



Società Italiana di Terapia Antinfettiva  
Antibatterica Antivirale Antifungina

# 12° CONGRESSO NAZIONALE

CATANIA | 17-18 novembre 2022



# Oxygen supply in COVID-19 Respiratory Insufficiency: what we learned from a 3-year pandemic

**Francesco Amati**

Assistant Professor

IRCCS Humanitas Research Hospital

## Conflitto di interessi

**DICHIARAZIONE AI SENSI DELLA LEGGE 24 Nov 2003, N. 326- ART 48 comma 25 AUTOCERTIFICAZIONE 2022**

Ai sensi dell'art. 76.4 sul Conflitto di Interessi dell'Accordo Stato-Regione del 2 febbraio 2017

***Nessun conflitto di interesse da dichiarare riguardo questa presentazione***

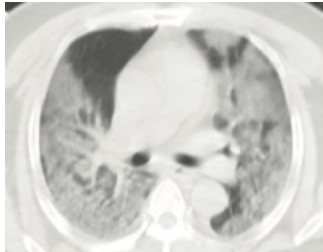
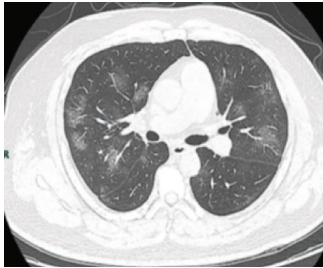
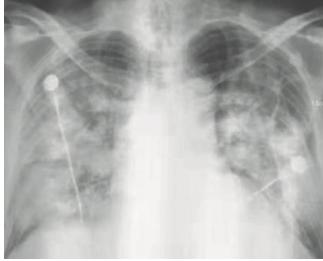
# COI: My COVID-19 Background

- Policlinico Hospital, Milan, Italy
- Opened March 11, 2020
- COVID-19 HDU
- 43 beds
- hARF COVID19 patients
- CPAP, NIV, HFNC, ETI
- Multidisciplinary team





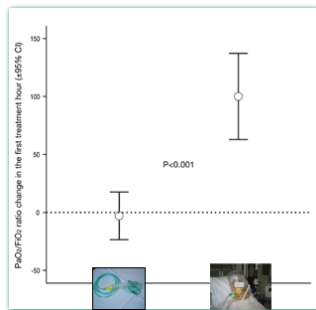
## Clinical picture of ARF due to COVID-19 pneumonia in 2020...



- Severe hypoxemia
- Hypocapnia
- Low-grade dyspnea
  
- TEP frequently associated

# Rationale: CPAP in ARF due to pneumonia

## CAPOVERSO



- 47 CAP patients
- P/F 210-285
- CPAP vs VM
- Objective: P/F > 315

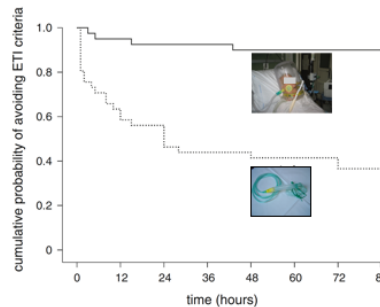
Cosentini R. Chest 2010; 138:114

## SCAPOVERSO

Intensive Care Med  
DOI 10.1007/s00134-014-3325-5

ORIGINAL

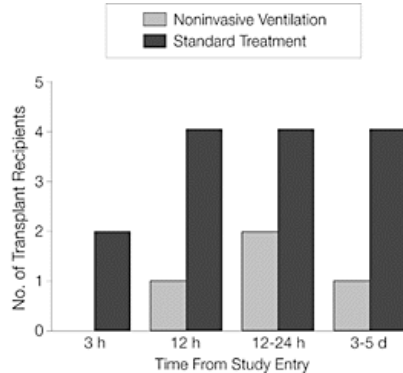
### Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia



- 81 pts with hARF due to pneumonia (P/F: 140)
- ETI Criteria  
15% CPAP vs. 63% VM  
p<0.001; NNT: 2

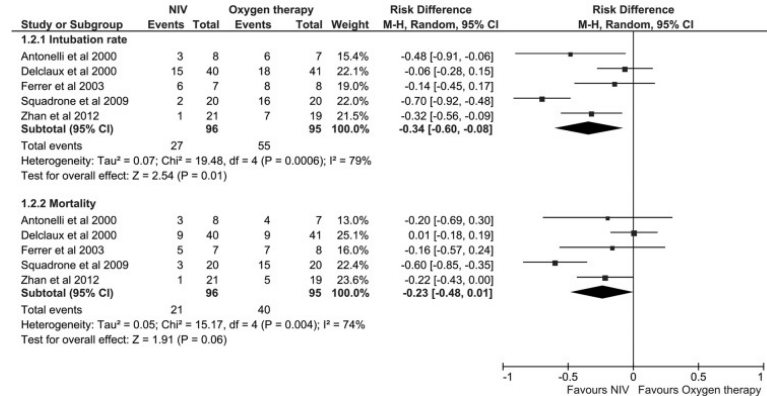
Brambilla AM. Intensive Care Med 2014; 40:942

# Rationale: CPAP in ARDS



- 40 haematological malignancy pts with ARDS
- Intubation required in 70% of the standard treatment group vs 20% in the CPAP group ( $P = .002$ )

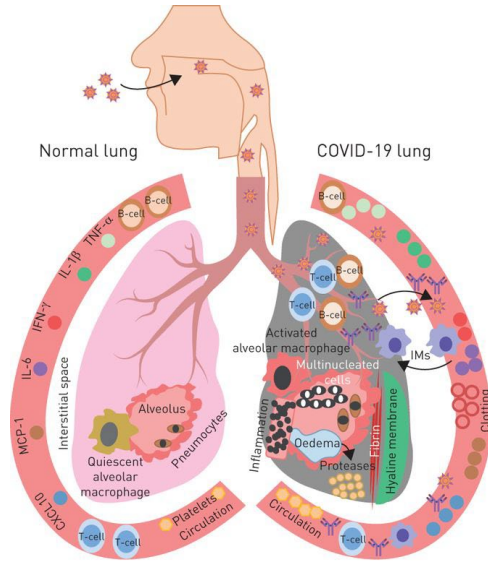
Antonelli; JAMA 2000



Pooled analysis demonstrated superiority of CPAP over standard treatment with oxygen supplementation

Sehgal; Ann Transl Med. 2016 Sep; 4(18): 349.

