

Ossigenoterapia nell'insufficienza respiratoria acuta: non è tutto oro ciò che luccica

Lara Pisani

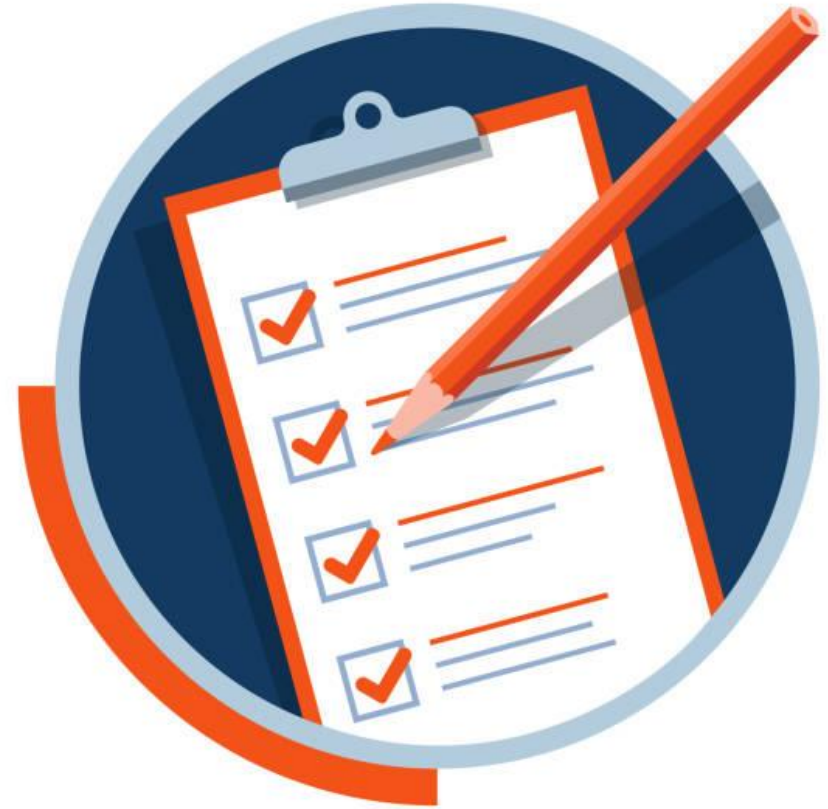
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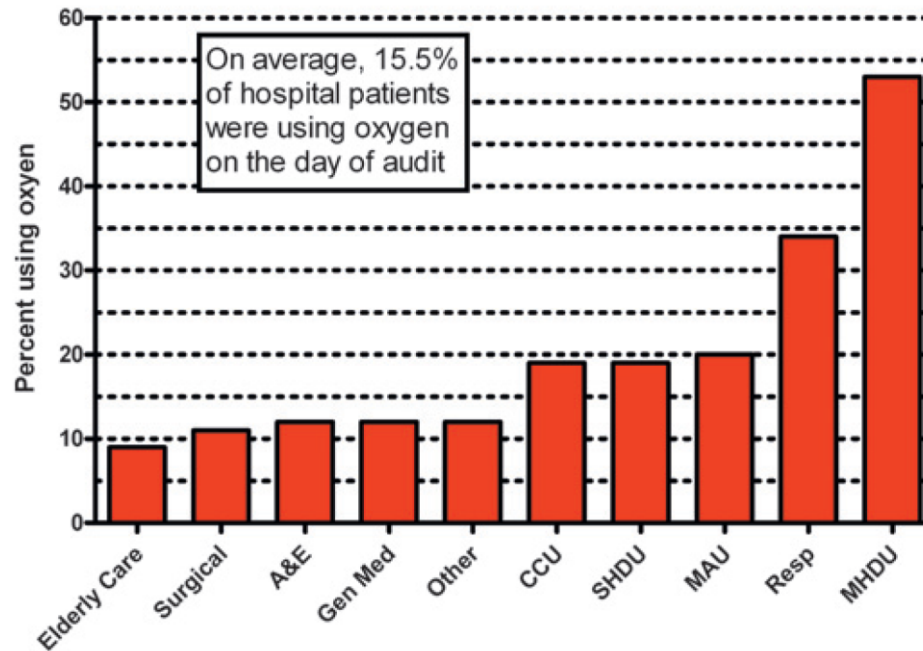
Agenda

- Standard Oxygen and HFNC
- Hyperoxia and its physiological effects
- Oxygen therapy for patients who are critically ill



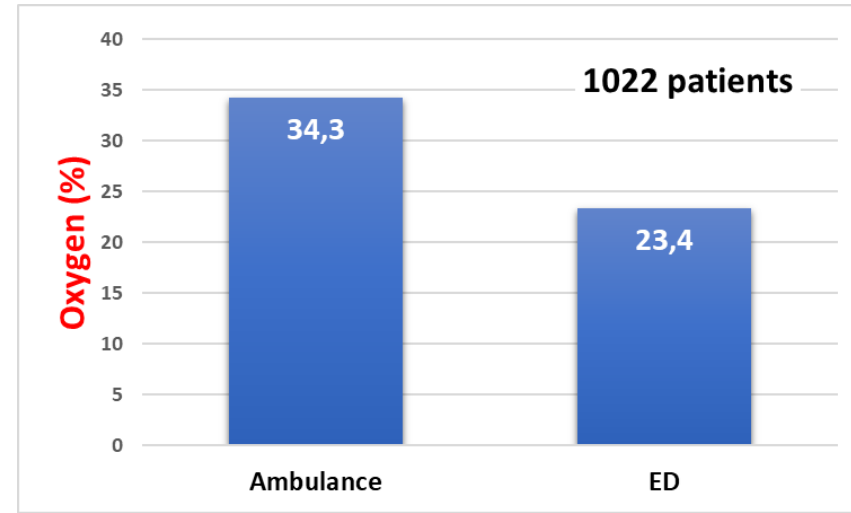
In-hospital

Year	Number of hospitals	Number of patients	Number of wards	On oxygen (%)*
2008	99	14 830	712	17.5
2010	90	22 017	1026	15.5



O'Driscoll BR et al. Thorax 2011;66:734-5

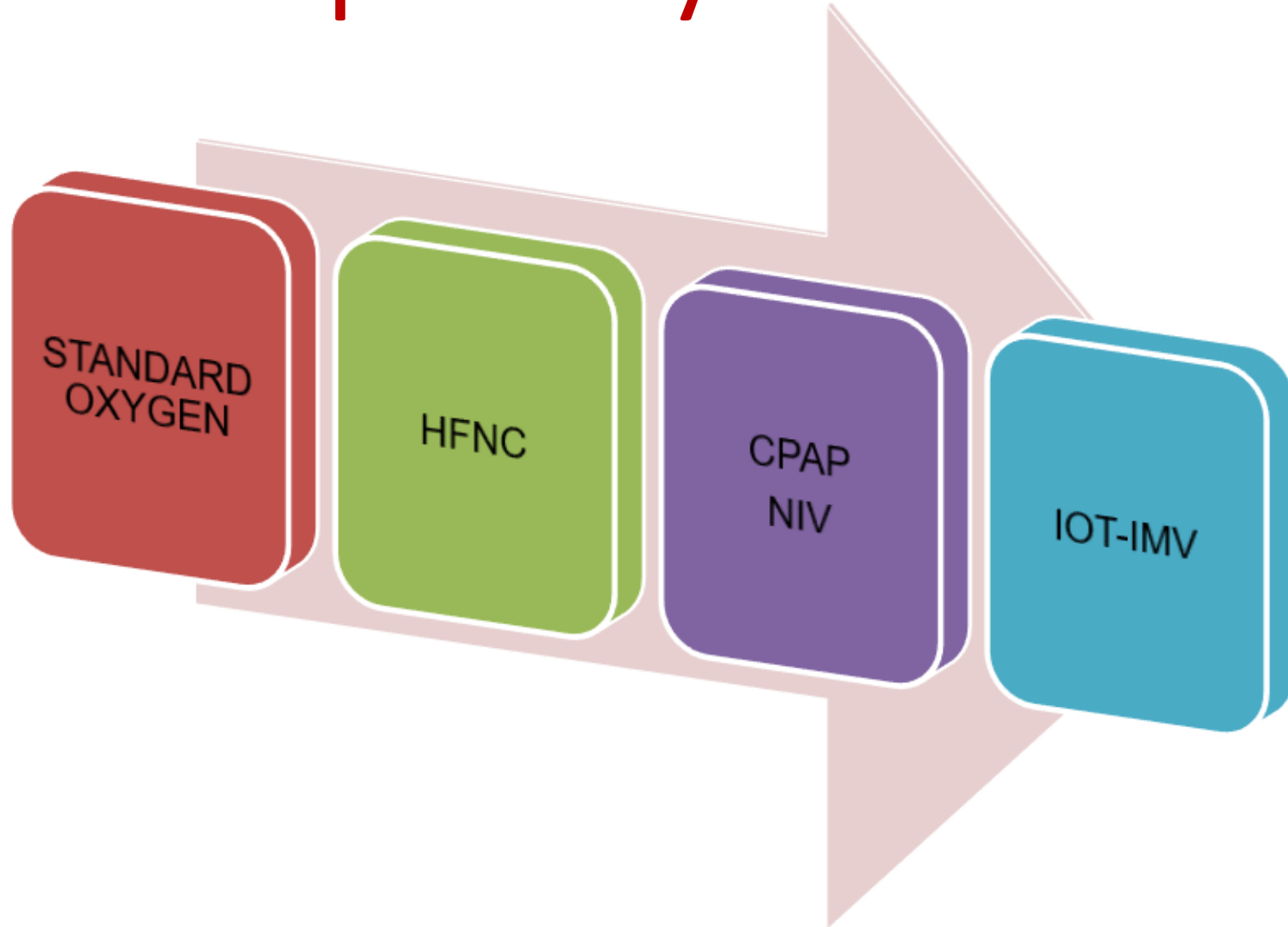
Prehospital & ED



Oxygen use in ambulances is very common, equivalent to 2.2 million episodes annually in the UK.

Hale KE et al. Emerg Med J. 2008;25:773-6

Treatment of acute respiratory failure



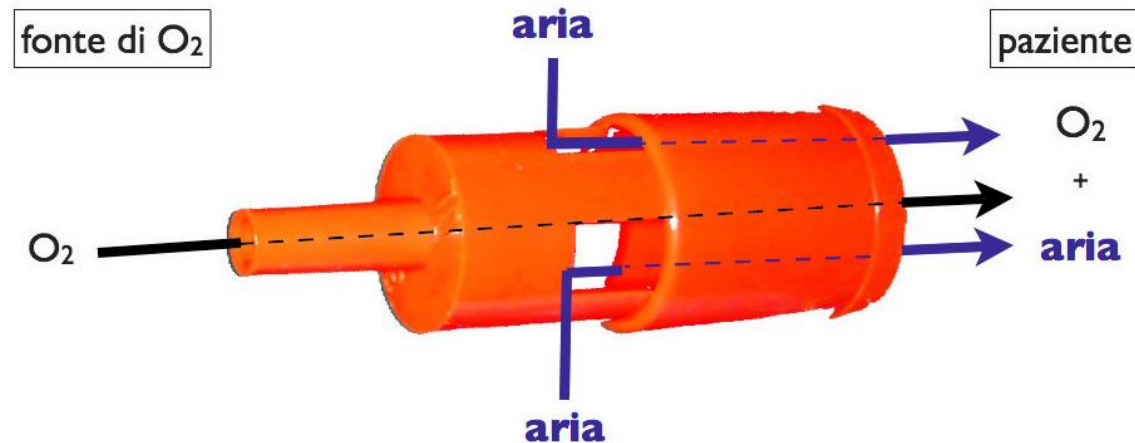
SISTEMI DI EROGAZIONE

- Occhialini
- Maschere di Venturi
- Maschera con Reservoir



EFFETTO VENTURI

Se la **velocità** di un fluido aumenta, la **pressione** diminuisce
(teorema di Bernoulli/ Legge di Poiseuille)



MASCHERA DI VENTURI



Sistema più preciso e costante per la somministrazione di
O₂ a concentrazioni intermedie



Aumentare il flusso non aumenta la
concentrazione di ossigeno !!!

