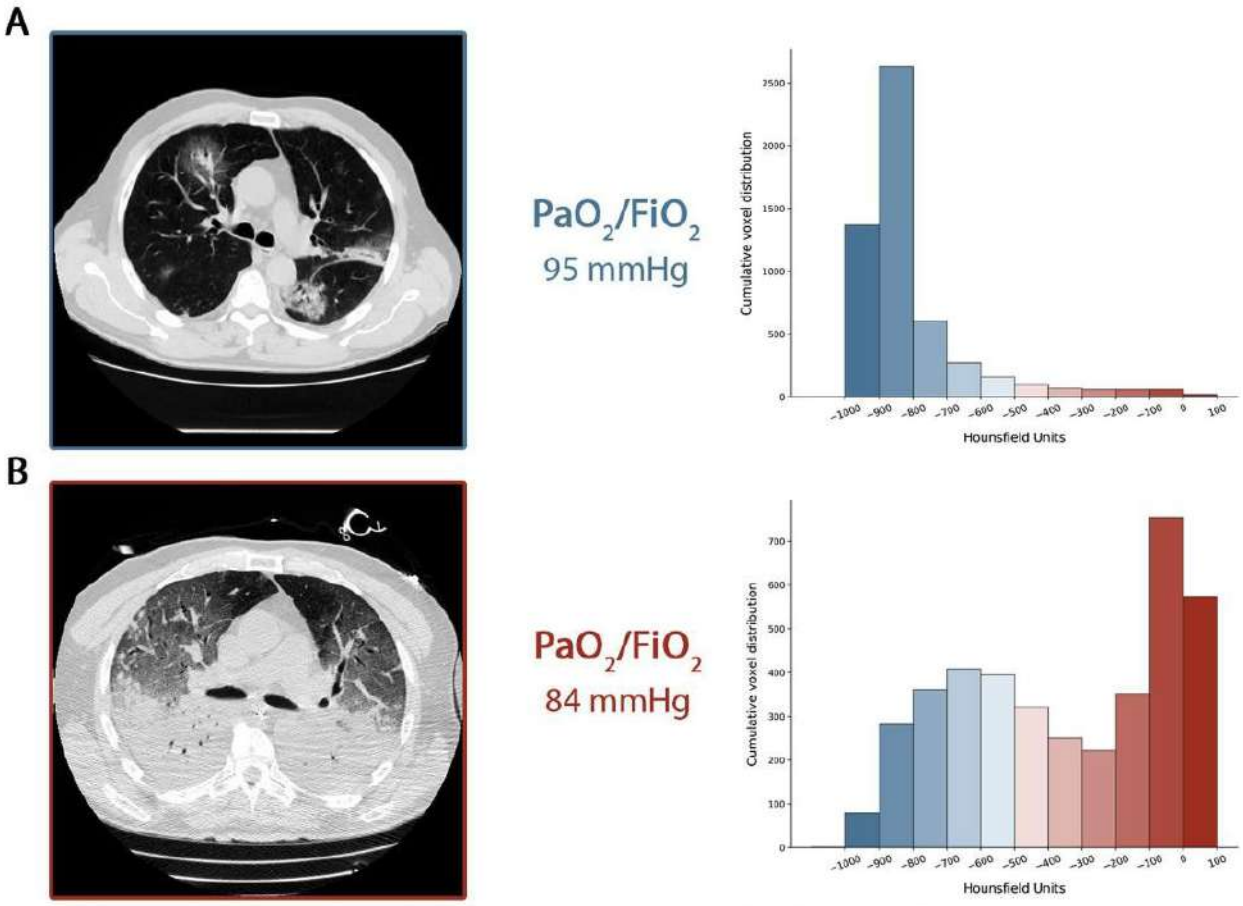


Fig. 1 **a** CT scan acquired during spontaneous breathing. The cumulative distribution of the CT number is shifted to the left (well-aerated compartments), being the 0 to − 100 HU compartment, the non-aerated tissue virtually 0. Indeed, the total lung tissue weight was 1108 g, 7.8% of which was not aerated and the gas volume was 4228 ml. Patient receiving oxygen with venturi mask inspired oxygen fraction of 0.8. **b** CT acquired during mechanical ventilation at end-expiratory pressure at 5 cmH_2O of PEEP. The cumulative distribution of the CT scan is shifted to the right (non-aerated compartments), while the left compartments are greatly reduced. Indeed, the total lung tissue weight was 2744 g, 54% of which was not aerated and the gas volume was 1360 ml. The patient was ventilated in volume controlled mode, 7.8 ml/kg of tidal volume, respiratory rate of 20 breaths per minute, inspired oxygen fraction of 0.7

Respiratory treatment

Given this conceptual model, it follows that the respiratory treatment offered to L-type and H-type patients must be different. The proposed treatment is consistent with what was observed in COVID-19, although the huge number of patients seen in this pandemic may limit its broad applicability.

1. The first step in reversing hypoxemia is through an increase in $_{FiO2}$ to which the type L patient responds well, particularly if not yet out of breath.
2. In type L patients with dyspnea, several noninvasive options are available: high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV).

At this stage, measurement (or estimation) of inspiratory esophageal pressure fluctuations is crucial. [87]
In the absence of esophageal manometry, surrogate measures of respiratory work should be evaluated,

[87] Gattinoni L, Giosa L, Bonifazi M, Pasticci I, Busana M, Macri M, Romitti F, Vassalli F, Quintel M.
Targeting transpulmonary pressure to prevent ventilator-induced lung injury.
Expert Rev Respir Med. 2019;13:737-746. doi: 10.1080/17476348.2019.1638767
https://www.minervamedica.it/it/riviste/minerva-anestesiologica/articolo.php?cod=R02Y2009N05A0293

such as fluctuations in central venous pressure[88] or clinical detection of excessive inspiratory effort. In intubated patients, it is also necessary to determine P0.1 ae $_{Pocclusion}$

High PEEP, in some patients, can reduce pleural pressure fluctuations and stop the vicious cycle that aggravates lung injury. However, high PEEP in patients with normal compliance may have detrimental effects on hemodynamics.

In any case, noninvasive options are questionable, as they may be associated with high failure rates and delayed intubation, in a disease that typically lasts several weeks.

3. The magnitude of inspiratory pleural pressure fluctuations can determine the transition from L-type to H-type phenotype. As esophageal pressure oscillations increase from 5 to 10 cm H2O-which are generally well tolerated-to over 15 cm $_{H2O}$, the risk of lung injury increases and therefore intubation should be performed as soon as possible.

4. Once intubated and deeply sedated, type L patients, if hypercapnic, can be ventilated with volumes above 6 ml/kg (up to 8-9 ml/kg), as high compliance results in tolerable effort without risk of VILI. Pronate positioning should be used only as a rescue maneuver, as lung conditions are "too good" for the effectiveness of prone position, which relies on improved stress and redistribution of tension. PEEP should be reduced to 8-10 $_{cmH2O}$, as recruitment is low and the risk of hemodynamic failure increases at higher levels. Early intubation can prevent transition to the H-type phenotype.

5. Type H patients should be treated as severe ARDS, including higher PEEP, if compatible with hemodynamics, pronated positioning, and extracorporeal support.

In conclusion, Type L and Type H patients are best identified by CT and are influenced by different pathophysiological mechanisms. If not available, the signs implicit in the definition of Type L and Type H could be used as surrogates: elasticity of the respiratory system and recruitability.