# CPAP in COVID-19 ARF



Lymphopenia  $\uparrow$   
 (CD4+ T, CD8+ T, NK and B-cell number)  $\downarrow$

Lymphocyte activation and dysfunction  
 Cytokine production, TNF- $\alpha$ , INF- $\gamma$ , IL-2  $\uparrow$

T-cells exhaustion markers  
 (PD-1, TIM3, NKG2A)  $\uparrow$

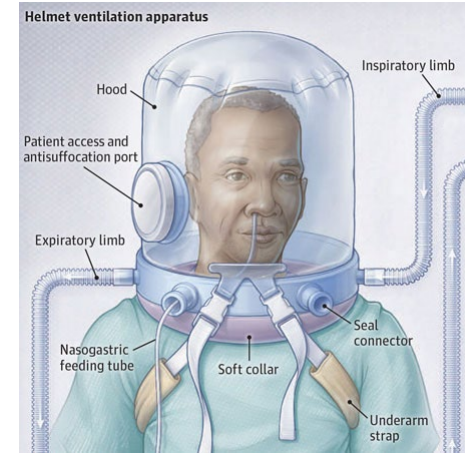
Granulocytes  
 Neutrophil  $\uparrow$  Eosinophil  $\downarrow$  Basophils  $\downarrow$

Monocytes  $\downarrow$

Cytokine storm  $\uparrow$   
 Inflammatory cytokines, IL-1 $\beta$ , IL-2, IL-6, IL-7,  
 IL-8, IL-10; G-CSF, GM-CSF, IP10, MCP1,  
 IFN- $\gamma$  and TNF- $\alpha$ .

Complement activation  
 (C3a, C5a, C5b-9)  $\uparrow$

Antibodies  
 (IgM and IgG)  $\uparrow$



# CPAP in COVID-19 ARF

## Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study

- Multicentric, observational, prospective study
- 7 March 2020 and 21 April 2020

**Indications** for helmet CPAP included all of the following:

- a diagnosis of pneumonia **as the only cause** of hARF
- **P/F ratio <300** evaluated during oxygen therapy

**The primary outcome**

- **CPAP failure** defined as the occurrence of **either intubation or death** due to any cause during HDU stay



# CPAP in COVID-19 ARF

## Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study

157 patients, median age: 64, median (IQR) P/F ratio 143

- An **increase of at least 30% in P/F ratio** during helmet CPAP application in comparison to oxygen therapy **was found only in 52% of the population**
- Median duration of helmet CPAP treatment: **6 days**

**CPAP failure** was observed in 70 **(44.6%)** patients:

- 34 (21.7%) were intubated
- 36 (22.9%) died during the HDU stay



# CPAP in COVID-19 ARF

## Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study

At the **multivariable analysis** (adjusted for sex, age, severe community-acquired pneumonia, interleukin-6, and  $\Delta P aO_2 / FIO_2$  ratio  $\geq 30\%$ ), **CPAP failure** was associated with:

- **severity of pneumonia on admission** (HR (95%CI) 2.9 (1.3–6.2),  $p=0.009$ )
- **higher baseline values of interleukin-6** (HR (95%CI) 1.0 (1.0–1.0),  $p<0.009$ )
- All-cause in-hospital mortality: 28.7%





# Different phenotypes or COVID-19 evolution?

**Type L**



Low

Low

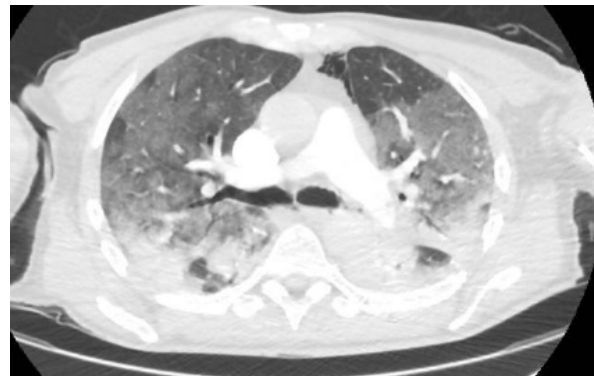
High

P-SILI



COVID-19  
Evolution

**Type H**



V/Q Ratio

Lung weight

Recruitability

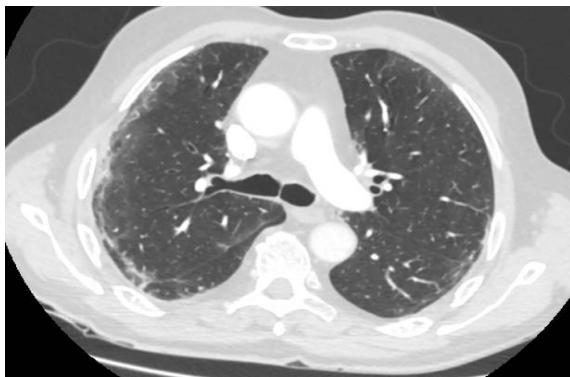
High

High

Low

# Different phenotypes or COVID-19 evolution?

**Type L**

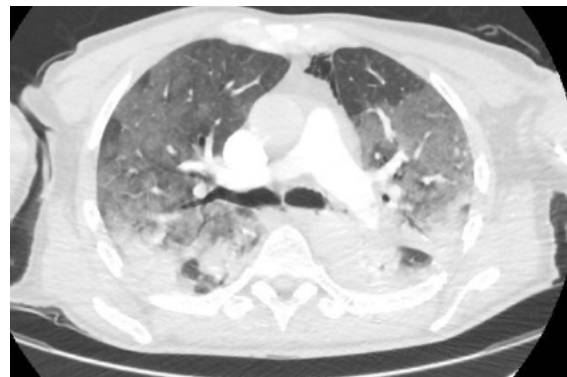


**TREATMENT:**

- **Increase FiO<sub>2</sub>:** low flow oxygen nasal cannula, Venturi Mask, Non rebreather mask
- **Non invasive support:** high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), noninvasive ventilation (NIV).