Estimating FiO₂

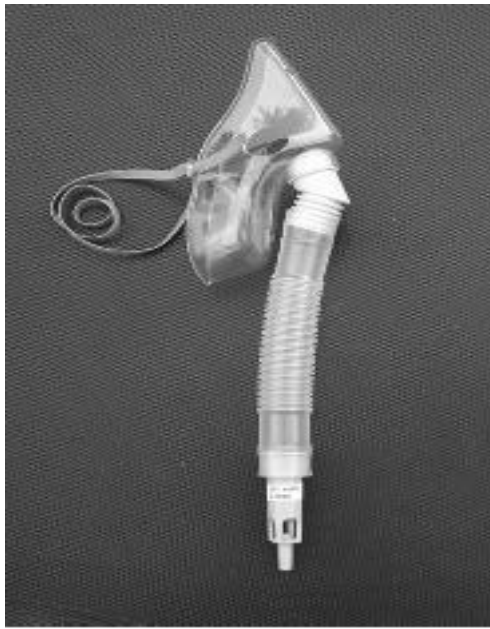
O ₂ Flow rate	FiO ₂	O ₂ Flow rate	FiO ₂	O ₂ Flow rate	FiO ₂
<u>Nasal cannula</u>		<u>Oxygen mask</u>		<u>Mask with reservoir</u>	
1	0.24	5-6	0.4	6	0.6
2	0.28	6-7	0.5	7	0.7
3	0.32	7-8	0.6	8	0.8
4	0.36			9	0.80+
5	0.4			10	0.80+
6	0.44				

Methods & interfaces for oxygen delivery

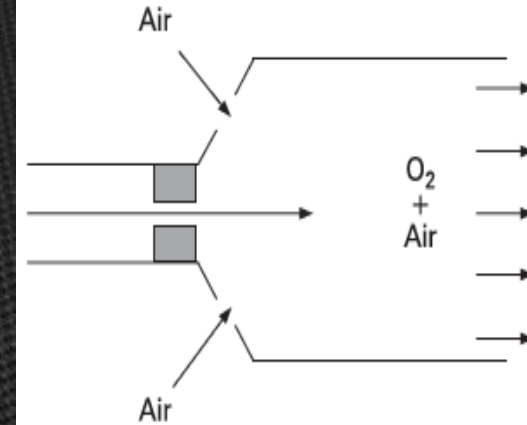


FiO_2 is unknown and highly dependent on:

1. O_2 flow
2. pt's insp. flow
3. breathing pattern



C

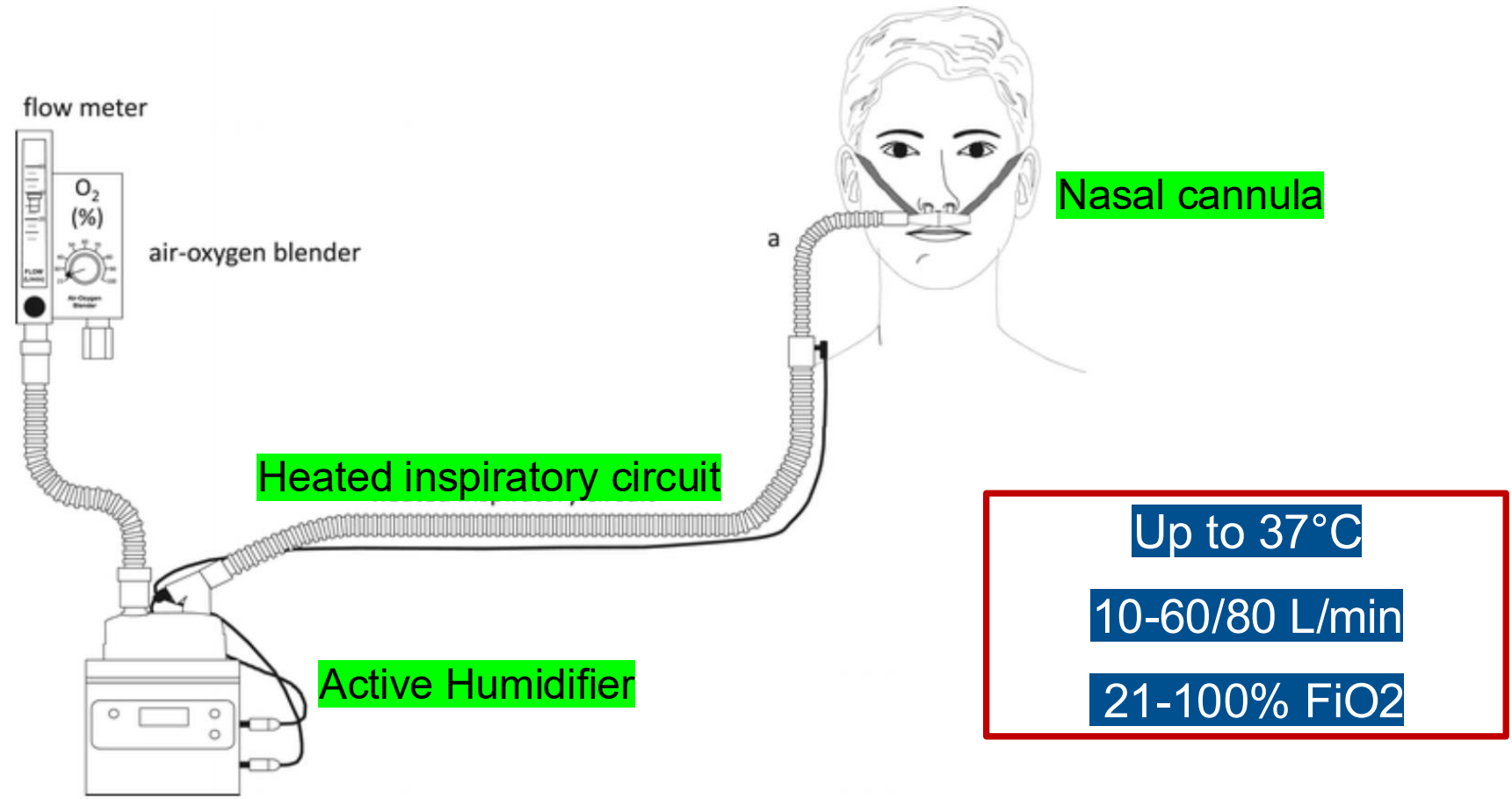


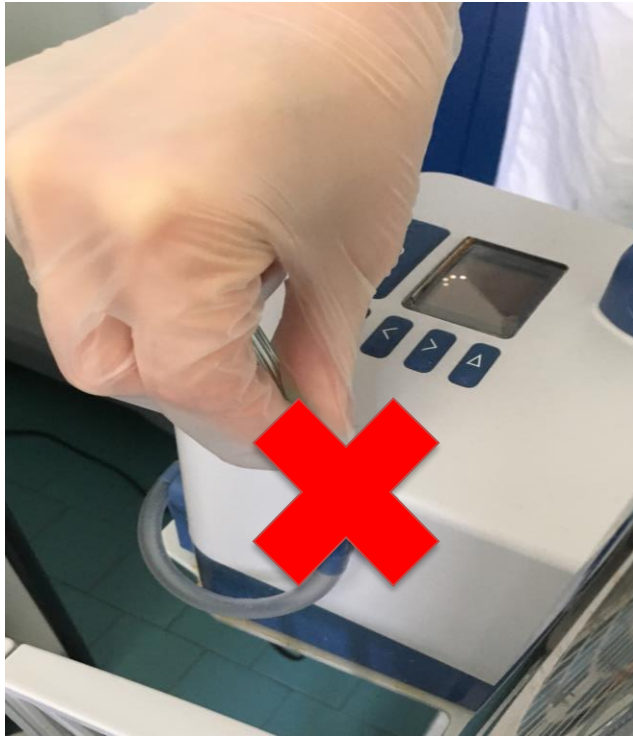
If the patient's ventilatory demand exceeds the flow provided by the device, the patient would breathe part of atmospheric air

NASAL HIGH FLOW THERAPY

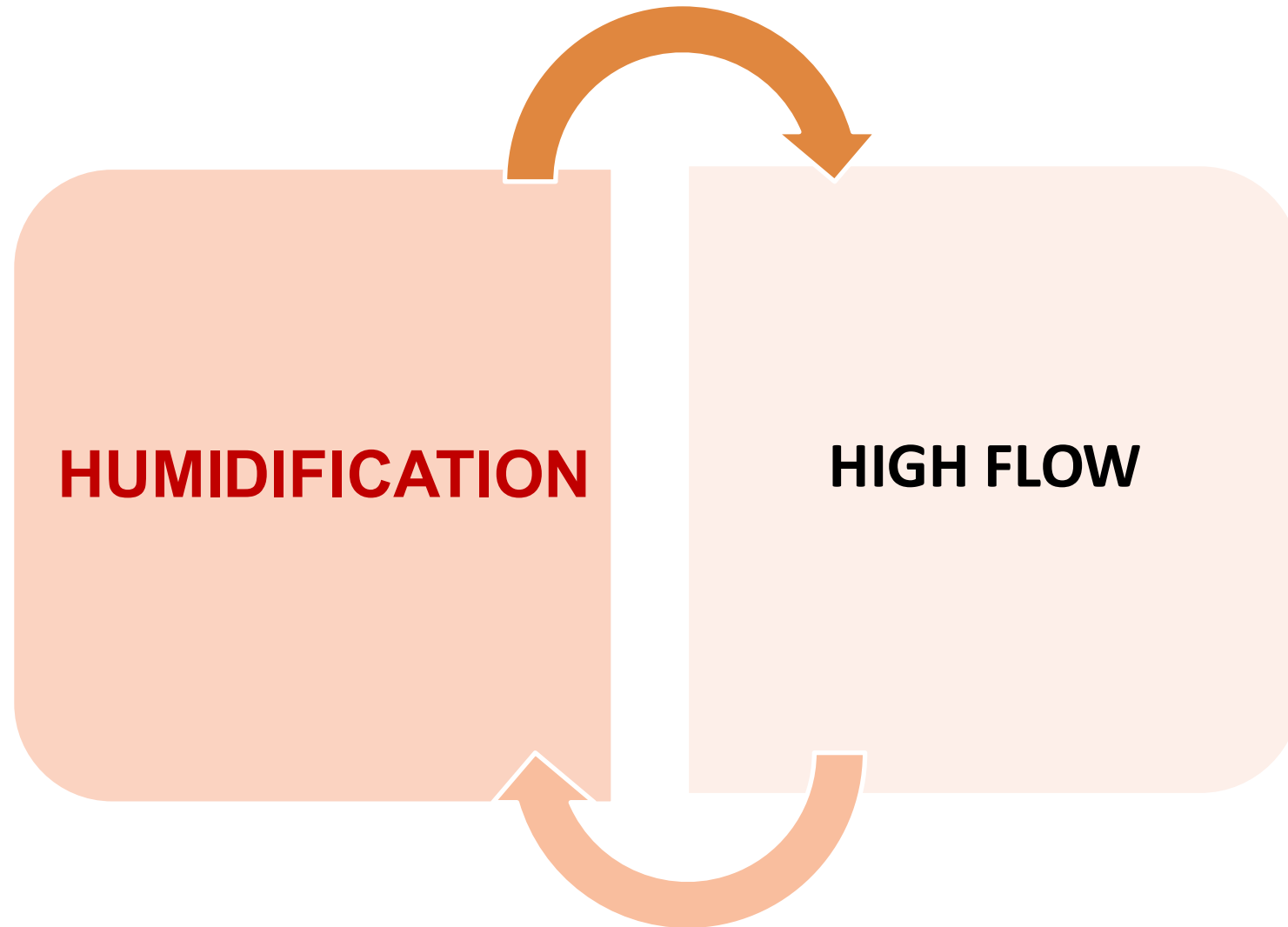
Flow generators

- Air-oxygen blender with a flow meter
- A dedicated standalone device
- NHF-capable mechanical ventilator