Patients who convert to type H can rapidly enter a spiral of hypoxemia, shunting, and ventilatory dead space toward full-blown ARDS. It follows that it is vital to recognize and interrupt phenotypic conversion and entry into the VILI vortex.

It should be noted that a case control was recently reported in the literature[89] that presented on admission an L phenotype then complicated by severe ARDS, multiorgan failure, cytokine release syndrome, and coagulopathy within 8 days during hospitalization, with conversion to the H phenotype and VILI ("VILI vortex") with fatal outcome.

Importance of cardiovascular stress [90]

Hypoxemia with decreased oxygen content requires an increase in cardiac output to ensure adequate oxygen transport (oxygen supply is calculated as the product of cardiac output and oxygen content).

[88] Walling PT, Savege TM.
A comparison of oesophageal and central venous pressures in the measurement of transpulmonary pressure change.
Br J Anaesth. 1976;48(5):475-479. doi:10.1093/bja/48.5.475
https://bjanaesthesia.org/article/S0007-0912(17)48695-8/pdf

[89] Deliwala SS, Ponnapalli A, Seedahmed E, Berrou M, Bachuwa G, Chandran A.
A 29-Year-Old Male with a Fatal Case of COVID-19 Acute Respiratory Distress Syndrome (CARDS) and Ventilator-Induced Lung Injury (VILI). Am J Case Rep. 2020;21:e926136. Published 2020 Jul 23. doi:10.12659/AJCR.926136
https://www.amjcaserep.com/download/index/idArt/926136

[90] Pfeifer M, Ewig S, Voshaar T, et al.
Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19.
Respiration. 2020;99(6):521-542. doi:10.1159/000509104
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7360514/

At the same time, due to hyperventilation, the heart can also be stressed by increased left ventricular recharge. Increased respiratory effort leads to an increase in negative intrathoracic pressure, so as to increase transmural pressure for the left ventricle.
Pathophysiologically, right heart strain may develop as part of the development of hypoxemia, but there is currently no indication of this for the early stage of the disease.

As with community-acquired pneumonia (CAP), the systemic inflammatory response can promote cardiac complications such as arrhythmias, heart failure, and coronary events, and the rate of cardiac manifestations in COVID-19 is higher than the rate in CAP (about 25 percent).
Another cause of cardiac damage may be myocarditis, but so far only a few significant cases are available.

How the increase in D-dimers reflects an increase in coagulopathy has not yet been elucidated.
In fact, the disease appears to be associated with an increased risk of thrombotic events and disorders of the coagulation system.
In a series of 81 critically ill COVID-19 patients, 25% had pulmonary embolism. [91] However, whether these were thrombo-embolic events or in situ thrombosis is still not fully clarified.

Protection of personnel [92]

In principle, aerosols can transmit infectious particles containing viruses.
Open or leaky systems (so-called vented masks) can increase the release of respirable particles.

Procedures requiring opening of the invasive ventilation system and endotracheal intubation are associated with an increased risk of infection.

Staff protection through personal protective equipment should be a very high priority, as fear of infection should not be a major reason for intubation.

In accordance with the requirements for protective equipment (eye protection, FFP2 or FFP-3 mask, gown), inhalation therapy, high nasal flow (NHF) therapy, CPAP therapy or NIV can be performed by staff according to the current state of knowledge without an increased risk of infection.

Recommendations for the management of ARDS in COVID-19 patients

Spontaneously breathing patients with acute hypoxemic failure have high respiratory effort (respiratory drive) with high tidal volumes and thus potentially harmful transpulmonary pressure fluctuations [93,76] .
As the patient's respiratory system is preserved with NIV, additional and, in particular, too much inspiratory pressure support can cause an increase in tidal volume, potentially too much and aggravate lung damage.
In these situations, NIV is no longer lung protective because current volumes considered protective cannot be applied[94] .

[91] Cui S, Chen S, Li X, Liu S, Wang F.
Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424. doi:10.1111/jth.14830
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7262324/

[92] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7360514/
[93] Brochard L, Slutsky A, Pesenti A.
Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure.
Am J Respir Crit Care Med. 2017;195(4):438-442. doi:10.1164/rccm.201605-1081CP
https://www.atsjournals.org/doi/pdf/10.1164/rccm.201605-1081CP

[94] Karagiannidis C, Bein T, Windisch W.
Was hat sich seit Publikation der S3-Leitlinie "Invasive Beatmung und Einsatz extrakorporaler Verfahren" getan?

As already seen, Gattinoni et al[95] in their study on atypical ARDS in COVID-19 recommend - referring to the studies of Brochard et al - in patients with clinical signs of excessive inspiratory breathing under CPAP or NIV, intubation should be preferred to avoid excessive negative intrathoracic pressures and self-induced lung damage (P-SILI)[74] .

A therapeutic attempt with noninvasive methods in the form of NIV, or mainly with CPAP and progression to an NIV, can be performed in cases of hypoxemic respiratory failure and insufficient response to pure oxygen administration or mild ARDS, and particularly in the case of hypercapnic respiratory failure (e.g., cardiac comorbidity, COPD, hypoventilation due to obesity, neuromuscular disease)[96] .
Current Italian recommendations mainly include the use of high CPAP pressures and only then to intensify NIV[97] .
On the other hand, only 11% of ICU patients in Lombardy were treated with NIV[98] .
Intubations were performed with a median $_{PaO2/FiO2}$ of 160; subsequently there was a high demand for PEEP.

A comparable approach to CPAP/NIV is expressed in the NHS recommendations in Great Britain[99] , however, with the important caveat that the intubation threshold should be low and immediate intubation and mechanical ventilation should be considered in the presence of clinical deterioration (increased $_{O2}$ requirements, steady or rapid reduction in $_{SaO2}$ and/or increased respiratory rate and increased work of breathing).
In their recent overview of therapies for severe community-acquired respiratory viral infections, Arabi et al. in analogy to previous evidence that NIV can be used in selected patients in the early stages and milder forms of acute hypoxemic respiratory failure[100] point out that in patients without early improvement, NIV only delays intubation but does not prevent it.

[Update and Comment on the German S3 "Clinical Guideline for Treating Acute Respiratory Insufficiency with Invasive Ventilation and Extracorporeal Membrane Oxygenation: Evidence-Based Recommendations"].
Pneumologie. 2020;74(1):46-49. doi:10.1055/a-1065-6230
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-1065-6230

[95] Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D.
COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome.
Am J Respir Crit Care Med. 2020;201(10):1299-1300. doi:10.1164/rccm.202003-0817LE
https://www.atsjournals.org/doi/pdf/10.1164/rccm.202003-0817LE

[96] Schönhofer B, Kuhlen R, Neumann P, Westhoff M, Berndt C, Sitter H.
Nichtinvasive Beatmung als Therapie der akuten respiratorischen Insuffizienz. Das Wichtigste der neuen S3-Leitlinie [Non-invasive ventilation as treatment for acute respiratory insufficiency. Essentials from the new S3 guidelines].
Anaesthesist. 2008;57(11):1091-1102. doi:10.1007/s00101-008-1449-0
https://link.springer.com/article/10.1007/s00101-008-1449-0

Rochwerg B, Brochard L, Elliott MW, et al.
Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure.
Eur Respir J. 2017;50(2):1602426. Published 2017 Aug 31. doi:10.1183/13993003.02426-2016
https://erj.ersjournals.com/content/50/2/1602426.long

[97] Managing the Respiratory care of patients with COVID-19.
https://ers.app.box.com/s/j09ysr2kdhmkcu1ulm8y8dxnosm6yi0h

[98] Grasselli G, Zangrillo A, Zanella A, et al.
Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy
[published online ahead of print, 2020 Apr 6]. JAMA. 2020;323(16):1574-1581. doi:10.1001/jama.2020.5394
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136855/

[99] Guidance for the role and use of non-invasive respiratory support in adult patients with coronavirus (confirmed or suspected) March 26, 2020
Version 2
https://amhp.org.uk/app/uploads/2020/03/Guidance-Respiratory-Support.pdf

[100] Arabi YM, Fowler R, Hayden FG.
Critical care management of adults with community-acquired severe respiratory viral infection.