P-SILI  
→  
COVID-19  
Evolution

**Type H**



**TREATMENT:**

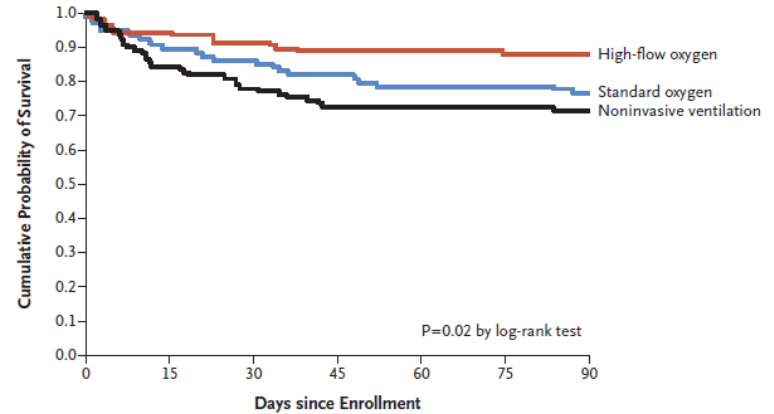
- **Treat as severe ARDS**, including higher PEEP, if compatible with hemodynamics, prone positioning and extracorporeal support.

# HFNC in ARF

## High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

Jean-Pierre Frat, M.D., Arnaud W. Thille, M.D., Ph.D., Alain Mercat, M.D., Ph.D.,  
Christophe Girault, M.D., Ph.D., Stéphanie Ragot, Pharm.D., Ph.D.,  
Sébastien Perbet, M.D., Gwénael Prat, M.D., Thierry Boulain, M.D.,

- 310 pz
- RR >25 a/min; PaO<sub>2</sub>/FiO<sub>2</sub> ≤300, PaCO<sub>2</sub> ≤45 mmHg
- No chronic respiratory diseases



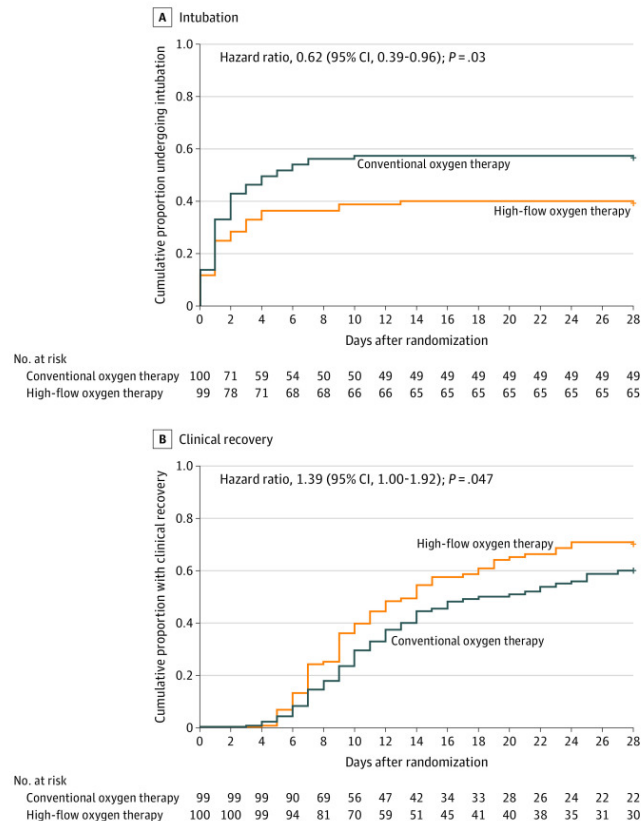
### No. at Risk

High-flow oxygen	106	100	97	94	94	93	93
Standard oxygen	94	84	81	77	74	73	72
Noninvasive ventilation	110	93	86	80	79	78	77

Figure 3. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

# HFNC in COVID-19 ARF

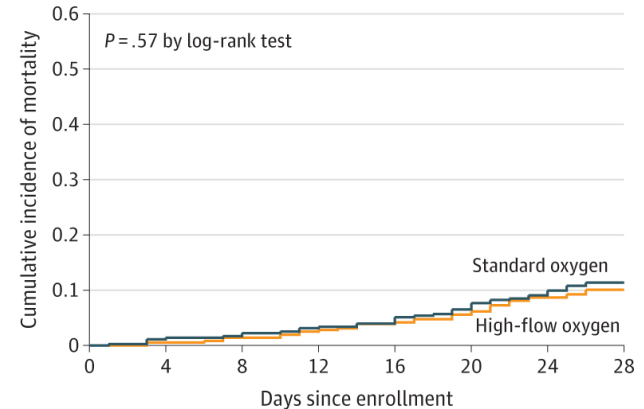
- Adult patients with **ARF** ( $Pao_2/Fio_2 < 200$ )
- Clinical signs of **respiratory distress** (e.g.: use of accessory muscles and respiratory rate greater than 25/min)
- Less than 6 hours elapsed since fulfilling the criteria of ARF



# HFNC in COVID-19 ARF

- Adult patients with **ARF ( $P_{aO_2}/F_{iO_2} < 200$ )**
- **Pulmonary infiltrates**
- Less than 6 hours elapsed since fulfilling the criteria of ARF

**A** Cumulative incidence of mortality (primary outcome)



No. at risk

High-flow oxygen	357	355	352	348	343	337	326	321
Standard oxygen	354	349	347	342	337	328	319	311