Physiological effects



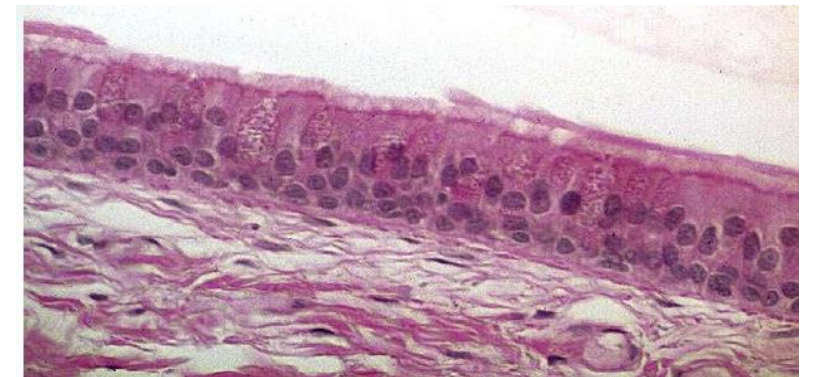
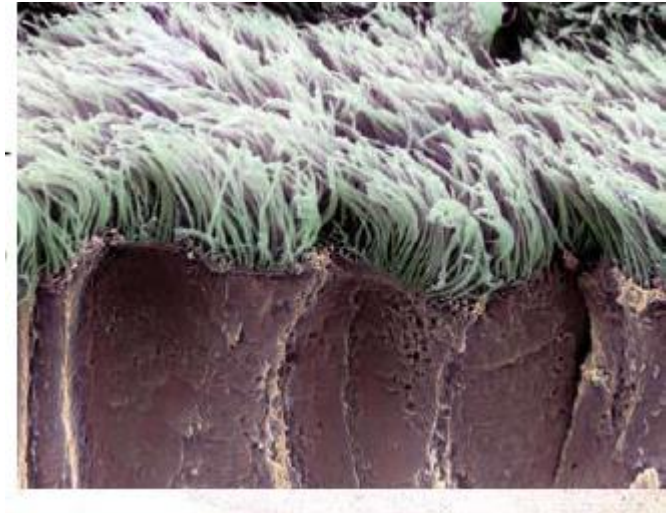
Physiological effects of **GAS** heating and **humidification**

Improvement of lung mucociliary clearance (↑ secretion clearance)

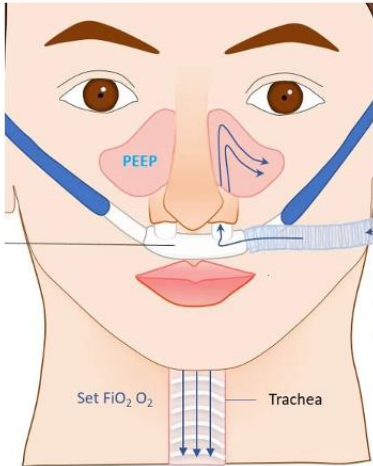
↓ Bronchoconstriction

↓ Metabolic cost of gas conditioning

Comfort



Physiological effects of **HIGH FLOW**



Matching pat's inspiratory flow
(stable FiO₂)