Similar results emerge from the currently available publications on ventilation for COVID-19.
The development from the onset of the first respiratory symptoms to ARDS to subsequent intubation can- especially with COVID-19-proceed rapidly within a few days, so sometimes a quick decision on ventilation must be made[101,80,102] .

The presence of bilateral pneumonia and progressive deterioration of thoracic CT are prognostically unfavorable signs of such development[103] .

The extent of ARI (acute respiratory failure) should be assessed by an analysis of arterial or capillary blood gases in the ambient air and calculation of oxygen delivery (measured by the variables of oxygen saturation, Hb value, Hüfner correction number, and cardiac output). [104]

During CPAP/NIV, a patient can deteriorate rapidly. For this reason, continuous monitoring
and the rapid performance of intubation if necessary must be ensured at all times.
If CPAP/NIV leads to further progression of ARI, intubation and subsequent invasive ventilation should be performed without delay unless a Do not Intubate (DNI) order is in place.

An extracorporeal lung replacement (ECMO) procedure should be considered in patients for whom invasive ventilation, when all measures taken in accordance with the guidelines have been exhausted, are not sufficient to ensure adequate oxygen uptake and $_{CO2}$ release, however, the increased risk of thrombosis in COVID-19 patients should be considered. [105]

To conclude, we report the table published in Lancet Respir Med "*COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted*?" on recommendations for the management of ARDS associated with COVID-19,[106] in which the following is reported regarding intubation time:

Intensive Care Med. 2020;46(2):315-328. doi:10.1007/s00134-020-05943-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7079862/

[101] Wang D, Hu B, Hu C, et al.
Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7].
JAMA. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7042881/

[102] Goh KJ, Choong MC, Cheong EH, et al.
Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from COVID-19 Infection.
Ann Acad Med Singapore. 2020;49(3):108-118.
http://www.annals.edu.sg/pdf/49VolNo3Mar2020/V49N3p108.pdf

[103] Shi H, Han X, Jiang N, et al.
Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study.
Lancet Infect Dis. 2020;20(4):425-434. doi:10.1016/S1473-3099(20)30086-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159053/

Du Y, Tu L, Zhu P, et al.
Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study.
Am J Respir Crit Care Med. 2020;201(11):1372-1379. doi:10.1164/rccm.202003-0543OC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7258652/

[104] Balzanelli G M, Distratis P, Aityan KS, Amatulli F, Catucci O, Cefalo A, et al.
Clinical Features in Predicting COVID-19.
Biomed J Sci & Tech Res 29(5)-2020. BJSTR. MS.ID.0048743.
https://biomedres.us/pdfs/BJSTR.MS.ID.004873.pdf

[105] Beyls C, Huette P, Abou-Arab O, Berne P, Mahjoub Y.
Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome and risk of thrombosis.
Br J Anaesth. 2020;125(2):e260-e262. doi:10.1016/j.bja.2020.04.079
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7198213/

[106] Fan E, Beitler JR, Brochard L, et al.
COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?
Lancet Respir Med. 2020;8(8):816-821. doi:10.1016/S2213-2600(20)30304-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7338016/

• Evidence from high-quality clinical trials addressing optimal intubation times is not available in the ARDS

• Intubation could be useful in patients with high respiratory drive (cough) and high risk Of self-inflicted lung damage by the patient

• Noninvasive ventilation was associated with worse outcomes when $_{PaO2}$ /$_{FiO2}$ ratio <150 in ARDS

• The harmful consequences of intubation and invasive ventilation (e.g., related to sedation, paralysis, and endotracheal tube complications) may outweigh the benefits, especially in patients with mild hypoxemia and without a high respiratory drive or work of breathing.

	Considerations	Potential course of action
Timing of intubation	• No high-quality clinical trial evidence addressing optimal timing of intubation in ARDS is available • Intubation might be beneficial in patients with high respiratory drive and at high risk of patient self-inflicted lung injury[13] • Non-invasive ventilation has been associated with worse outcomes when PaO_2/FiO_2 ratio <150 in ARDS[39] • Detrimental consequences of intubation and invasive ventilation (eg, related to sedation, paralysis, and endotracheal tube complications) might outweigh benefits, especially in patients with mild hypoxaemia and without high respiratory drive or work of breathing; consequences for other patients because of bed and ventilator shortages in the ICU should be considered	• Consider timely intubation as indicated by refractory hypoxaemia or hypercapnia, and by objective evidence of high work of breathing on clinical examination (eg, phasic [not tonic] contraction on palpation of sternomastoid)[40] or by oesophageal manometry[41]
Tidal volume	• Low tidal volume ventilation results in improved outcomes in patients with and without ARDS and should be the starting point for ventilatory management of patients with ARDS (ie, 6 mL/kg PBW)	• Lower tidal volume as needed to 4 mL/kg PBW to keep plateau pressure <30 cm H_2O[17] • Liberalise tidal volume (up to 8 mL/kg PBW) in patients who are double triggering, or if inspiratory airway pressure decreases below PEEP, keeping plateau pressure <30 cm H_2O[36] • Ideally, keep driving pressure ≤14 cm H_2O[42]
PEEP	• Higher PEEP might be beneficial in patients with high recruitability, with better gas exchange and reduced risk of ventilator-induced lung injury • Higher PEEP can be harmful in patients with low recruitability, who have hypoxaemia due largely to pulmonary vascular pathology; high PEEP can lead to adverse haemodynamic effects or barotrauma • Improvement in partial pressure of arterial oxygen with increased PEEP can be misleading	• Individualise PEEP;[28] consider higher PEEP in patients with evidence of higher potential for recruitment (eg, as suggested by CT scan or recruitment to inflation index[16]) or with a body habitus or clinical exam that suggests high pleural pressures are likely • Evaluate response to changes in PEEP at the bedside[43]
Prone positioning	• Prone positioning is associated with improved outcomes in patients with moderate or severe ARDS, with improved ventilation or perfusion matching, more homogeneous distribution of ventilation, and reduced risk of ventilator-induced lung injury[44] • Staffing and resource demands can limit feasibility during surges in case volume • Efficacy and safety of prone positioning in awake, non-intubated patients remain unclear[45–47] and are being evaluated in clinical trials in patients with COVID-19 (NCT04350723, NCT04347941, NCT04365959)	• In the absence of contraindications, use prone positioning in mechanically ventilated patients with PaO_2/FiO_2 ratio <150[48]
Venovenous ECMO	• Patients can develop refractory hypoxaemia or have mechanics leading to potentially injurious levels of mechanical ventilation, despite optimisation of conventional measures • Staffing and resource demands can limit feasibility during an increase in the number of cases	• Consider venovenous ECMO in patients with refractory hypoxaemia or high driving pressures or respiratory acidosis despite conventional lung-protective measures (eg, higher PEEP or prone positioning)[49]

ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. ICU=intensive care unit. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure.