# Prone positioning

The New England Journal of Medicine

## EFFECT OF PRONE POSITIONING ON THE SURVIVAL OF PATIENTS WITH ACUTE RESPIRATORY FAILURE

LUCIANO GATTINONI, M.D., GIANNI TOGNONI, M.D., ANTONIO PESENTI, M.D., PAOLO TACCONI, M.D., DANIELE MASCHERONI, M.D., VIOLETA LABARTA, M.S., ROBERTO MALACRIDA, M.D., PAOLA DI GIULIO, R.N., M.S.C., ROBERTO FUMAGALLI, M.D., PAOLO PELOSI, M.D., LUCA BRAZZI, M.D., AND ROBERTO LATINI, M.D., FOR THE PRONE-SUPINE STUDY GROUP\*

*The* **NEW ENGLAND**  
**JOURNAL of MEDICINE**

ESTABLISHED IN 1812

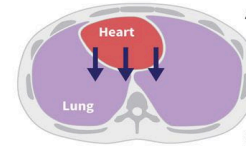
JUNE 6, 2013

VOL. 368 NO. 23

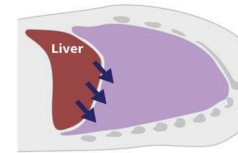
## Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecœur, M.D., Marc Gannier, M.D., Ph.D., Frédérique Bayle, M.D., Gaël Bourdin, M.D., Véronique Leray, M.D., Raphaële Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group\*

### Supine position



Gravitational pressure of heart and mediastinum on the lungs.

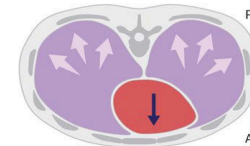


Compressive effects of the abdominal organs on the lungs.

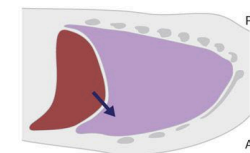


Expansion of the chest wall and overall less homogeneous chest wall compliance.

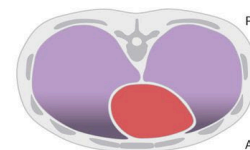
### Prone position



Decreased gravitational pressure of heart and mediastinum on the lungs.

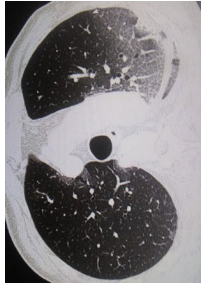
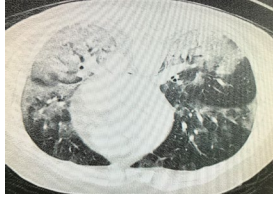
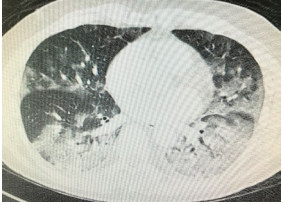


Decreased compressive effects of the abdominal organs on the lungs.



More homogeneous chest wall compliance due to restriction of anterior chest wall movement.

## Prone and lateral positioning for awake, non-intubated patients with COVID-19 pneumonia

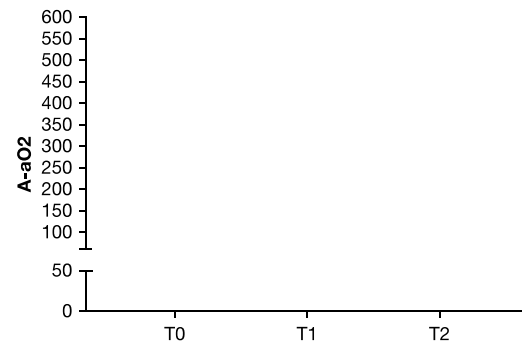
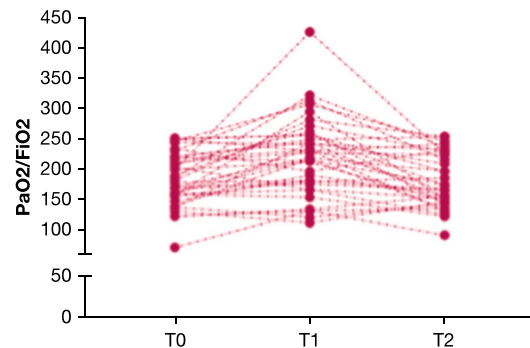




# Prone positioning

Prone and Lateral  
Positioning in Spontaneously  
Breathing Patients With  
COVID-19 Pneumonia  
Undergoing Noninvasive  
Helmet CPAP Treatment

- A pilot, observational, prospective study
- March and April 2020
- **PaO<sub>2</sub>:FIO<sub>2</sub>** ratio during helmet CPAP treatment was persistently **<250 after at least 48 hours**
- Prone or lateral positioning (**at least 1 hour**)
- CPAP with a median P/F ratio of 180 and A-aO<sub>2</sub> of 207



# Prone positioning

Prone and Lateral  
Positioning in Spontaneously  
Breathing Patients With  
COVID-19 Pneumonia  
Undergoing Noninvasive  
Helmet CPAP Treatment

The primary outcome was the **success of the prone/lateral positioning trial**, defined as the occurrence of **all of the following criteria** at T1 in comparison with T0:

1. a decrease of the alveolar–arterial gradient (A-aO<sub>2</sub>) of at least 20%
2. Equal or reduced respiratory rate
3. Equal or reduced dyspnea (BORG scale)
4. SBP  $\geq$  90 mm Hg.

## 15% of trials were successful:

- The median decrease of A-aO<sub>2</sub> of 20%
- 7.7% showed a A-aO<sub>2</sub> decrease of at least 30% in comparison with baseline values
- 46% showed a decrease of <20% of A-aO<sub>2</sub>

## 38% of trials failed

# Prone positioning

Prone and Lateral  
Positioning in Spontaneously  
Breathing Patients With  
COVID-19 Pneumonia  
Undergoing Noninvasive  
Helmet CPAP Treatment

The primary outcome was the **success of the prone/lateral positioning trial**, defined as the occurrence of **all of the following criteria** at T1 in comparison with T0:

1. a decrease of the alveolar–arterial gradient (A-aO<sub>2</sub>) of at least 20%
2. Equal or reduced respiratory rate
3. Equal or reduced dyspnea (BORG scale)
4. SBP  $\geq$  90 mm Hg.