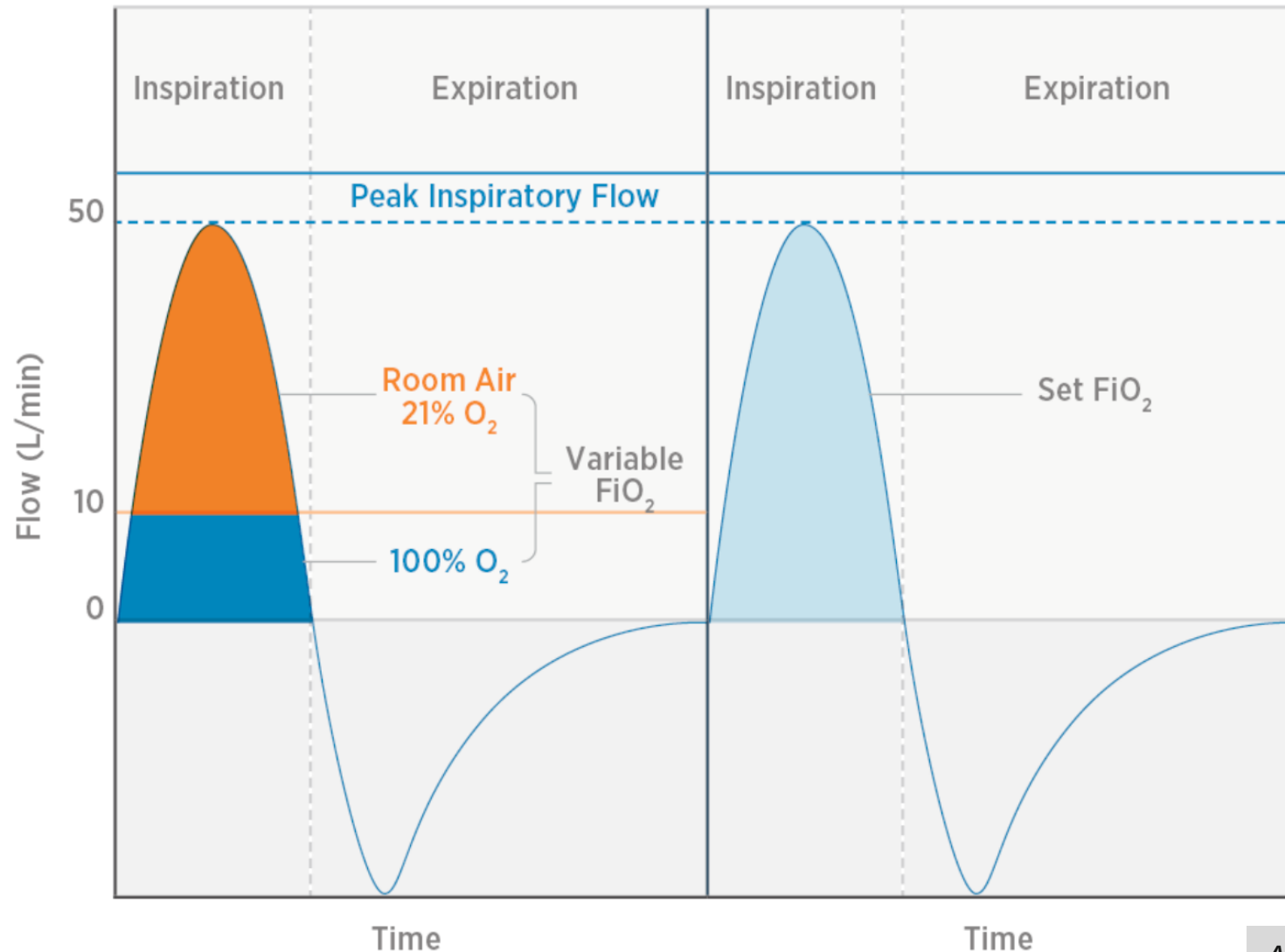
Washout of the upper airway
deadspace

The positive pressure in the
airways

More accurate and stable FiO_2 delivery

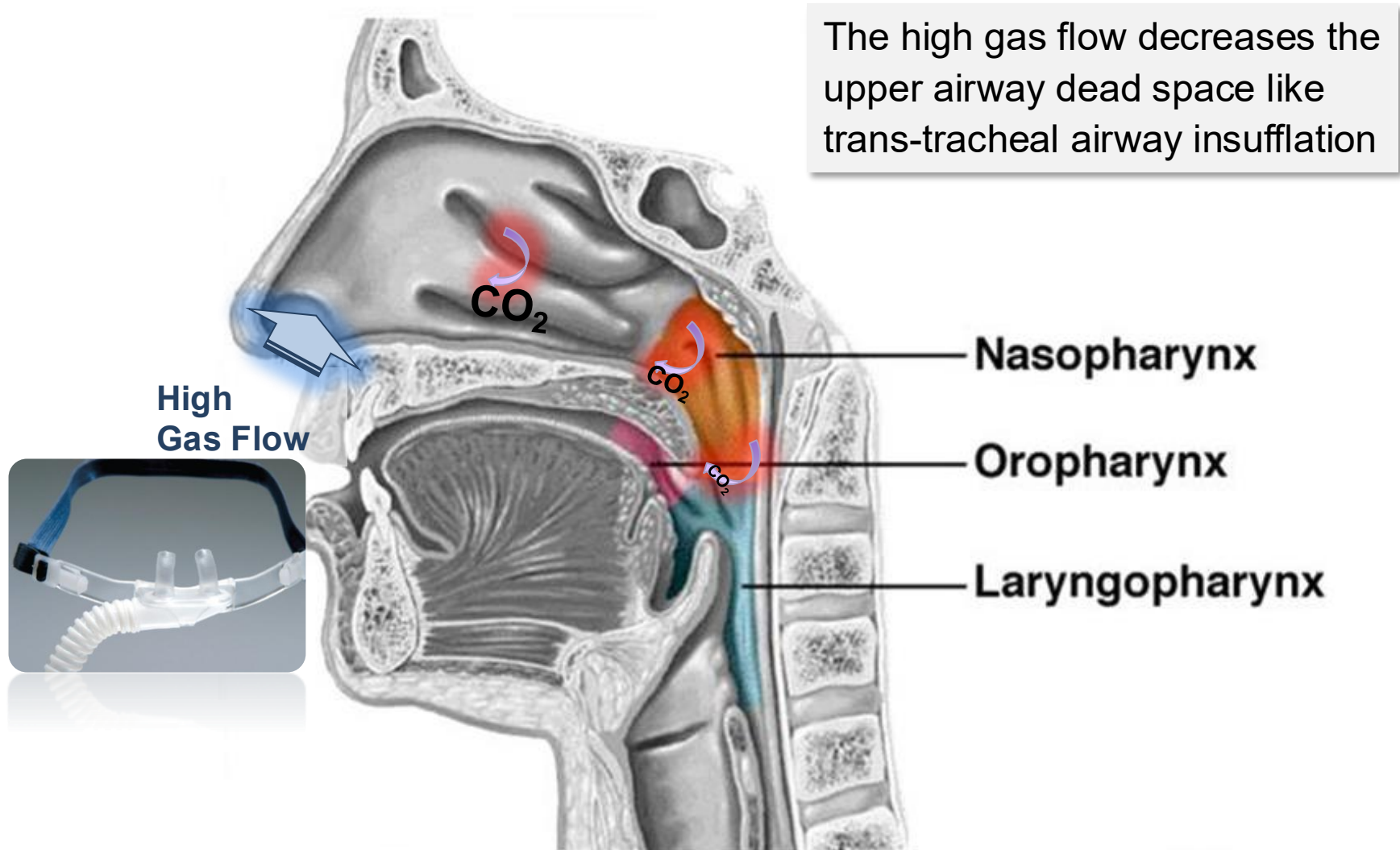
Face mask oxygen
therapy 10L/min

NHF
50L/min

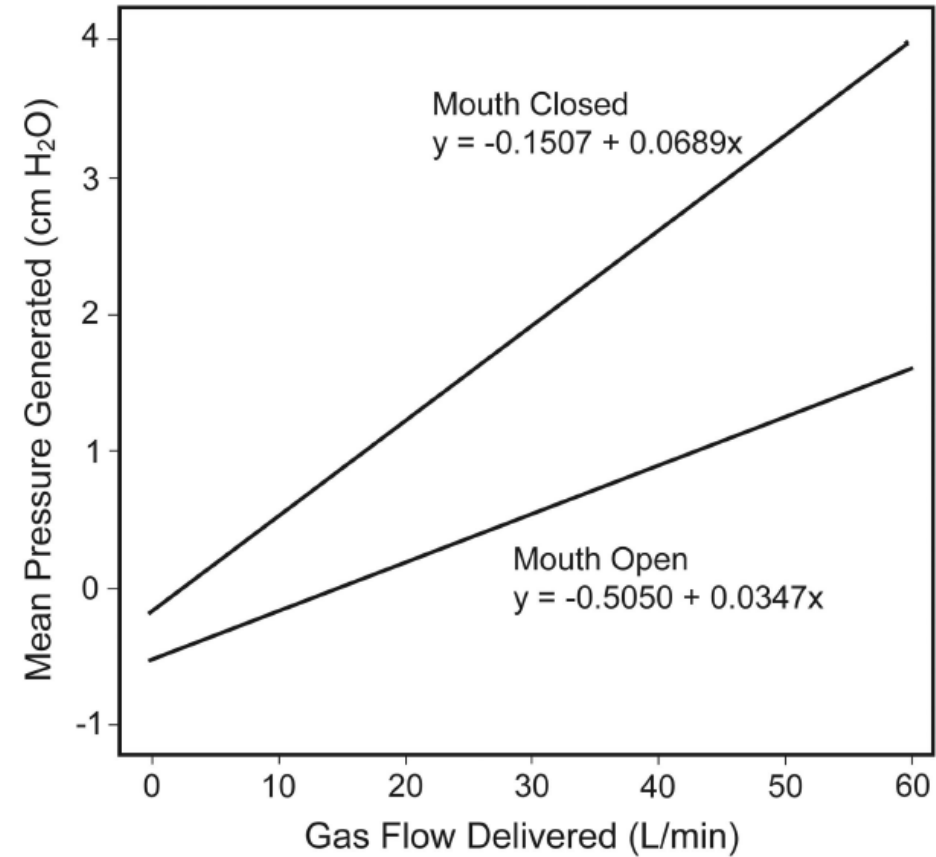
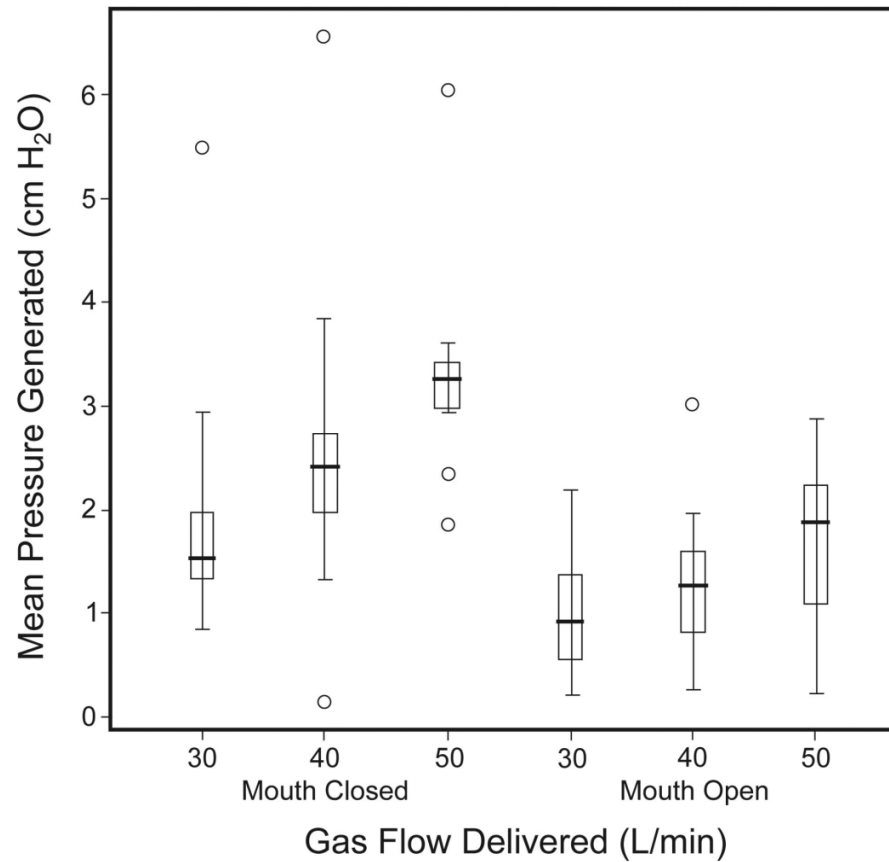


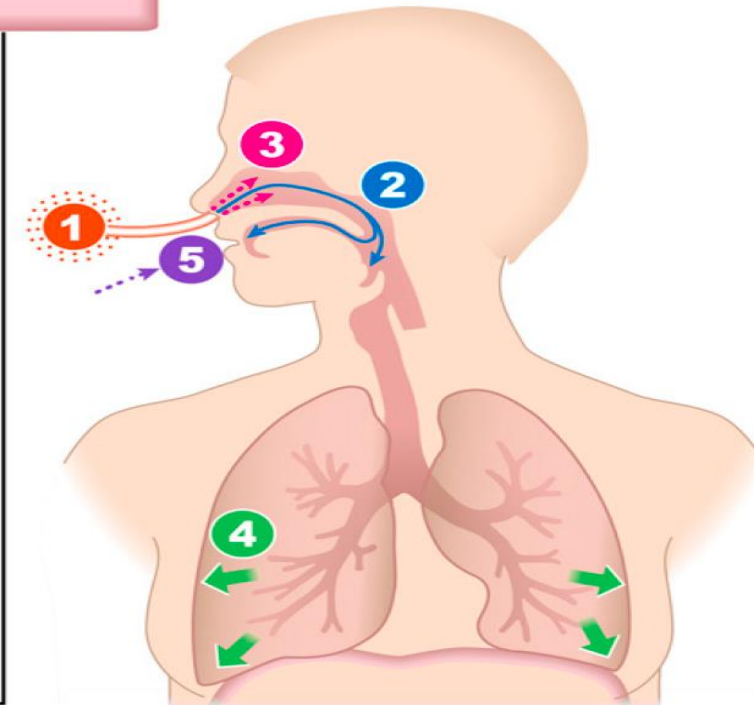
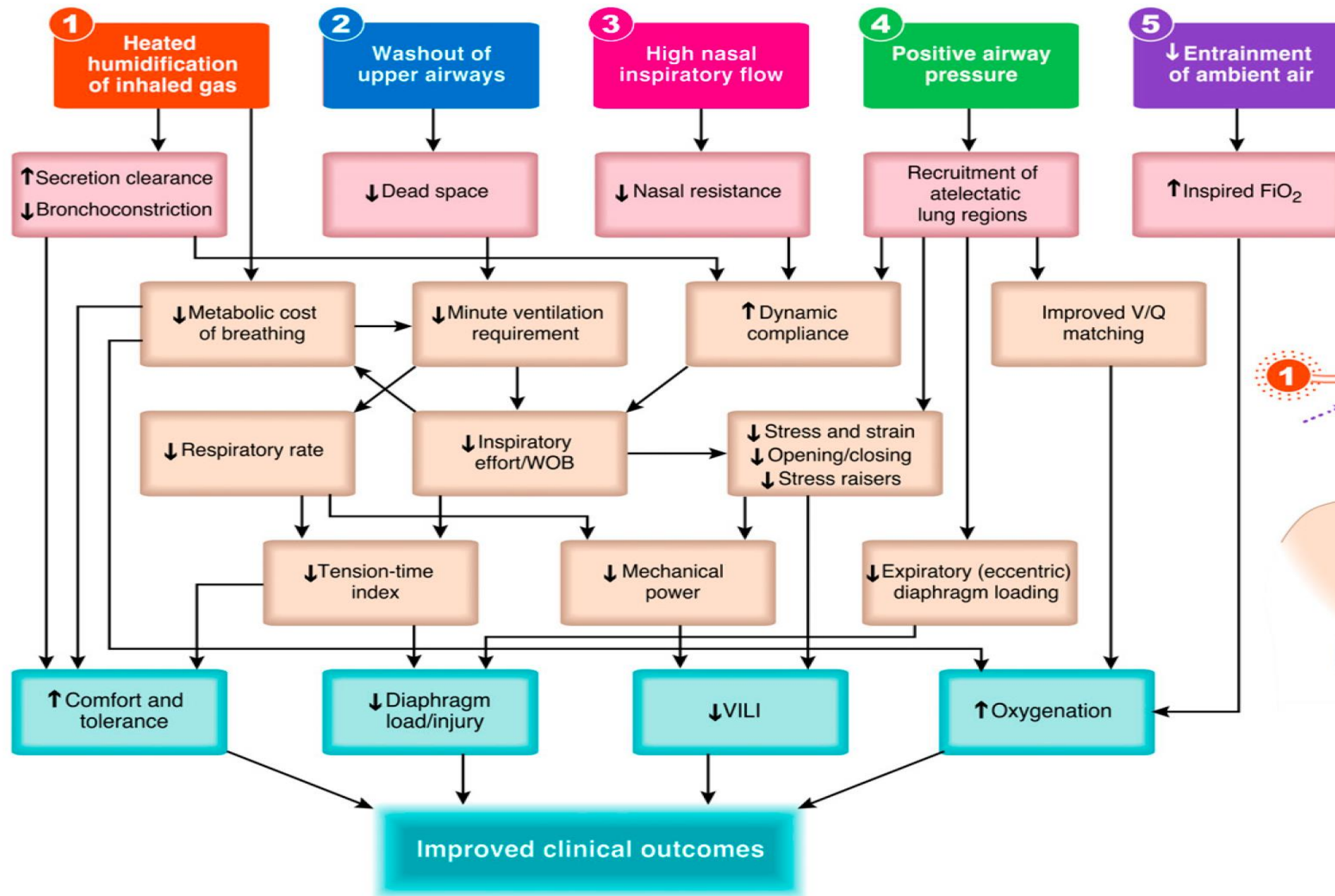
Adapted from Masclans et al .2012

Washout of nasopharyngeal dead space



HFNC can provide a distending pressure







Eur Respir J 2022; 59: 2101574

ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure

Simon Oczkowski^{1,2,26}, Begüm Ergan ^{3,26}, Lieuwe Bos ^{4,5}, Michelle Chatwin⁶, Miguel Ferrer⁷, Cesare Gregoretti^{8,9}, Leo Heunks¹⁰, Jean-Pierre Frat^{11,12}, Federico Longhini ¹³, Stefano Nava^{14,15}, Paolo Navalesi ^{16,17}, Aylin Ozsancak Uğurlu¹⁸, Lara Pisani^{14,15}, Teresa Renda¹⁹, Arnaud W. Thille ^{11,12}, João Carlos Winck ²⁰, Wolfram Windisch²¹, Thomy Tonia²², Jeanette Boyd²³, Giovanni Sotgiu ²⁴ and Raffaele Scala²⁵

CONFERENCE REPORTS AND EXPERT PANEL

The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline

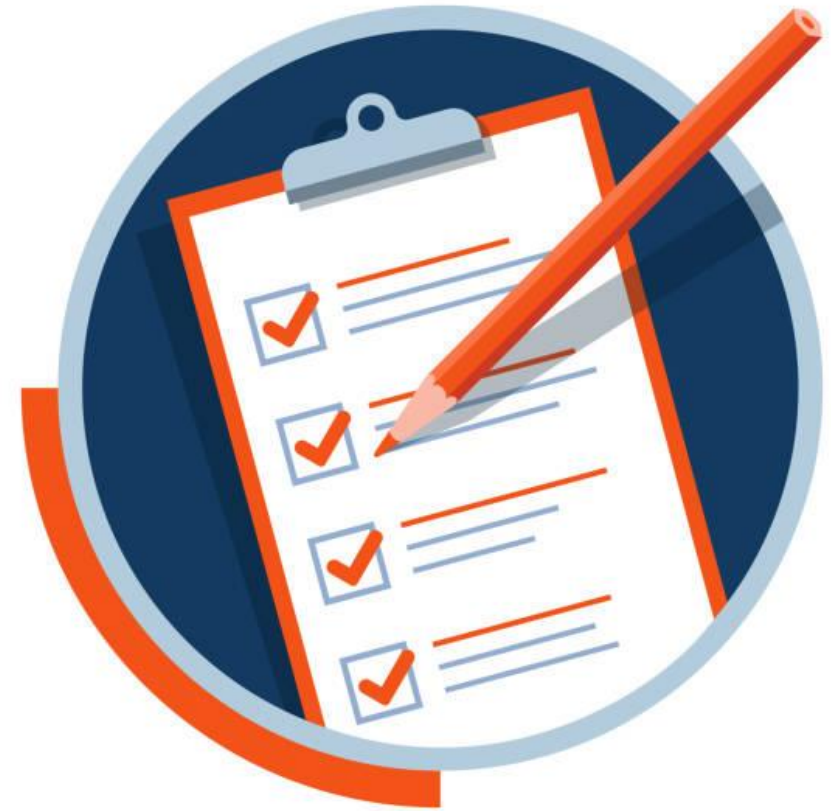


Intensive Care Med (2020) 46:2226–2237

Bram Rochweg^{1,2}, Sharon Einav^{3,4}, Dipayan Chaudhuri ¹, Jordi Mancebo⁵, Tommaso Mauri^{6,7}, Yigal Helviz³, Ewan C. Goligher^{8,9}, Samir Jaber¹⁰, Jean-Damien Ricard^{11,12}, Nuttapol Rittayamai¹³, Oriol Roca^{14,15}, Massimo Antonelli^{16,17}, Salvatore Maurizio Maggiore¹⁸, Alexandre Demoule^{19,20}, Carol L. Hodgson^{21,22}, Alain Mercat²³, M. Elizabeth Wilcox^{8,9}, David Granton¹, Dominic Wang¹, Elie Azoulay²⁴, Lamia Ouanes-Besbes^{25,26}, Gilda Cinnella²⁷, Michela Rauseo²⁷, Carlos Carvalho²⁸, Armand Dessap-Mekontso^{29,30}, John Fraser^{31,32}, Jean-Pierre Frat³³, Charles Gomersall³⁴, Giacomo Grasselli^{6,7}, Gonzalo Hernandez³⁵, Sameer Jog³⁶, Antonio Pesenti³⁷, Elisabeth D. Riviello³⁸, Arthur S. Slutsky^{9,39,40}, Renee D. Stapleton⁴¹, Daniel Talmor⁴², Arnaud W. Thille⁴³, Laurent Brochard^{9,40} and Karen E. A. Burns^{2,9,40*}