Table 2: **Clinical and physiological considerations in the management of patients with COVID-19-associated ARDS**

EPIDEMIOLOGICAL FINDINGS ON PATIENT OUTCOMES IN ICU

From what has been presented so far, it is clear that the induction of VILI in patients with ARDS is a critical issue of
great relevance. [107]

Studies done in patients with typical ARDS (who account for about 10% of ICU admissions, of whom normally **23%** are on mechanical ventilation) report a very high mortality rate, about **39%**, and unfortunately, current protective ventilation strategies do not seem to have significant benefit in lowering the incidence of mortality. [108]

Zangrillo et al recently made available in the online Appendix "*Characteristics, Treatment, Outcomes, and Cause of Death of Invasively Ventilated Patients with COVID-19 ARDS in Milan, Italy*" the results on 1591 COVID-19 patients admitted to ICUs[109] :

[107] Nieman GF, Gatto LA, Andrews P, et al.
Prevention and treatment of acute lung injury with time-controlled adaptive ventilation: physiologically informed modification of airway pressure release ventilation.
Ann Intensive Care. 2020;10(1):3. Published 2020 Jan 6. doi:10.1186/s13613-019-0619-3
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6944723/

[108] Bellani G, Laffey JG, Pham T, et al.
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries
[published correction appears in JAMA. 2016 Jul 19;316(3):350]. JAMA. 2016;315(8):788- 800. doi:10.1001/jama.2016.0291
https://jamanetwork.com/journals/jama/fullarticle/2492877

Máca J, Jor O, Holub M, et al.
Past and Present ARDS Mortality Rates: A Systematic Review.
Respir Care. 2017;62(1):113-122. doi:10.4187/respcare.04716
http://rc.rcjournal.com/content/62/1/113/tab-pdf

Phua J, Badia JR, Adhikari NK, et al.
Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review.
Am J Respir Crit Care Med. 2009;179(3):220-227. doi:10.1164/rccm.200805-722OC
https://www.atsjournals.org/doi/pdf/10.1164/rccm.200805-722OC

Rezoagli E, Fumagalli R, Bellani G.
Definition and epidemiology of acute respiratory distress syndrome.
Ann Transl Med. 2017;5(14):282. doi:10.21037/atm.2017.06.62
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537110/

Villar J, Blanco J, Kacmarek RM.
Current incidence and outcome of the acute respiratory distress syndrome.
Curr Opin Crit Care. 2016;22(1):1-6. doi:10.1097/MCC.0000000000000266
https://pubmed.ncbi.nlm.nih.gov/26645551/

McNicholas BA, Rooney GM, Laffey JG.
Lessons to learn from epidemiologic studies in ARDS.
Curr Opin Crit Care. 2018;24(1):41-48. doi:10.1097/MCC.0000000000000473
https://pubmed.ncbi.nlm.nih.gov/29135617/

Raymondos K, Dirks T, Quintel M, et al.
Outcome of acute respiratory distress syndrome in university and non-university hospitals in Germany.
Crit Care. 2017;21(1):122. Published 2017 May 30. doi:10.1186/s13054-017-1687-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448143/

Cochi SE, Kempker JA, Annangi S, Kramer MR, Martin GS.
Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999 to 2013.
Ann Am Thorac Soc. 2016;13(10):1742-1751. doi:10.1513/AnnalsATS.201512-841OC
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5122485/

[109] Characteristics, Treatment, Outcomes, and Cause of Death of Invasively Ventilated Patients with COVID-19 ARDS in Milan, Italy
https://ccr.cicm.org.au/config/cicm-ccr/media/PDF/June-COVID-19/OA2/CCR_Zangrillo128_Sept2020_Online_Appendix.pdf
Grasselli G, Zangrillo A, Zanella A, et al.
Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy
[published online ahead of print, 2020 Apr 6]. JAMA. 2020;323(16):1574-1581. doi:10.1001/jama.2020.5394
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136855/

68% (95% CI, 65% -71%) of patients had at least 1 comorbidity. Hypertension was the most common comorbidity, affecting 509 (49% [95% CI, 46% -52%]) of 1043 patients with available data. The second most common comorbidities were cardiovascular disease (223 patients, 21% [95% CI, 19% -24%]) and hypercholesterolemia (188 patients, 18% [95% CI, 16% -20%]). Only 42 patients (4% [95% CI, 3% -5%]) had a history of chronic obstructive pulmonary disease. All patients older than 80 years had at least 1 comorbidity, and 496 out of 650 patients (76% [95% CI, 73% -80%]) older than 60 years had at least 1 comorbidity.

Of 1300 patients admitted to the ICU at IRCCS San Raffaele (Milan) with available respiratory support data, 1287 (99% [95% CI, 98% -99%]) required respiratory support, of which 1150 (88% [95% CI, 87% -90%]) received **mechanical ventilation** and 137 (11% [95% CI, 9% -12%]) received **noninvasive ventilation**.

It is also important to report the results of the study published on April 23, 2020 by the same authors[110] : Of the 73 patients included in the study, most were **men (83.6%)**, the mean age was **61 years** (interquartile range [IQR], 54-69 years), and **hypertension** affected **52.9%** of patients.
Lymphocytopenia (median, 0.77 x 10^3 per mm^3 ; IQR, 0.58-1.00 x 10^3 per mm^3), **hyperinflammation** with C-reactive protein (median, 184.5 mg / dL; IQR, 108.2-269.1 mg / dL) and **pro-coagulant state** with D-dimer (median, 10.1 µg / m2; IQR, 5.0-23.8 µg / m^2) were present. Median tidal volume was 6.7 mL/kg (IQR, 6.0-7.5 mL/kg) and median positive end-expiratory pressure was 12 cmH2O (IQR, 10-14 cmH2O). In the first 3 days, prone positioning (12-16 h) was used in 63.8% of patients and extracorporeal membrane oxygenation in five patients (6.8%).

After a **median follow-up of 19.0 days** (IQR, 15.0-27.0 days), 17 patients (**23.3%**) had **died**, 23 (**31.5%**) had been **discharged from the** ICU, and 33 (**45.2%**) were receiving **invasive mechanical ventilation** in the ICU. Older age (odds ratio [OR], 1.12; 95% CI, 1.04-1.22; P = 0.004) and hypertension (OR, 6.15; 95% CI, 1.75-29.11; P = 0.009) were associated with mortality, whereas early improvement in the ratio of arterial partial pressure of oxygen ($_{PaO2}$) to fraction of inspired oxygen ($_{FiO2}$) was associated with ICU discharge (P = 0.002 for interaction).

At present, the incidence of mortality associated with the use of mechanical ventilation, particularly invasive ventilation, and the association between the hypercoagulative status of COVID- 19 patients in the ICU and mortality from ventilator lung injury has not been evaluated in the statistical analysis of the data presented, as instrumental and analytical screening aimed at this purpose has not been carried out at admission and admission to the ICU, and only partially at discharge or death by autopsy. Therefore, the impact of the choice to use invasive ventilation, and its timing, on the mortality of patients in the ICU remains to be defined for these patients.
The choice of using such high percentages of invasive ventilation in critically ill patients in ICUs had already been questioned by Dr. Samuele Ceruti, an emergency and intensive care physician, whose excerpt from his March 8, 2020 report is quoted[111] :
"In Italy, the suggestion has come from some colleagues of known clinical experience to manage these respiratory failures by proceeding immediately to Oro-Tracheal Intubation (IOT), by-passing normal management by Non-Invasive Ventilation (NIV), for supposed reasons of improvement of the pathology - a fact yet to be demonstrated (technically we speak of "expert opinion"); the NEJM and JAMA have not yet demonstrated a real survival benefit of this more aggressive therapeutic approach. The ESICM (European Society of Intensive Care Medicine).