## Prone positioning:

- 33% trials succeeded
- 41% trials showed a decreased A-aO<sub>2</sub> (<20%)
- 25% trials failed

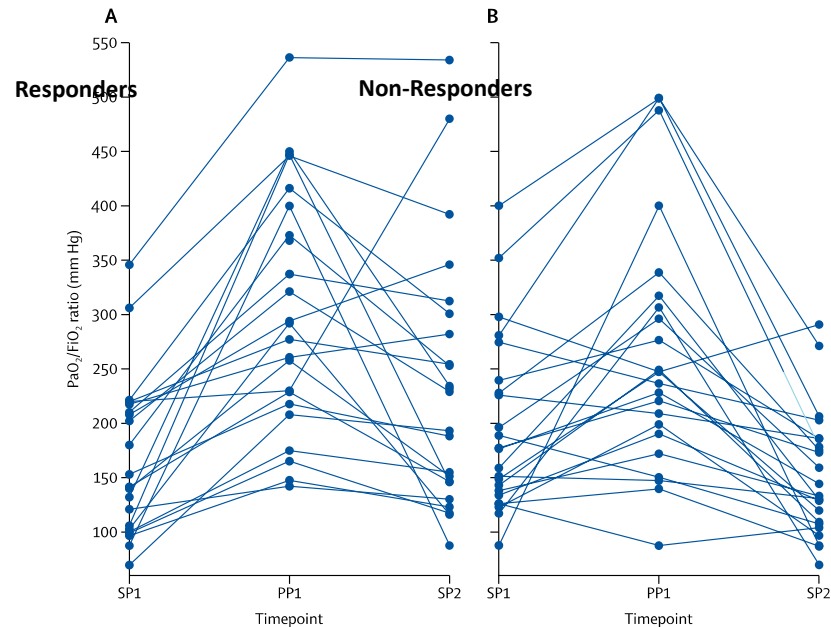
## Lateral positioning:

- 8% trials succeeded
- 52% trials showed a decrease of A-aO<sub>2</sub> (<20%)
- 40% trials failed

# Prone positioning

Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study

- 56 adults patients with COVID-19 pneumonia
  - Supplemental oxygen or non-invasive continuous positive airway pressure
  - Prone positioning was **feasible in 84%**
  - **PaO<sub>2</sub>/FiO<sub>2</sub> ratio 180 → 285, p<0.0001**
- 
- After resupination, improved oxygenation was **maintained in 50%** but not significant
  - **No difference in rates of intubation** was seen in those who maintained oxygenation (responders) compared with those who did not (non-responders).

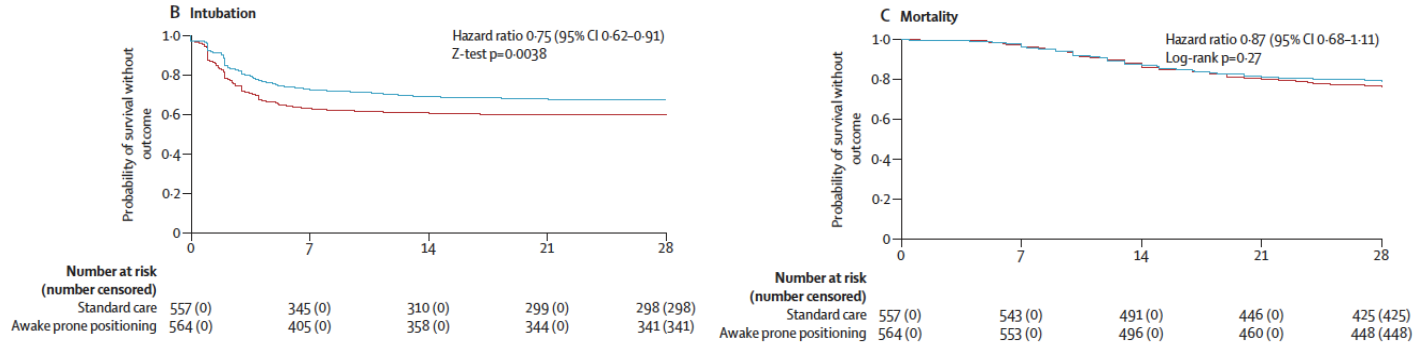


## Prone positioning

### Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial

- Prospective, meta-trial of **six open-label superiority RCTs**
- Adults who required respiratory support with HFNC for **hARF** due to COVID-19
- **Awake prone positioning vs standard care**
- **Primary composite outcome:** treatment failure, defined as the proportion of patients intubated or dying within 28 days of enrolment
- 1126 patients

# Prone positioning



	Awake prone positioning group (n=564)	Standard care group (n=557)	RR (95% CI), HR (95% CI), or mean difference (95% CI)
<b>Secondary outcomes</b>			
Intubation rate at day 28	185/564 (33%)	223/557 (40%)	..
Mortality at day 28			
All patients	117/564 (21%)	132/557 (24%)	RR 0.87 (0.71 to 1.07)
Invasively mechanically ventilated patients	79/185 (43%)	98/223 (44%)	..

Lancet Respir Med 2021

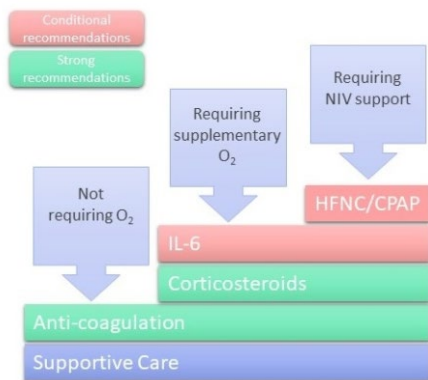
Published Online  
August 20, 2021

**14 patients needed to be treated with awake prone positioning to avoid one intubation**

# Prone positioning

## Management of hospitalised adults with coronavirus disease-19 (COVID-19): A European Respiratory Society living guideline

James D. Chalmers, Megan L. Crichton, Pieter C. Goeminne, Bin Cao, Marc Humbert, Michal Shteinberg, Katerina M. Antoniou, Charlotte Suppli Ulrik, Helen Parks, Chen Wang, Thomas Vandendriessche, Jieming Qu, Daiana Stolz, Christopher Brightling, Tobias Welte, Stefano Aliberti, Anita K. Simonds, Thomy Tonia, Nicolas Roche



**PICO 11:** In patients with hospitalised COVID-19 should continuous positive airway pressure or high flow nasal cannula oxygen with or without adjunctive strategies such as prone positioning be used versus standard of care (defined as the absence of these interventions or invasive mechanical ventilation)?