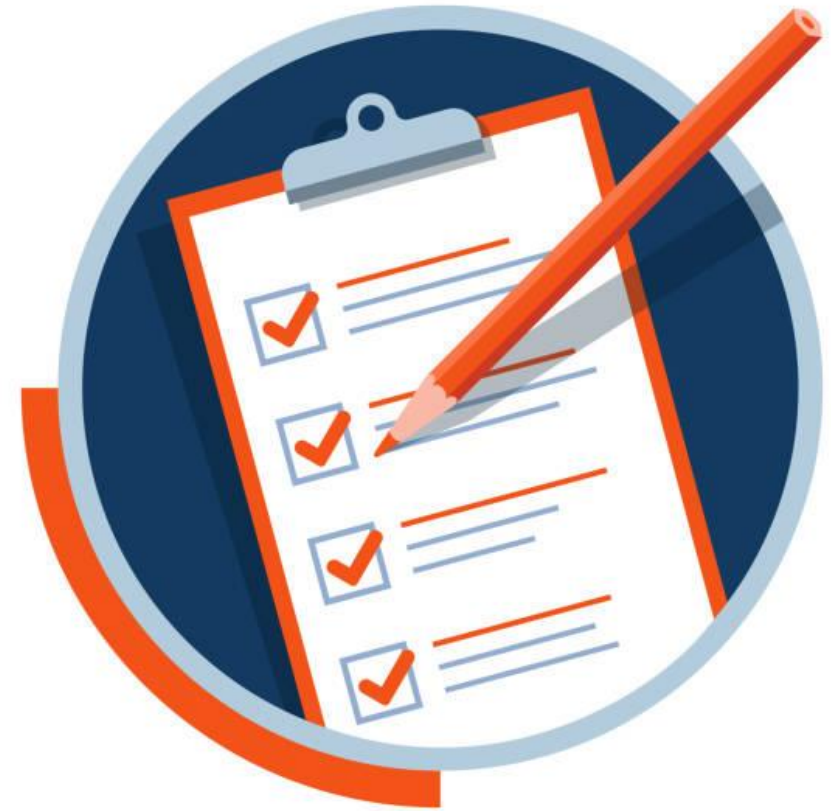
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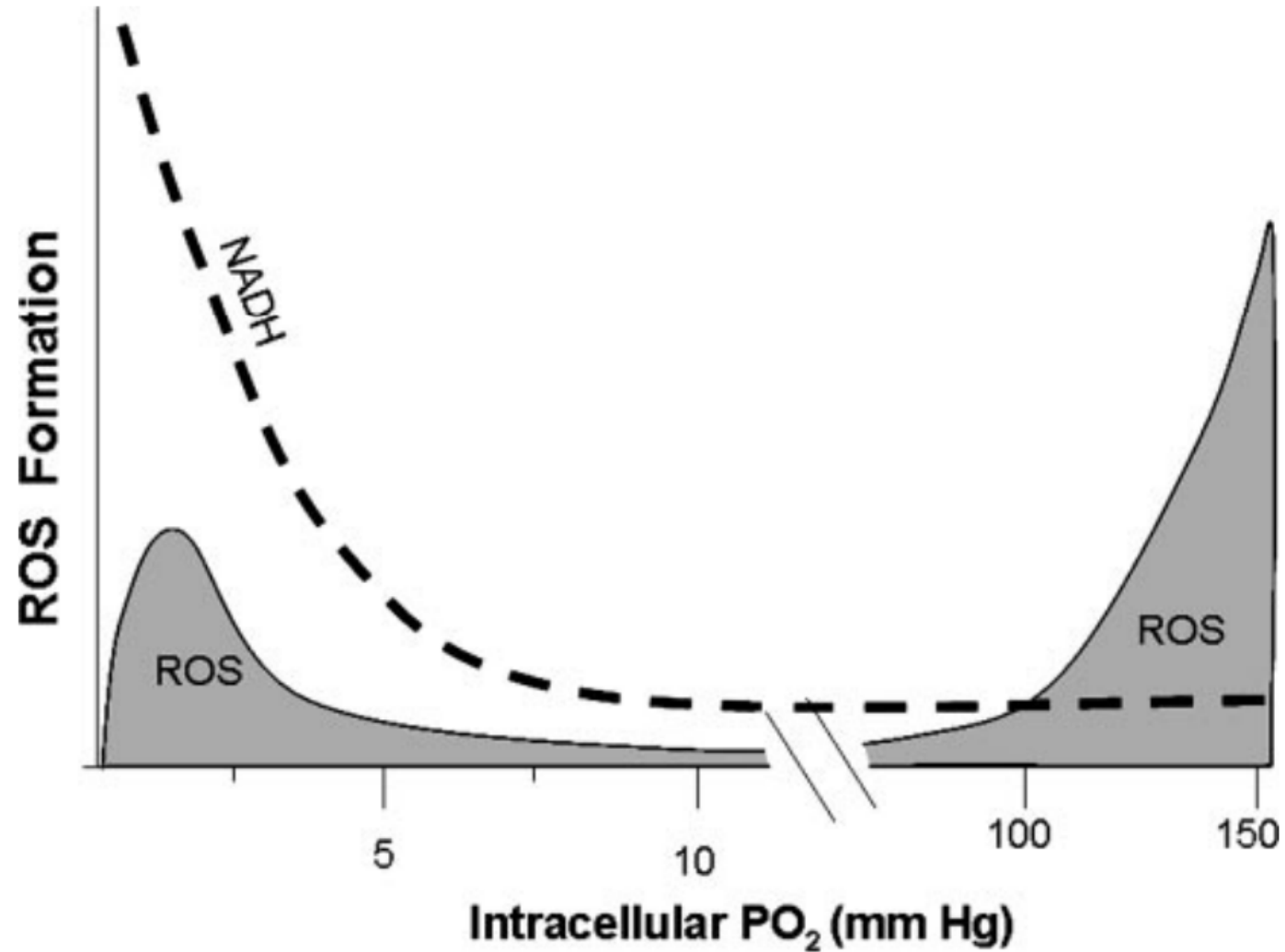
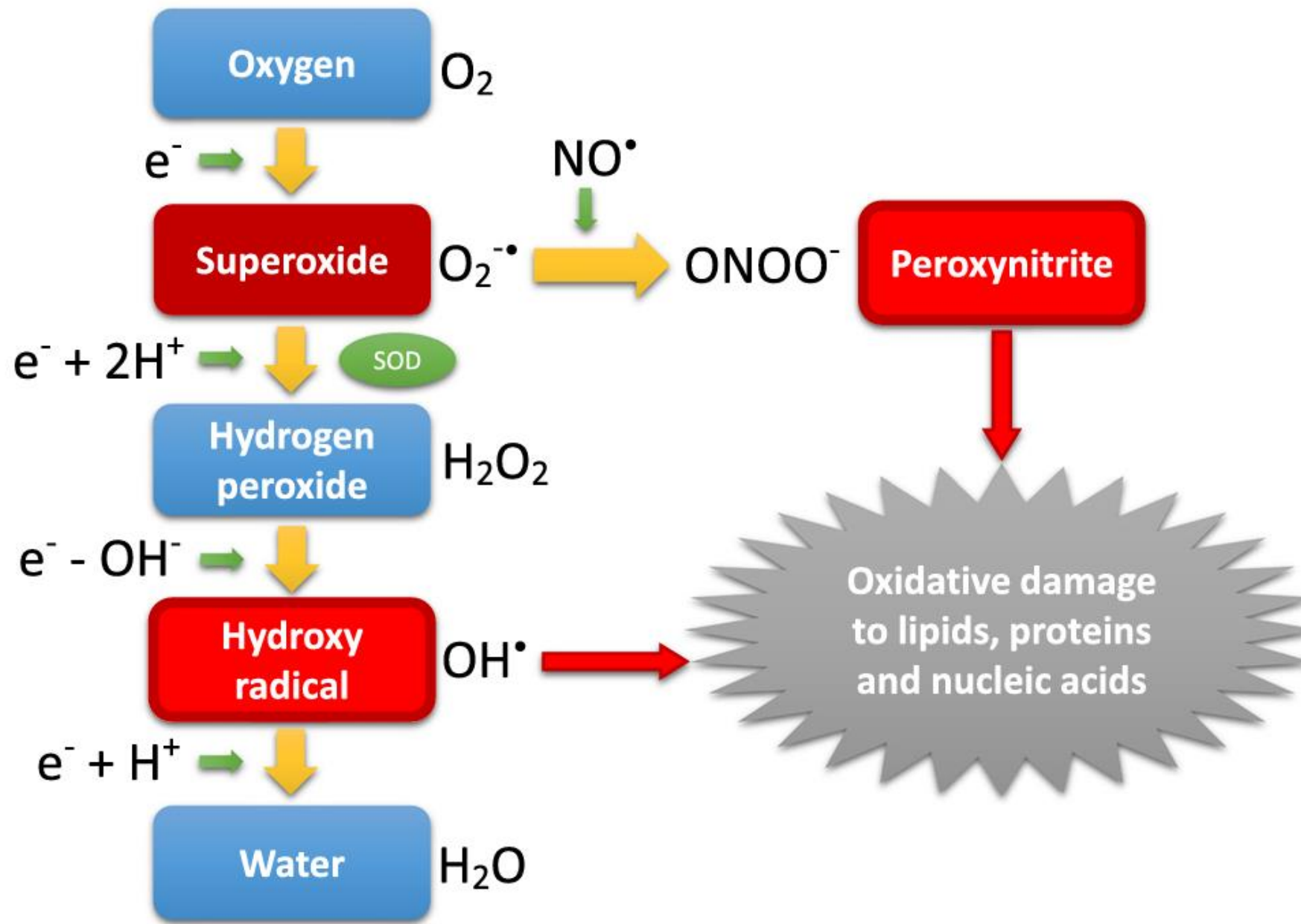


Fig. 1. Depiction of the proposed bimodal distribution of reactive oxygen species (ROS) formation as a function of PO₂ in which conditions of both hypoxia and hyperoxia support elevations in ROS formation.





In contrast to **hypoxia**, humans have not evolved any specific adaptation to counter **hyperoxia**