Grasselli G, Pesenti A, Cecconi M.
Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response [published online ahead of print, 2020 Mar 13]. JAMA. 2020;10.1001/jama.2020.4031. doi:10.1001/jama.2020.4031
https://jamanetwork.com/journals/jama/fullarticle/2763188

[110] Zangrillo A, Beretta L, Scandroglio AM, et al.
Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy [published online ahead of print, 2020 Apr 23]. Crit Care Resusc. 2020;
https://pubmed.ncbi.nlm.nih.gov/32353223/
[111] https://bit.ly/SAMUELE_CERUTI

supports and suggests this possibility; the discussion is somewhat technical, but for completeness it will be stated. Since these patients have extremely high *lung compliance* despite interstitial lung damage (which explains partial respiratory failure without impaired ventilation and increased $_{pCO2}$), non-invasive ventilation cannot afford ventilation at high PEEP values (the diaphragmatic work would be such that it would not be objectively and subjectively tolerable by the patient) and especially *Tidal Volume* control because the patient is awake and compliant, so increasing the time of VNI increases the risk of ventilatory lung damage. Therefore, one should proceed with sedation, IOT, high PEEP values and low Tidal Volume (4-6 ml/Kg), possible permissive hypercapnia with pH up to 7.3 (although good compliance never seems to lead to such a problem) and curarization, with PEEP titration according to *PV-tool* rather than using lung ultrasound (either in the choice for PEEP titration and/or pronation).
It is undeniable that avoiding NIV to proceed to IOT dramatically increases the need for immediate ICU admission; therefore, a medical decision has been made that at the moment must be considered *suggestive*, but still at the level of *expert opinion*, not supported by strong scientific data that this really leads to benefit - resulting in an increased need for ICU, a need that with "usual" management would have increased but not to the values that are indicated."

More recent data confirm these critical issues and the urgency to more accurately define risk factors which potentiate mechanical ventilation injury and increase mortality in COVID-19 patients. [112]

It must be considered, however, on the other hand, that NIPPV is quickly poorly tolerated by the patient due to the uncomfortableness of the garrisons, noise, thirst and heat. Patients in this condition precipitate toward delirium[113] which can become a condition of difficult, if not impossible, clinical management.

In a sample of some of the largest epidemiologic studies of patients with COVID-19 to date, rates of invasive mechanical ventilation among patients admitted to the ICU ranged from **29.1%** in a Chinese study to **89.9%** in a U.S. study and anywhere from 2.3% of hospitalized patients to 33.1%.
[114]

[112] Schünemann HJ, Khabsa J, Solo K, et al.
Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence.
Ann Intern Med. 2020;173(3):204-216. doi:10.7326/M20-2306
https://www.acpjournals.org/doi/10.7326/M20-2306

Rochwerg B, Solo K, Darzi A, Chen G, Khamis AM.
Update Alert: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19
[published online ahead of print, 2020 Jul 31]. Ann Intern Med. 2020;L20-0944. doi:10.7326/L20-0944
https://www.acpjournals.org/doi/10.7326/L20-0944?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

[113] Chan KY, Cheng LS, Mak IW, Ng SW, Yiu MG, Chu CM.
Delirium is a Strong Predictor of Mortality in Patients Receiving Non-invasive Positive Pressure Ventilation.
Lung. 2017;195(1):115-125. doi:10.1007/s00408-016-9955-3
https://link.springer.com/content/pdf/10.1007/s00408-016-9955-3.pdf

[114] Wunsch H.
Mechanical Ventilation in COVID-19: Interpreting the Current Epidemiology.
Am J Respir Crit Care Med. 2020;202(1):1-4. doi:10.1164/rccm.202004-1385ED
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7328308/

Table 1. Comparison of Rates of Invasive Mechanical Ventilation in a Sample of Epidemiology Studies of Patients with COVID-19

Study	Location	Hospitalized (*n*)	ICU Admission (*n*)	Invasive Mechanical Ventilation		
				n	Percent of ICU Patients	Percent of Hospitalized Patients
Richardson (4)	New York City	5,700	1,281	1,151	89.9	20.2
Petrilli (17)	New York City	1,999	534*	445	83.3	22.3
Goyal (13)	New York City	393	NA	130	NA	33.1
ICNARC (14)	UK	NA	3,883	2,291†	59.0	NA
Grasselli (15)	Lombardy, Italy	NA	1,300‡	1,150	88.5	NA
Zhou (18)	Wuhan, China	191	50	32	64.0	16.8
Wang (3)	Wuhan, China	NA	344	100	29.1	NA
Guan (19)	China	1,099	55	25	45.5	2.3

Definition of abbreviations: COVID-19 = coronavirus disease; ICNARC = Intensive Care National Audit & Research Centre; NA = not available.
*Excludes 116 patients deemed critically ill who were discharged to hospice or died without either intensive care or mechanical ventilation.
†Within first 24 hours.
‡1,591 admitted to ICU but only 1,300 with respiratory support information.

Table 2. Reported Data on Mechanically Ventilated ICU Patients and Outcomes for Selected Cohorts with Possible Range of ICU or Hospital Mortality Accounting for Patients Still Receiving Care

Study	Location	Total (*n*)	Died (*n*)	Survived to ICU Discharge (*n*)	Still Receiving Care (*n*)	Range of Possible Mortality (%)
Richardson (4)	New York City	1,151	282	38 (hospital)	831	24.5–96.7
ICNARC (14)	UK	2,291*	698†	355	1,238	30.5–84.5
Grasselli (15)‡	Lombardy, Italy	1,581	405	256	920	25.6–83.8

Definition of abbreviation: ICNARC = Intensive Care National Audit & Research Centre.
Lower bound assumes everyone receiving care survives; upper bound assumes they all die.
*Mechanically ventilated within first 24 hours.
†Received advanced organ support; may include patients who received mechanical ventilation after the first 24 hours.
‡All patients in ICU, not just those mechanically ventilated.

Lodigiani et al[115] recently published results on the incidence of coagulation complications in patients admitted to Humanitas Hospital (Milan, Italy): thromboembolic events occurred with a cumulative rate of **21%.** 8 events occurred in ICU patients (16.7%; 95% CI 8.7% -29.6%) corresponding to a cumulative rate of **27.6%**. 20 events occurred in general medical ward patients (6.4%; 95% CI 4.2% -9.6%) corresponding to a cumulative rate of **6.6%.**

44 patients underwent VTE imaging tests, and in 16 patients (36%) VTE was confirmed. Computed tomography pulmonary angiography (CTPA) was performed in 30 patients, corresponding to 7.7% of the total (a very small number that may hide an important underestimation of the incidence), and pulmonary embolism was confirmed in 10 (33% CTPA).
The rates of ischemic stroke and ACS/IM were 2.5% and 1.1%, respectively. Overt DIC was present in 8 patients (2.2%).