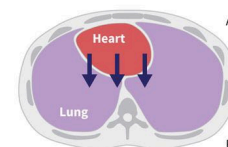
**Recommendation:** We suggest high flow nasal cannula oxygen (HFNC) or non-invasive continuous positive airway pressure (CPAP) delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure in the absence of immediate indications for invasive mechanical ventilation (conditional recommendation, very low quality of evidence)

Notes accompanying this recommendation: HFNC and non-invasive CPAP are classified as aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protecting equipment

HFNC and non-invasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment

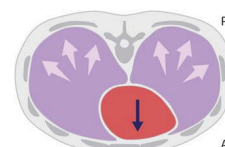
Prone positioning may improve oxygenation in non-intubated patient with acute hypoxaemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.

**Supine position**

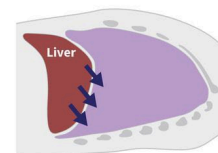


Gravitational pressure of heart and mediastinum on the lungs.

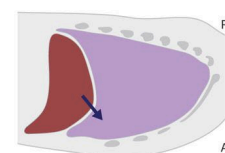
**Prone position**



Decreased gravitational pressure of heart and mediastinum on the lungs.



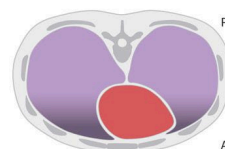
Compressive effects of the abdominal organs on the lungs.



Decreased compressive effects of the abdominal organs on the lungs.



Expansion of the chest wall and overall less homogeneous chest wall compliance.

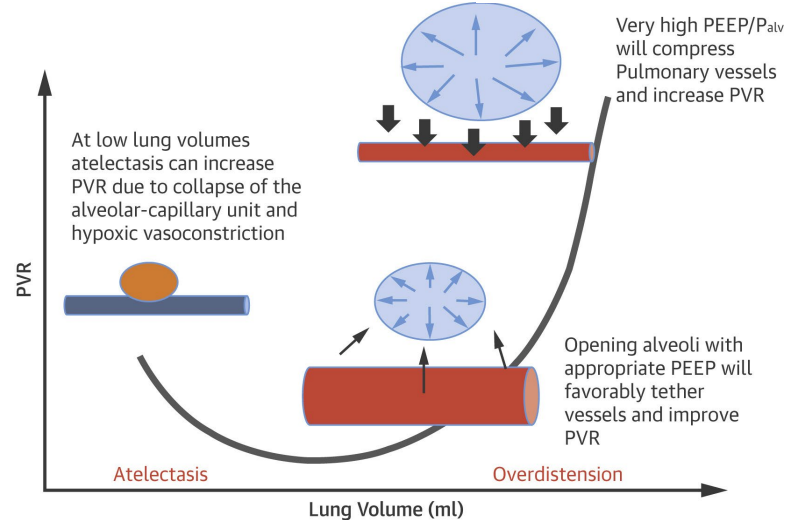
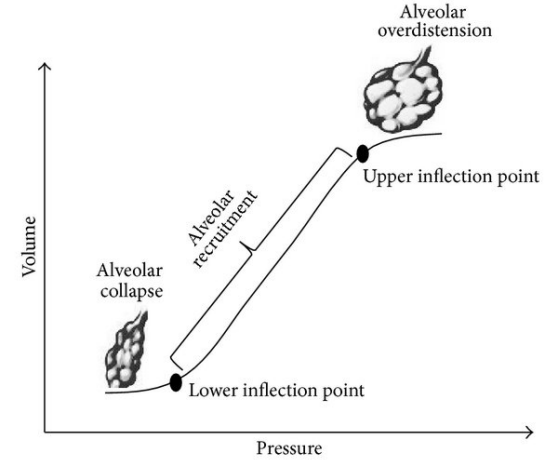


More homogeneous chest wall compliance due to restriction of anterior chest wall movement.



# ZEEP-PEEP Test

- To identify the **lowest PEEP**
- Recruitment vs. Over distention
- **Changes over time**
- Hemodynamic and Respiratory parameters



# ZEEP-PEEP Test

- Consecutive adults ( $\geq 18$  years) with **hARF** and with an indication for helmet CPAP
- Indications for helmet CPAP treatment:
  1. Diagnosis of COVID-19 **pneumonia as the only cause of hARF**
  2. **P/F  $< 300$**
- Standardized and non-invasive lung recruitability test (LRT) through the evaluation of **vitals and blood gas analysis parameters every 30 minutes** at **different PEEP values** (0–baseline-, 2.5, 5, 7.5, 10, 12.5, and 15 cmH<sub>2</sub>O)

	Reservoir (se possibile)	ZEEP 7.5	PEEP 5	PEEP 7.5	PEEP 10	PEEP 12.5	PEEP 15
FI02 (LA MINIMA PER SpO2 92% e SEMPRE LA STESSA)		40	40	40	40	40	
<b>PARAMETRI VITALI</b>							
PA		102/58	104/55	100/52	102/50	106/55	
FC		99	98	95	100	103	
FR		22	22	25	26	25	
SpO2		97	98	99	96	95	
Vena cava diametro INSP ed ESP		2.88	/	/	/	/	
Vena cava Kissing (si/no)		no	no	no	no	no	
<b>DISTRESS</b>							
Uso muscoli accessori (si/no)		no	no	si	si	si	
Disincronia toraco-addominale (si/no)		no	no	no	no	no	
Intolleranza al casco (si / no)		no	no	no	no	no	
Mancanza di fiato (VAS 0-10)		no	no	no	no	no	
<b>EGA</b>							
pH		7.46	7.46	7.47	7.45	7.44	
pCO2		36	37	31	30	32	
pO2		74	76	70	71	75	
BE		+0.3	+2.1	+0.2		-1.6	
HCO3		24.7	24.5	24.8	23.5	23.7	
PaO2/FiO2		85	80	80	80	75	
Delta A-a		191	187	165		158	
SpO2		2.3	2.3	2.1	2.4	2.3	
Lattato							