American Medical Research Expedition to Everest

John B. West

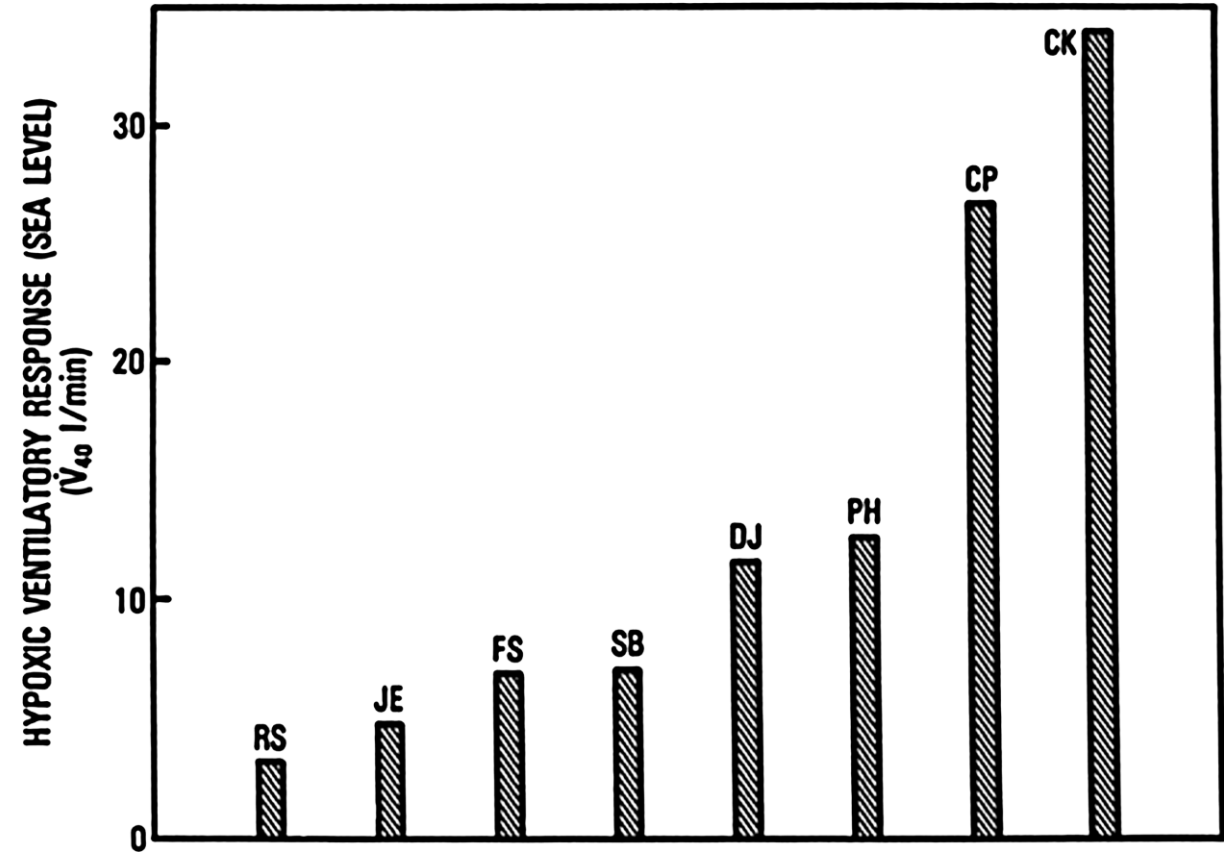
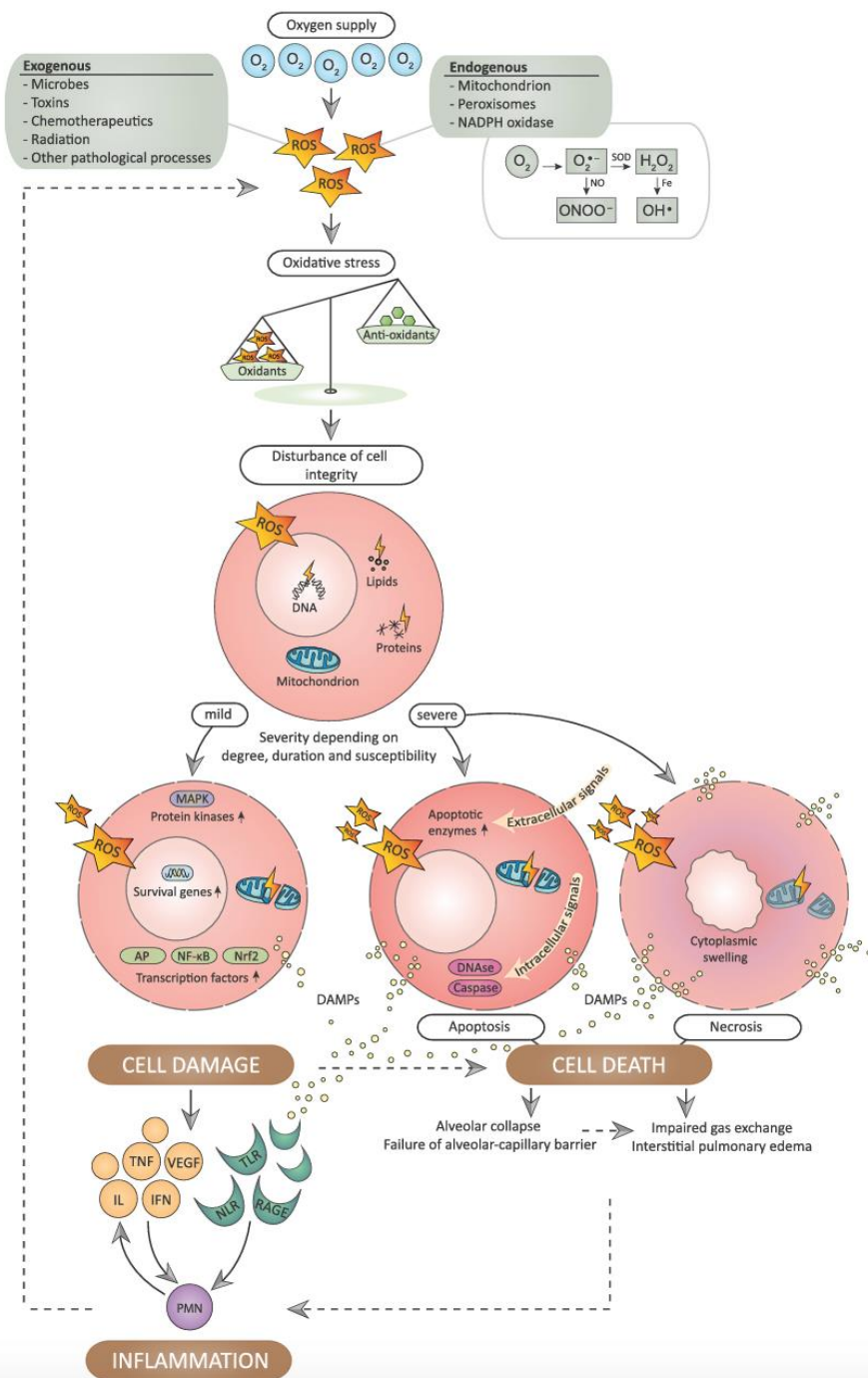


TABLE 1. ALVEOLAR GAS AND ESTIMATED ARTERIAL BLOOD VALUES ON THE SUMMIT OF MT. EVEREST

Altitude (m)	Barometric pressure (mmHg)	Inspired PO ₂ (mmHg)	Alveolar PO ₂ (mmHg)	Arterial			
				PO ₂ (mmHg)	Pco ₂ (mmHg)	pH	SaO ₂
8848 (summit)	253	43	35	28	7.5	>7.7	70
Sea level	760	149	100	95	40	7.4	97

West et al., 1983b.



$\text{FIO}_2 > 0.21$

Hyperoxaemia (i.e. arterial $\text{PaO}_2 > 100 \text{ mmHg}$)

Hyperoxia (increased tissue O_2 concentration)

ROS formation



Pre-hospital oxygen therapy in acute exacerbations of chronic obstructive pulmonary disease

M. Wijesinghe,¹ K. Perrin,^{1,2} B. Healy,¹ K. Hart,¹ J. Clay,² M. Weatherall^{2,3} and R. Beasley^{1,2}

¹Medical Research Institute of New Zealand, ²Capital and Coast District Health Board and ³Department of Medicine, University of Otago Wellington, Wellington, New Zealand

Results: Of 250 patients 77 (31%) died, required assisted ventilation or were in respiratory failure. Increased oxygen flow was associated with increasing risk of death, assisted ventilation or respiratory failure with an odds ratio (OR) of 1.2 (95% CI 1.0–1.4) per 1 L/min oxygen flow. Increasing PaO₂ was associated with a greater risk of a poor outcome with an OR of 1.1 (95% CI 1.0–1.3) per 10 mmHg higher PaO₂. Home oxygen (OR 2.8, 95% CI 1.5–5.1), previous respiratory failure (OR 2.6, 95% CI 1.5–4.6), previous ventilation (OR 3.2, 95% CI 1.7–5.9) and home nebulizer use (OR 2.4, 95% CI 1.4–4.3) were associated with an increased risk of a poor outcome.

Conclusion: In AECOPD high flow oxygen in the ambulance is associated with poor clinical outcomes. A number of easily identified markers of chronic disease severity indicate an increased risk of a poor clinical outcome.

VIEWPOINT

Oxygen-induced hypercapnia in COPD: myths and facts

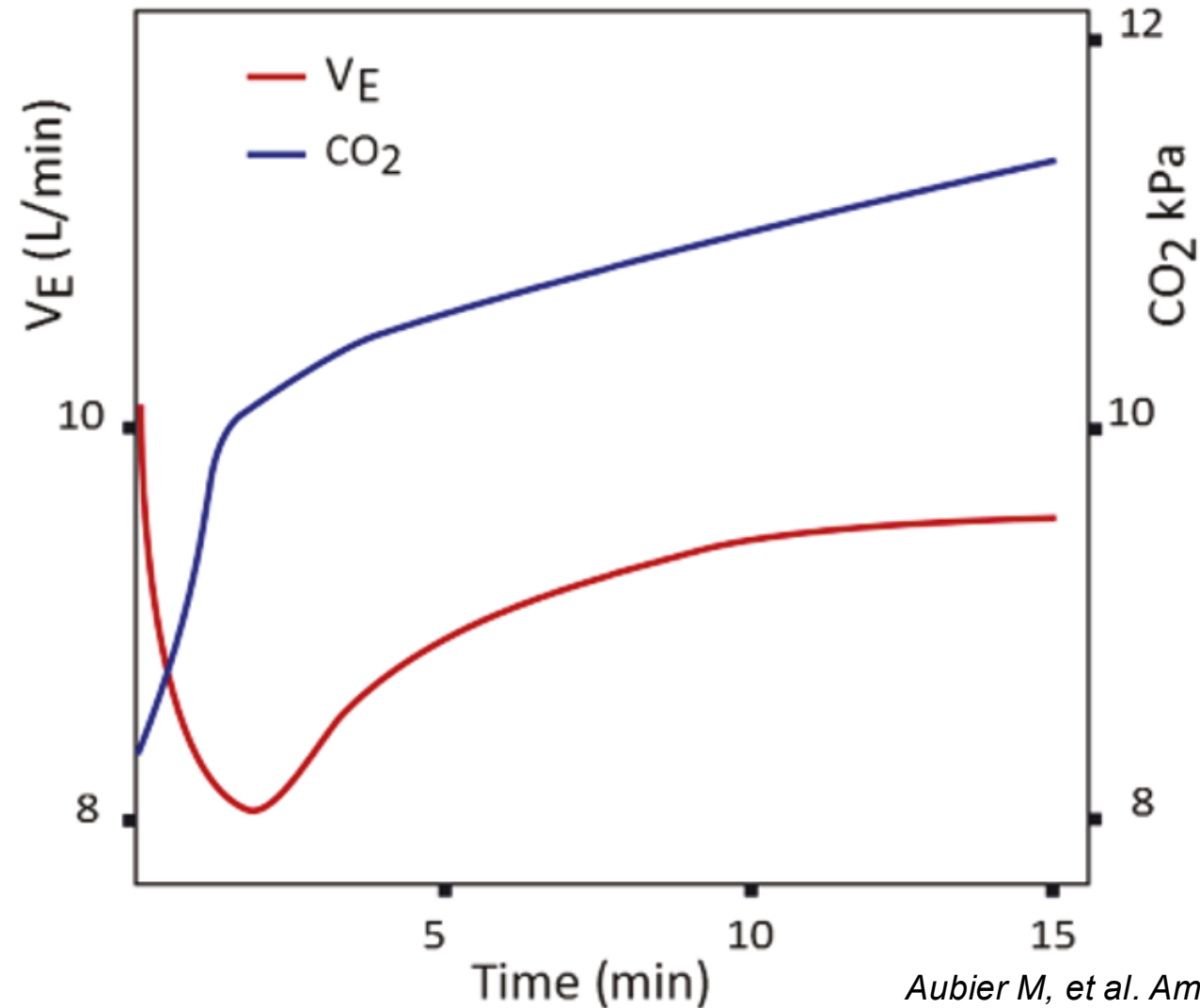
Wilson F Abdo* and Leo MA Heunks

Table 11 Physiological effects of acute hypoxaemia and hyperoxaemia

	Hypoxaemia		Hyperoxaemia	
	Effects	Risks	Effects	Risks
Respiratory system	Increased ventilation Pulmonary vasoconstriction	Pulmonary hypertension	Decreased ventilation (minimal)	Worsened ventilation/perfusion matching Absorption atelectasis
Cardiovascular system	Coronary vasodilation Decreased systemic vascular resistance (transient) Increased cardiac output Tachycardia	Myocardial Ischaemia/infarction Ischaemia/infarction of other critically perfused organs Hypotension Arrhythmias		Myocardial ischaemia (in context of decreased haematocrit) Reduced cardiac output Reduced coronary blood flow Increased blood pressure Increased peripheral resistance
Metabolic system	Increased 2,3-DPG Increased CO ₂ carriage (Haldane effect)	Lactic acidosis	Decreased 2,3-DPG Decreased CO ₂ carriage (Haldane effect)	Increased reactive oxygen species
Neurological system	Increased cerebral blood flow due to vasodilation	Confusion Delirium Coma	Decreased cerebral blood flow	
Renal system	Renin–angiotensin axis activation Increased erythropoietin production	Acute tubular necrosis		Reduced renal blood flow

2,3-DPG, 2,3-diphosphoglycerate.