Although the study reports that half of the thromboembolic events were diagnosed within 24 hours of hospitalization, the authors point out that during the period considered for data analysis, no VTE screening strategy was in place at the study site among COVID-19 patients: VTE imaging tests were performed in subjects with signs or symptoms of DVT (deep vein thrombosis) or unexplained clinical worsening of respiratory function, assessed primarily using the P_{aO_2}/F_{IO_2} *ratio or by a rapid increase in D-dimer levels.*

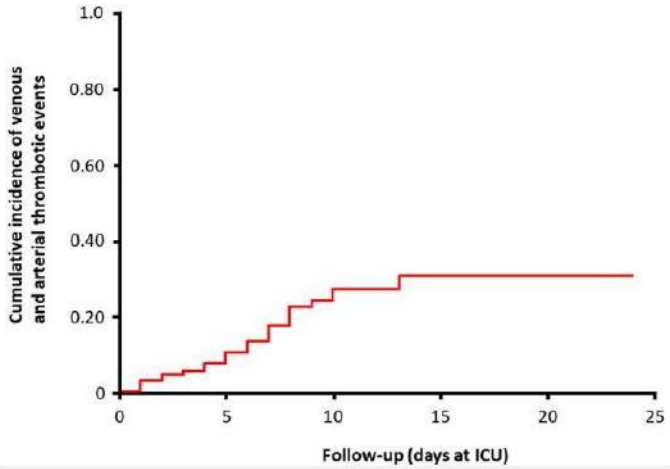
[115] Lodigiani C, Iapichino G, Carenzo L, et al.
Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy.
Thromb Res. 2020;191:9-14. doi:10.1016/j.thromres.2020.04.024
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177070/

Median D-dimer levels in survivors and non-survivors during hospitalization.

Group	Setting	Days 1–3	Days 4–6	Days 7–9
Survivors	Total	*n* = 215	*n* = 163	*n* = 121
		353 (236–585)	389 (246–685)	529 (303–1138)
	ICU	615 (456–1005)	605 (370–824)	3137 (1486–6571)
	General ward	329 (304–386)	378 (337–412)	472 (386–650)
Non-survivors	Total	*n* = 70	n = 38	*n* = 22
		869 (479–2103)	943 (611–2618)	1494 (633–6320)
	ICU	1022 (615–3681)	1301 (961–28,397)	7746 (2914–12,578)
	General ward	868 (600–1119)	847 (624–1643)	1093 (658–3397)

The analysis was restricted to closed cases. D-dimer levels are presented as median (Q1-Q3) and expressed in ng/mL. ICU, intensive care unit.

Other data come from a study at two Dutch hospital centers on mechanical ventilation strategies in COVID-19 patients[116] , in which the cumulative incidence of **venous and arterial thrombotic complications** was **31%** (95% CI 20-41%), of which CTPA and/or ultrasonography confirmed **VTE** (venous thromboembolism) in **27%** (95% CI 17-37%) and **arterial thrombotic events** in **3.7%** (95% CI 0-8.2%). **PE** (pulmonary embolism) was the most frequent thrombotic complication (n = 25, **81%**) and none of the patients developed DIC (disseminated intravascular coagulation).



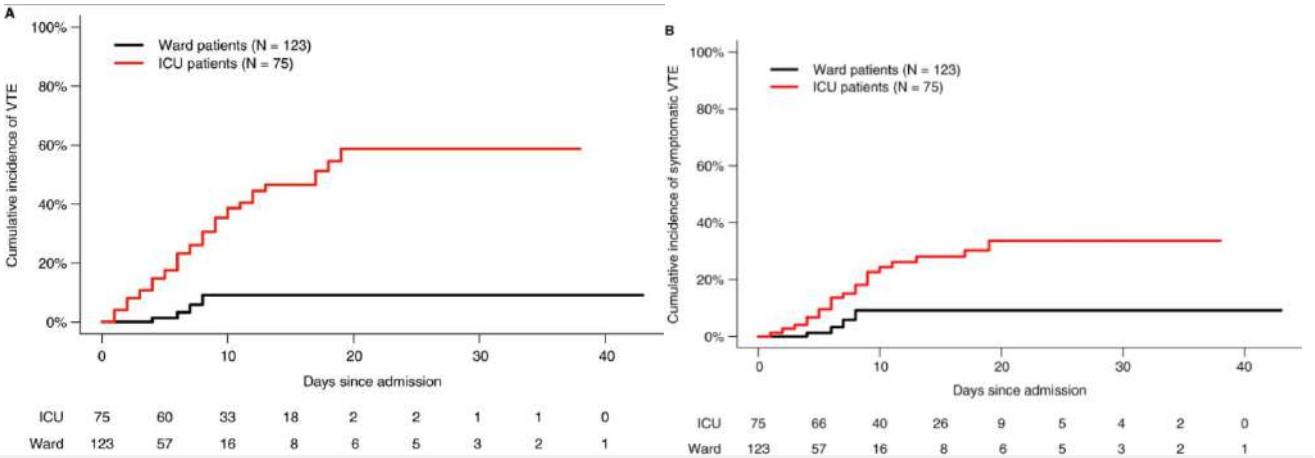
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146714/
Cumulative incidence of venous and arterial thrombotic complications during ICU admission of patients with proven COVID-19 pneumonia.

[116] Klok FA, Kruip MJHA, van der Meer NJM, et al.
Incidence of thrombotic complications in critically ill ICU patients with COVID-19.
Thromb Res. 2020;191:145-147. doi:10.1016/j.thromres.2020.04.013
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146714/

Middeldorp S, Coppens M, van Haaps TF, et al.
Incidence of venous thromboembolism in hospitalized patients with COVID-19.
J Thromb Haemost. 2020;18(8):1995-2002. doi:10.1111/jth.14888
https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14888

These results are in agreement with another Dutch single-center cohort study of 198 hospitalized patients of whom 38% were admitted to the ICU: the **cumulative incidences of VTE in ICU patients at 7, 14, and 21 days were 16%** (95% CI, 10-22), **33%** (95% CI 23-43), and **42%** (95% CI 30-54), respectively.
For symptomatic VTE, these were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30) and 25% (95% CI 16-36).

VTE appeared to be associated with mortality (adjusted HR, 2.4; 95% CI, 1.02-5.5) and **the cumulative incidence of VTE was higher in ICU** (**26%** (95% CI, 17-37), **47%** (95% CI, 34-58) and **59%** (95% CI, 42-72) **at 7, 14 and 21** days)
compared with patients on the wards (5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21) and 9.2% (2.6-21) at 7, 14 and 21 days).



https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14888
A, Venous thromboembolism in intensive care unit and ward patients. **B,** Symptomatic venous thromboembolism in ICU and ward patients. ICU, intensive care unit; VTE, venous thromboembolism.

The presence of a hypercoagulation profile in COVID-19 patients has led physicians to modify the protocol for thromboprophylaxis and treatment of ICU patients[117] . However, the debate on the necessity and effectiveness in reducing mortality of this protocol is still debated among experts.
[118]

[117] Patti G, Lio V, Cavallari I, et al.
Antithrombotic therapies in patients with SARS-CoV-2 infection: from current evidence to reasonable recommendations - Position paper from the Italian Working Group on Atherosclerosis, Thrombosis and Vascular Biology [Antithrombotic treatments in patients with SARS-CoV-2 infection: from current evidence to reasonable recommendations - A position paper from the Italian Working Group on Atherosclerosis, Thrombosis and Vascular Biology].
G Ital Cardiol (Rome). 2020;21(7):489-501. doi:10.1714/3386.33634
https://www.giornaledicardiologia.it/articoli.php?archivio=yes&vol_id=3386&id=33634

Guglielmetti G, Quaglia M, Sainaghi PP, et al.
"War to the knife" against thromboinflammation to protect endothelial function of COVID-19 patients.
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Malato A, Dentali F, Siragusa S, et al.
The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes.
Blood Transfus. 2015;13(4):559-568. doi:10.2450/2015.0277-14
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Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis.
Crit Care Med. 2002;30(4):771-774. doi:10.1097/00003246-200204000-00008
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Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2
[published online ahead of print, 2020 Apr 3]. J Thromb Thrombolysis. 2020;1-4. doi:10.1007/s11239-020-02105-8
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COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET).
Blood Transfus. 2020;18(3):167-169. doi:10.2450/2020.0083-20
http://www.sah.org.ar/pdf/covid-19/083-20_pre-publishing.pdf

Cattaneo M, Morici N.
Is thromboprophylaxis with high-dose enoxaparin really necessary for COVID-19 patients? A new "prudent" randomized clinical trial.