**Lung Recruitability of COVID-19 Pneumonia in Patients Undergoing Helmet CPAP**

# ZEEP-PEEP Test

**Successful LTR** was defined as the occurrence of all the following:

- (1) A decrease of the alveolar-arterial gradient (A-aO<sub>2</sub>) of at least 20% compared to baseline
- (2) Equal or reduced respiratory rate (RR) compared to baseline
- (3) Absence of hemodynamic instability
- (4) Equal or increase SpO<sub>2</sub> values compared to baseline
- (5) Absence of patient's discomfort

**Failure of LRT** was defined as the occurrence of at least one of the following before reaching success criteria:

- (1) An increase in RR compared to baseline
- (2) An increase of A-aO<sub>2</sub> compared to baseline
- (3) hemodynamic instability
- (4) SpO<sub>2</sub> <90%
- (5) Respiratory distress
- (6) Patient's discomfort.

**Partial success of LTR** was defined by all the criteria mentioned above but decrease of A-aO<sub>2</sub> less than 20%

# ZEEP-PEEP Test

## RESULTS

**LRT was successful in 9 (26.5%) patients**

60% at 10 cmH<sub>2</sub>O

Partial success of LRT occurred in 17 (50%) patients

**LTR failed in 8 (23.5%) patients**

- hemodynamic instability (14.7%)
- respiratory distress (2.9%)
- increase in RR (5.9%)

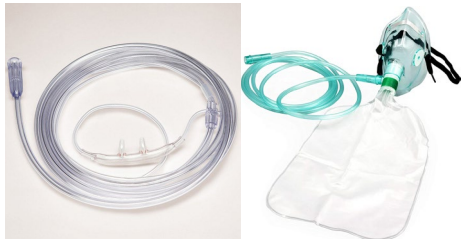
Lung Recruitability of COVID-19 Pneumonia in  
Patients Undergoing Helmet CPAP

# Bottom line...

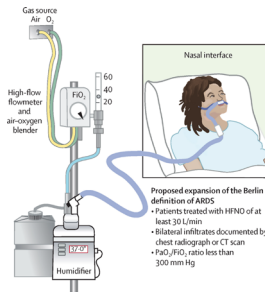
## The RECOVERY-RS Randomized Clinical Trial

- Parallel group, open-label, adaptive, **3-group, randomized clinical trial**
- 1273 patients with **ARF due to COVID**
- Required O<sub>2</sub> at a fraction of inspired oxygen (**FiO<sub>2</sub>**) of at least 40%
- **Suitable for tracheal intubation** if treatment escalation was required