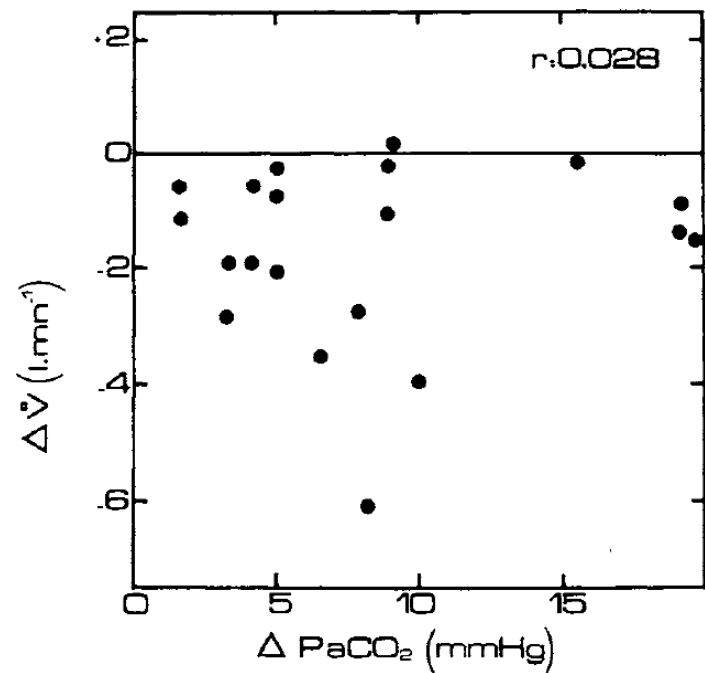
Effect of minute ventilation during 15 minutes of high oxygen administration



20 COPD patients with acute respiratory failure
FEV1(% pred) 25.3 ± 2.8

Effect of O2

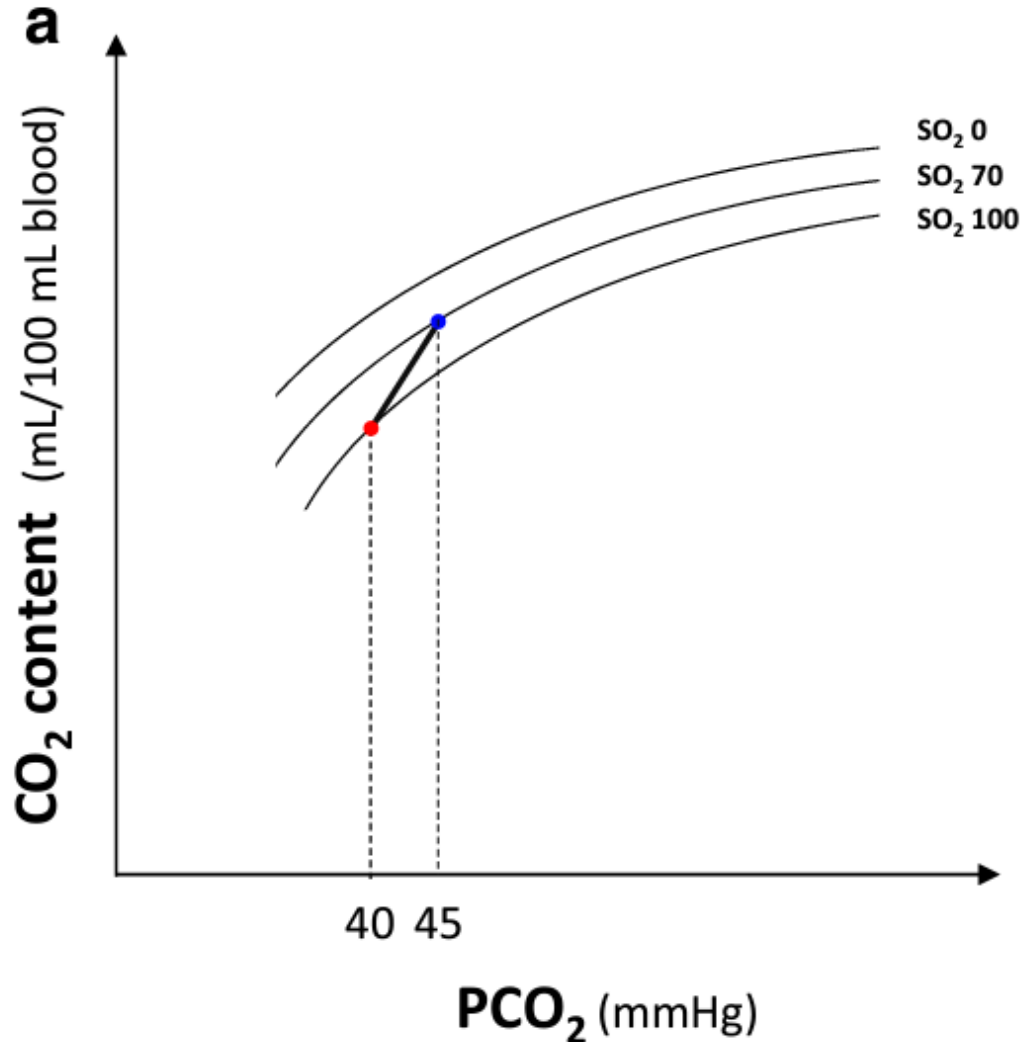
	P_{aO_2} (mm Hg)	PaCO2	V_E	VT	Fr	Ti (s)	TE (s)	Ti/TTOT	Vt/Ti (ml/s)	P0.1
Acute air	37.2 ± 1.8 *	59 ± 2.4 *	11.8 ± 0.8 *	395 ± 31 NS	31 ± 3 ↑	0.73 ± 0.07 *	1.4 ± 0.14 ↑	0.342 ± 0.009 NS	569 ± 31 ↑	8.1 ± 0.8 *
Acute O ₂	108.6 ± 12	69.1 ± 4	10.1 ± 0.6	405 ± 31 ↓	27 ± 0.3	0.79 ± 0.07	1.64 ± 0.10 ↓	0.328 ± 0.009	530 ± 28	4.9 ± 0.08



40% ↓

The reduction in respiratory drive is not a major contributor to oxygen induced hypercapnia in AECOPD patients

The Haldane effect



Il legame dell'O₂ con Hb favorisce l'eliminazione della CO₂, la curva di dissociazione della CO₂ è spostata verso il basso

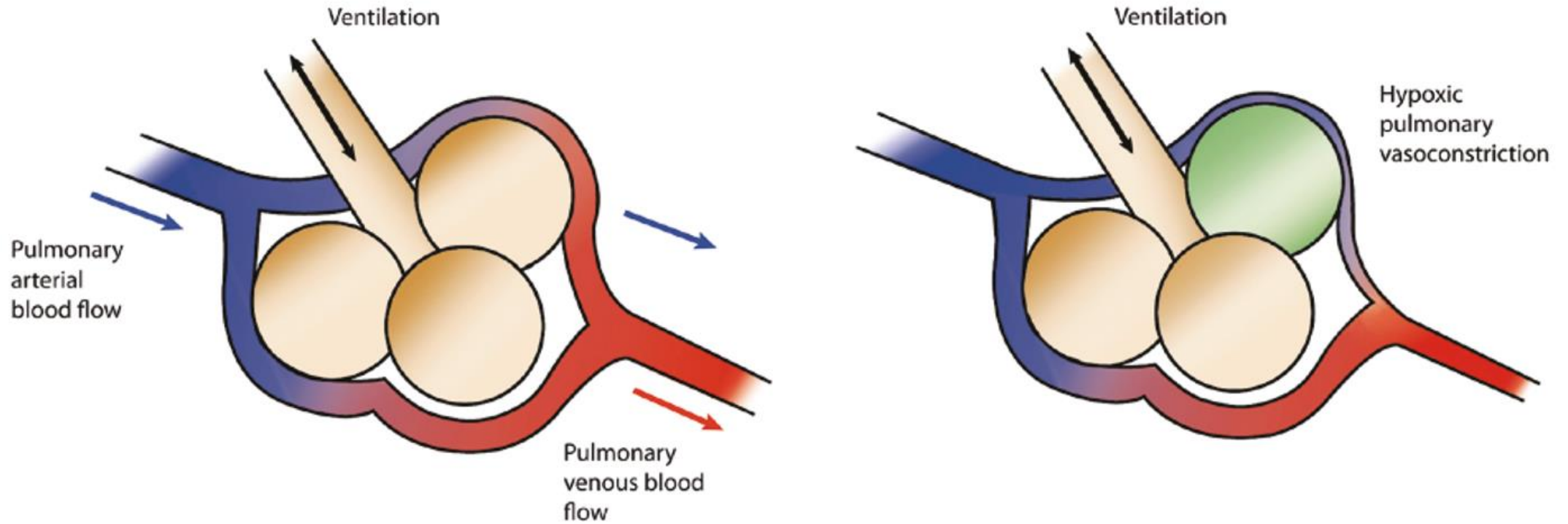
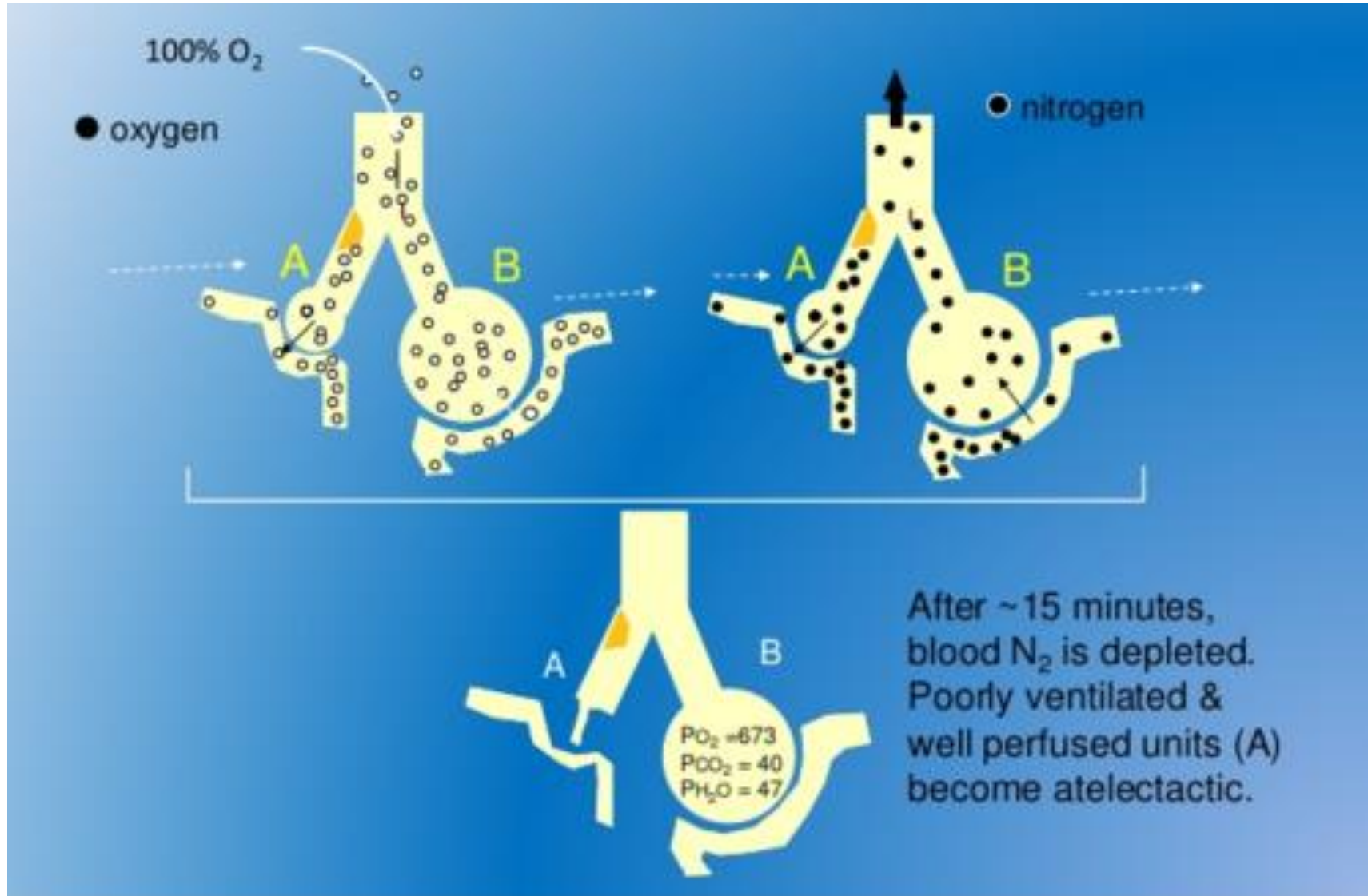
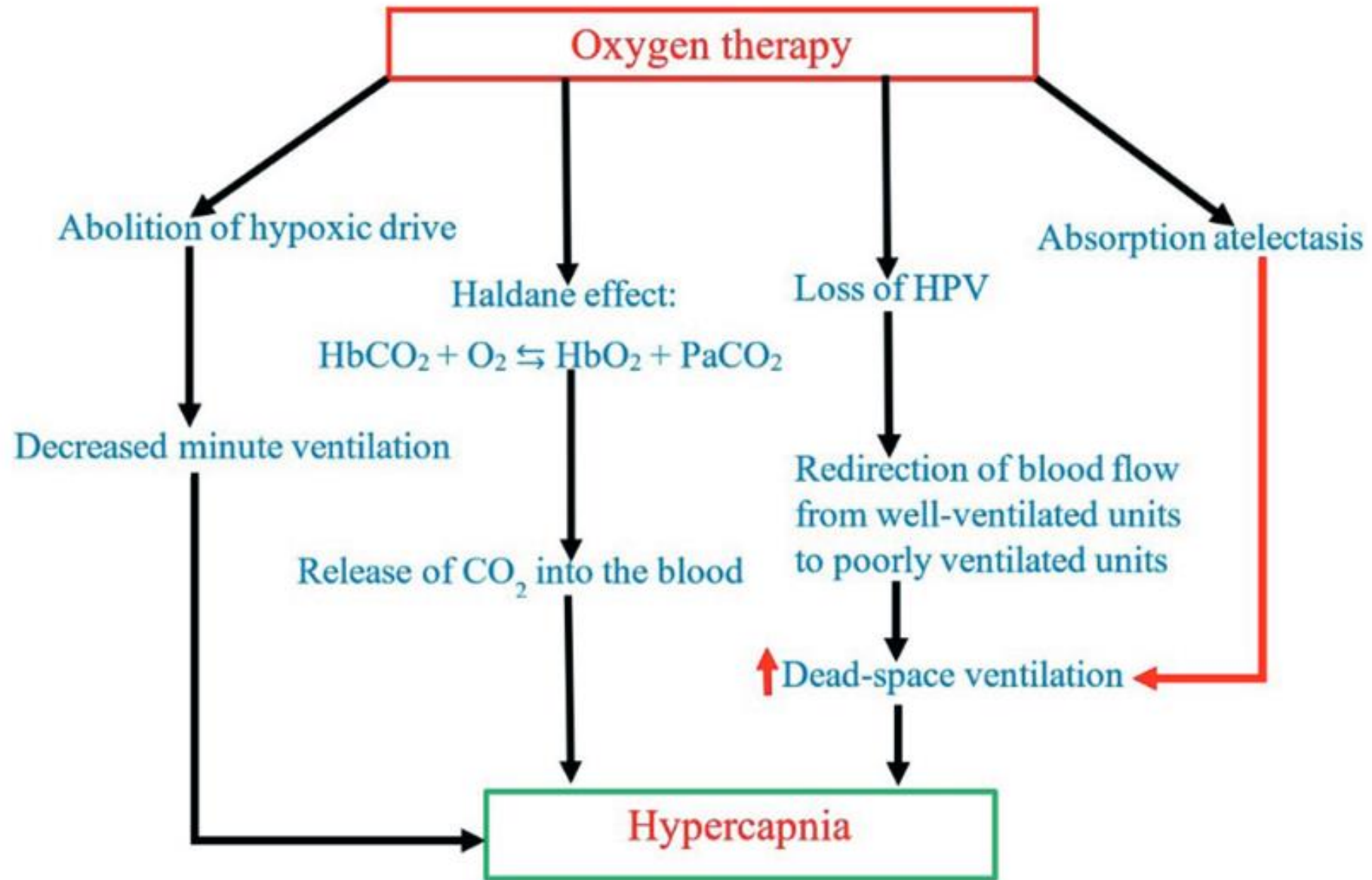