Risk factors of venous thromboembolism in ICU patients include:

- mechanical ventilation (OR 1.56),
- immobility (OR 2.14),
- the femoral venous catheter (OR 2.24),
- the sedatives (OR 1.52)
- the paralytic drugs (OR 4.81) [119]

It is relevant to report that mechanical ventilation has been identified as an independent risk of VTE acquired in the ICU.

Both ventilation and PEEP tend to decrease right and left ventricular preload, increase right ventricular afterload, and decrease left ventricular afterload.

The sum of these effects is that cardiac output may decrease, especially in the presence of hypovolemia or in individuals with impaired cardiovascular reflexes, and the resulting exacerbation of venous stasis increases the risk of VTE. [120]

This is in agreement with the results of studies in which increased in vivo cardiovascular markers[121] , increased cell-free DNA and MPO-DNA (myeloperoxidase-DNA), two markers associated with microvascular thrombosis (particularly neutrophil extracellular traps- NET, discussed later) were found in hospitalized patients receiving mechanical ventilation compared with hospitalized patients breathing room air. [122]

Blood Transfus. 2020;18(3):237-238. doi:10.2450/2020.0109-20
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250693/

Marietta M, Tripodi A.
Rebuttal to letter "Is thromboprophylaxis with high-dose enoxaparin really necessary for COVID-19 patients? A new "prudent" randomized clinical trial."
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250695/

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COVID-19, coagulopathy and venous thromboembolism: more questions than answers
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7352087/

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Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients.
J Crit Care 2000;15:127-32.
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[120] Zochios, V. A., & Keeshan, A.
Pulmonary Embolism in the Mechanically-Ventilated Critically Ill Patient: Is it Different?
Journal of the Intensive Care Society, (2013) 14(1), 36-44. https://doi.org/10.1177/175114371301400109
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[121] Baumann P, Wiegert S, Greco F, Wellmann S, L'Abate P, Cannizzaro V.
Mechanical ventilation strategies alter cardiovascular biomarkers in an infant rat model.
Physiol Rep. 2018;6(2):e13553. doi:10.14814/phy2.13553
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Neutrophil extracellular traps in COVID-19.
JCI Insight. 2020;5(11):e138999. Published 2020 Jun 4. doi:10.1172/jci.insight.138999
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7308057/

The peculiar susceptibility of COVID-19 patients to hypercoagulation makes them particularly at risk of developing VTE and PE with the use of mechanical ventilation.

It is therefore of considerable importance to ascertain whether thromboembolic complications in these patients are in fact VILIs or are due to the complication itself of the disease, even in the absence of assisted ventilation, and to determine with what incidence they occur in order to direct diagnosis and therapy in the most appropriate way.

This susceptibility to fatal injury from invasive mechanical ventilation (IV) is especially supported by the study carried out by Jing Hua et al[123] *"Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan*" published on 06/26/2020, in which data of 469 COVID-19 ICU patients admitted from February 2020 to the end of March in 13 ICUs in Wuhan were collected and analyzed.

The authors found that **the mortality rate in the IV** (Invasive Ventilation) **group was 92%,** compared with the other two groups: **6.4% in the NV** (No Ventilation, nasal oxygen cannula) group, **40.8% in the NIV** (non-invasive ventilation BiPAP, CPAP, HFNO: High-flow nasal oxygen) **group**

In addition, patients in group IV had developed a **higher rate of serious comorbidities** such as acute kidney injury (AKI) that required continuous renal replacement therapy (CRRT) (26.5%) compared with the NV (2.9%) and NIV (5.3%) groups. 10 patients (8.8%) in the IV group had also received ECMO implementation.

In their discussion of the results, the authors point out that it appears from the data collected that patients in group IV were older with a higher rate of hyperinflammatory state on admission than the other two groups, and that these factors may lead to the rapid progression of respiratory failure and fatal outcome [124].

Some of the COVID-19 patients who developed progressively worsening respiratory distress were refractory to NIV and suggest that intubation is unavoidable in these cases, but that sometimes physicians may be too hasty to proceed with intubation.

They also state that it is well known that invasive ventilation can cause many complications including hypotension, ventilator-related infection (VAP), alterations in volaemia, and sedation-related delirium, and that the decision to intubate is based primarily on clinical judgments and varies from case to case.

In conclusion, from the data from Wuhan presented in this article, COVID-19 patients undergoing invasive ventilation showed very poor outcomes. This suggests that early intubation may not help patients but even lead to the opposite outcome.

[123] Hua J, Qian C, Luo Z, Li Q, Wang F.
Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan.
Crit Care. 2020;24(1):348. Published 2020 Jun 16. doi:10.1186/s13054-020-03044-9
https://ccforum.biomedcentral.com/track/pdf/10.1186/s13054-020-03044-9

[124] Mehta P, McAuley DF, Brown M, et al.
COVID-19: consider cytokine storm syndromes and immunosuppression.
Lancet. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7270045/

The authors recommend that IV should be avoided and NIV should be used in the early phase of respiratory failure until IV is unavoidable[125] and then that physicians should rethink the intubation threshold in the management of COVID-19. [126]

In the study, "*Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors,*"[127] the incidence of VTE in hospitalized non-ICU patients was determined and it was found that of the 71 patients examined, 16 developed VTE (22.5%) and 7 PE (10%) despite adequate thromboprophylaxis.

It is worth reporting in patients undergoing invasive ventilation the increase in D-dimer, a predictive factor for venous thromboembolism.

[125] Li J, Fink JB, Ehrmann S.
High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion.
Eur Respir J. 2020;55(5):2000892. Published 2020 May 14. doi:10.1183/13993003.00892-2020
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J Intensive & Crit Care (2020) Vol.6 No.2:7 doi:10.36648/2471-8505.6.2.7
https://criticalcare.imedpub.com/dilemmas-in-covid19-respiratory-distress-early-vs-late-intubation-high-tidal-volume-and-low-peep-vs-traditional-approach.php?aid=28250

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COVID-19 Lung Injury and "Typical" ARDS: The Danger of Presumed Equivalency [published online ahead of print, 2020 May 20].
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https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.202005-405LE
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Reply: COVID-19 Lung Injury and "Typical" ARDS: The Danger of Presumed Equivalency
[published online ahead of print, 2020 May 20]. Ann Am Thorac Soc. 2020;10.1513/AnnalsATS.202005-430LE. doi:10.1513/AnnalsATS.202005-430LE
https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.202005-430LE

Li X, Ma X.
Acute respiratory failure in COVID-19: is it "typical" ARDS?
Crit Care. 2020;24(1):198. Published 2020 May 6. doi:10.1186/s13054-020-02911-9
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202792/

[127] Artifoni M, Danic G, Gautier G, et al.
Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors.
J Thromb Thrombolysis. 2020;50(1):211-216. doi:10.1007/s11239-020-02146-z
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7246965/

Table 2 Clinical features, laboratory results on admission, and outcomes of the study patients