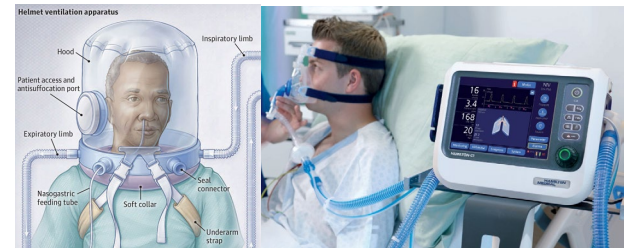
### Conventional oxygen



### HFNC

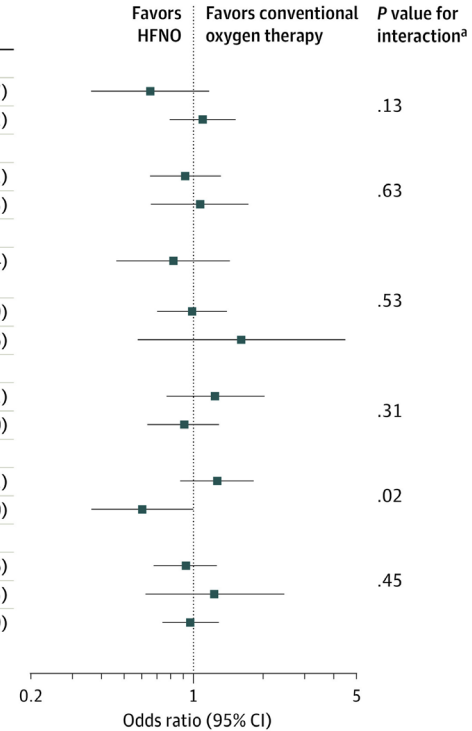


### CPAP

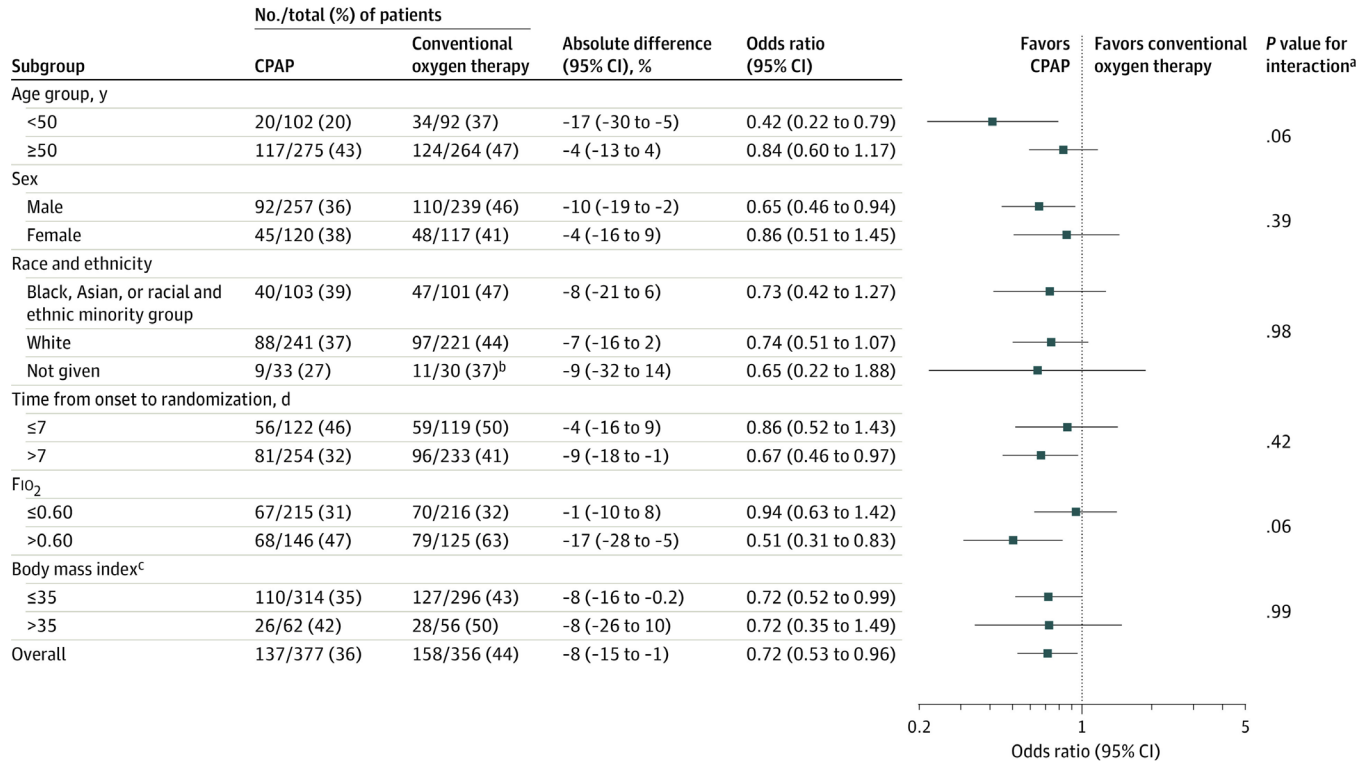


# Recovery Trial

	No./total (%) of patients		Absolute difference (95% CI), %	Odds ratio (95% CI)
Subgroup	HFNO	Conventional oxygen therapy		
Age group, y				
<50	31/108 (29)	37/97 (38)	-9 (-22 to 3)	0.65 (0.36 to 1.17)
≥50	153/307 (50)	129/271 (48)	2 (-6 to 10)	1.09 (0.79 to 1.52)
Sex				
Male	126/271 (46)	116/239 (49)	-2 (-11 to 7)	0.92 (0.65 to 1.31)
Female	58/144 (40)	50/129 (39)	2 (-10 to 13)	1.07 (0.66 to 1.73)
Race and ethnicity				
Black, Asian, or racial and ethnic minority group	46/106 (43)	44/91 (48)	-5 (-19 to 9)	0.82 (0.47 to 1.44)
White	122/275 (44)	110/246 (45)	-0.4 (-9 to 8)	0.99 (0.70 to 1.39)
Not given	16/34 (47)	10/28 (36) <sup>b</sup>	11 (-13 to 36)	1.60 (0.57 to 4.46)
Time from onset to randomization, d				
≤7	75/132 (57)	68/132 (52)	5 (-7 to 17)	1.24 (0.76 to 2.01)
>7	107/280 (38)	94/232 (41)	-2 (-11 to 6)	0.91 (0.64 to 1.30)
FiO <sub>2</sub>				
≤0.60	106/263 (40)	83/238 (35)	5 (-3 to 14)	1.26 (0.88 to 1.81)
>0.60	72/139 (52)	75/117 (64)	-12 (-24 to -0.3)	0.60 (0.36 to 1.00)
Body mass index <sup>c</sup>				
≤35	141/333 (42)	137/309 (44)	-2 (-10 to 6)	0.92 (0.67 to 1.26)
>35	42/80 (53)	26/55 (47)	5 (-12 to 22)	1.23 (0.62 to 2.45)
Overall	184/415 (44)	166/368 (45)	-1 (-8 to 6)	0.97 (0.73 to 1.29)



# Recovery Trial





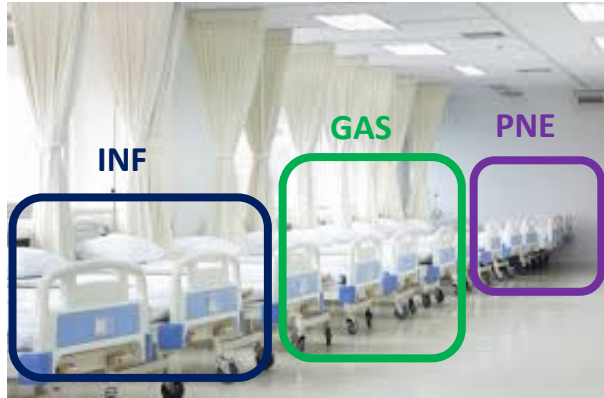
# Recovery Trial

## LIMITATIONS

- **Crossover** between interventions occurred in **17.1%** of participants (15.3% in the CPAP group, 11.5% in the HFNC group, and 23.6% in the conventional oxygen therapy group).
- **Lack of blinding**
- **Low recruitment** due to declining COVID-19 case numbers in the UK and the end of the funded recruitment period
- **No standardized criteria for intubation**

# Bottom line...

## UO COVID



1 UO COVID

1 Coordinator

Each UO take responsibility of patients

## UO INTERNAL MEDICINE



COVID beds within each UO



Bottom line: moving to a tailored approach

## Conclusion: a tailored approach

- CPAP or HFNC treatment choice should be based on several factors **not limited on P/F ratio** (e.g.: respiratory distress)
- **Prone positioning** might be a valid option in a selected category of patients
- In case of CPAP treatment use the **lowest PEEP possible** (change over time)
- **NIV** with a face mask should be the first choice in case of **chronic obstructive comorbidities or hypoxemic-hypercapnic respiratory failure**

THANK YOU