	All ($n = 469$)	No ventilation ($n = 204$)	Invasive ventilation ($n = 113$)	Noninvasive ventilation ($n = 152$)	*P*
Age	68 ± 13	67 ± 15	71 ± 10	67 ± 13	0.030
Sex					0.034
Male	266 (56.7)	108 (52.9)	76 (67.3)	82 (53.9)	
Female	203 (43.3)	96 (47.1)	37 (32.7)	70 (46.1)	
Comorbidities, no. (%)					
Hypertension	240 (51.4)	99 (48.5)	56 (49.6)	85 (56.7)	0.288
Diabetes	110 (23.6)	41 (20.1)	28 (24.8)	41 (27.3)	0.268
Coronary artery disease	84 (18.0)	44 (21.6)	20 (17.9)	20 (13.3)	0.137
Chronic obstructive lung disease	52 (11.1)	13 (6.4)	8 (7.1)	31 (20.7)	< 0.001
Chronic kidney disease	42 (9.0)	21 (10.3)	8 (7.1)	13 (8.7)	0.623
Laboratory results on admission					
White blood cell count, × 10^9/L	9.4 ± 6.0	6.9 ± 3.6	12.7 ± 8.0	10.2 ± 5.2	< 0.001
Neutrophil count, × 10^9/L	8.5 ± 9.2	5.7 ± 6.4	12.6 ± 11.9	8.6 ± 5.1	< 0.001
Lymphocyte count, × 10^9/L	0.9 ± 0.6	1.0 ± 0.5	0.7 ± 0.8	0.9 ± 0.6	0.002
NLR (neutrophil/lymphocyte ratio)	13.1 ± 13.5	7.8 ± 9.3	21.3 ± 16.0	13.9 ± 13.0	< 0.001
Monocytes, count, × 10^9/L	0.5 ± 0.4	0.5 ± 0.6	0.5 ± 0.4	0.5 ± 0.3	0.947
Platelet count, × 10^9/L	214 ± 112	225 ± 97	180 ± 123	223 ± 118	0.001
C-reactive protein (mg/L)	78.7 ± 83.6	47.0 ± 51.4	116.1 ± 94.2	92.6 ± 93.8	< 0.001
Procalcitonin (ng/ml)	1.9 ± 8.8	0.7 ± 4.7	2.8 ± 10.5	2.7 ± 10.9	0.078
ALT (U/L)	47.1 ± 95.2	31.6 ± 30.2	80.8 ± 179.1	44.3 ± 40.9	< 0.001
AST (U/L)	60.2 ± 227.0	31.2 ± 25.0	110.7 ± 429.4	60.9 ± 138.3	0.019
Total bilirubin (μmol/L)	14.7 ± 11.5	11.0 ± 5.7	18.1 ± 13.2	16.8 ± 14.1	< 0.001
Direct bilirubin (μmol/L)	8.1 ± 7.5	5.0 ± 5.1	9.9 ± 9.2	10.6 ± 7.3	< 0.001
Albumin (g/L)	32.0 ± 5.6	32.7 ± 4.6	30.1 ± 7.0	32.4 ± 5.4	< 0.001
d-dimer (ug/mL)	5.9 ± 11.9	3.1 ± 5.3	13.2 ± 20.5	4.5 ± 7.0	0.276
Glucose (mmol/L)	8.7 ± 4.7	7.1 ± 3.3	10.3 ± 6.8	9.5 ± 3.9	< 0.001
Serum creatine (Scr) (μmol/L)	128.3 ± 190.7	124.5 ± 197.5	119.2 ± 165.2	140.2 ± 199.9	0.636
SOFA score on day 1	4.2 ± 3.1	2.2 ± 2.2	6.0 ± 3.0	5.5 ± 2.7	< 0.001
Continuous renal replacement therapy (CRRT), no. (%)	44 (9.4)	6 (2.9)	30 (26.5)	8 (5.3)	< 0.001
Extracorporeal membrane oxygenation (ECMO), no. (%)	10 (3.1)	0 (0.0)	10 (8.8)	0 (0.0)	< 0.001
Length of hospital stay (days)	20.4 ± 13.2	27.3 ± 14.7	17.9 ± 12.3	16.1 ± 9.6	< 0.001
Mortality, no. (%)	179 (38.2)	13 (6.4)	104 (92.0)	62 (40.8)	< 0.001

https://ccforum.biomedcentral.com/track/pdf/10.1186/s13054-020-03044-9

These results confirm Chinese studies on the treatment of SARS by mechanical ventilation in which the negative impact of invasive versus noninvasive ventilation on clinical response and mortality had already emerged. [128]

To conclude, the results of the study "*Severity of respiratory failure and outcome of patients needing ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation" are* reported. [129], describing the population of patients with severe respiratory failure due to COVID- 19 infection in need of ventilatory support who presented to the Emergency Department of a large hospital in Bergamo, Italy at the beginning of the pandemic in Italy. Due to the lack of intensive care resources, most of the

[128] Yam LY, Chan AY, Cheung TM, et al.
Non-invasive versus invasive mechanical ventilation for respiratory failure in severe acute respiratory syndrome.
Chin Med J (Engl). 2005;118(17):1413-1421.
https://pubmed.ncbi.nlm.nih.gov/16157043/

[129] Duke A, Memaj I, Zanardi F, et al.
Severity of respiratory failure and outcome of patients needing ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation.
EClinicalMedicine. 2020;24:100419. Published 2020 Jun 18. doi:10.1016/j.eclinm.2020.100419
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7301102/

patients was treated with noninvasive ventilation and the outcome was recorded after a 2-month follow-up period.

All patients who had started directly with IMV died. None of the NIV patients were intubated and 4 (57.1%) died. 39 patients who started CPAP (54.9%) died before intubation; 26 (36.6%) were intubated and 15 of them (57.7%) died after intubation.
NIV failure, considered as death or intubation, occurred in 88.5% of patients.

Table 4

Outcome on 10th of May. NIV Failure = death or intubation. CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive Pressure Ventilation; IMV = Invasive Mechanical Ventilation.

	CPAP	NIPPV	IMV	Total	*p* Value	Test
n	71	7	7	85		
Death *n* (%)	54(76.1)	4(57.1)	7(100)	65(76.5)	0.164	Pearson χ^2
Intubation *n* (%)	26(36.6)	0(0)	7(100)	33(38.8)		
Death before intubation *n* (%)	39(54.9)	4(57.1)	nv	43(55.1)		
NIV failure (death + intubation) *n* (%)	65(91.5)	4(57.1)	nv	69(88.5)		
Death after intubation						
n	26	0	7	33		
N (%)	15(57.7)	0(0)	7(100)	22(66.7)	0.067	Fisher's Exact test

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7301102/

The mortality rates of patients who required ventilatory support (76.5%) are comparable to those previously reported in China related to critically ill patients with A R D S [[2],[3],[4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17]] 130

The high mortality rate could be explained by the fact that the patient cohort was a very select cohort of critically ill patients seen in the emergency department during the first wave of the epidemic, all hypoxic at maximum oxygen therapy and all in need of ventilatory support.

NIV failure rates are, as expected, very high (88.5 percent); however, in the context of limited resources without the ability to intubate all patients with respiratory failure due to pneumonia, the policy of starting these patients on NIV seems the only option available to buy some time to free up an ICU bed, and from the data reported by the study as of May 10, this strategy may have helped save the lives of 23.5% of patients who were hypoxic on maximal oxygen therapy, did not have the option of being intubated in the emergency department, and would likely have died without any ventilatory support.

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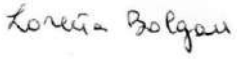

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