Figure 2. Hypoxic pulmonary vasoconstriction. The left frame shows normal alveolar ventilation and perfusion. In the right frame, reduced ventilation (thus O_2 tension) in the alveolus (green) leads to a reduced perfusion because of the hypoxic pulmonary vasoconstriction mechanism. Reprinted with permission from BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health [13].

Absorption atelectasis

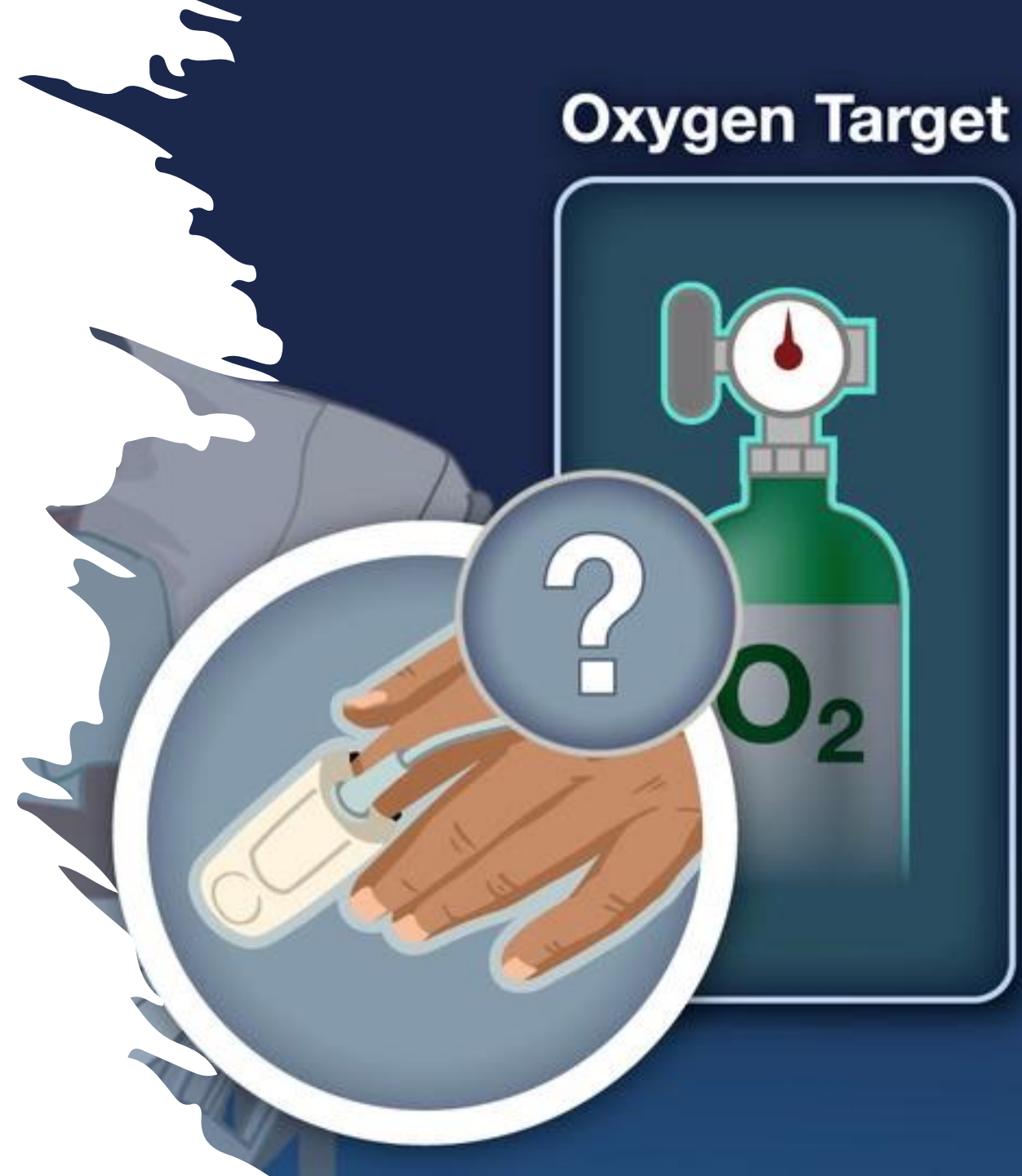




AECOPD

target range 88–92%

O'Driscoll BRet al. Thorax 2017;72:i1–i90.

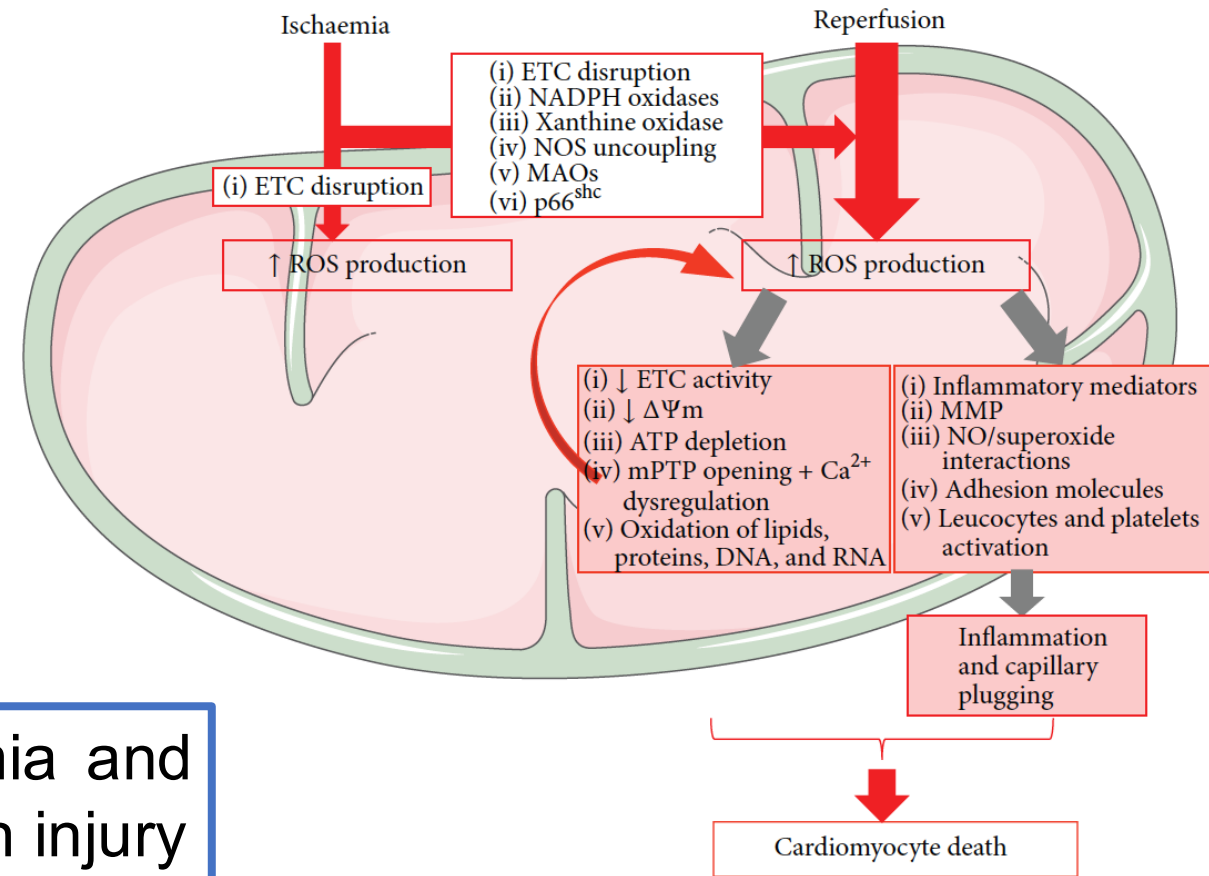


Effects on the Heart

Hyperoxia can:

-  vascular resistance in the coronary artery
-  the coronary blood flow
-  myocardial oxygen consumption

Paradoxical increase in myocardial ischemia and aggravated myocardial ischemia reperfusion injury



2023 ESC Guidelines for the management of acute coronary syndromes

Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)



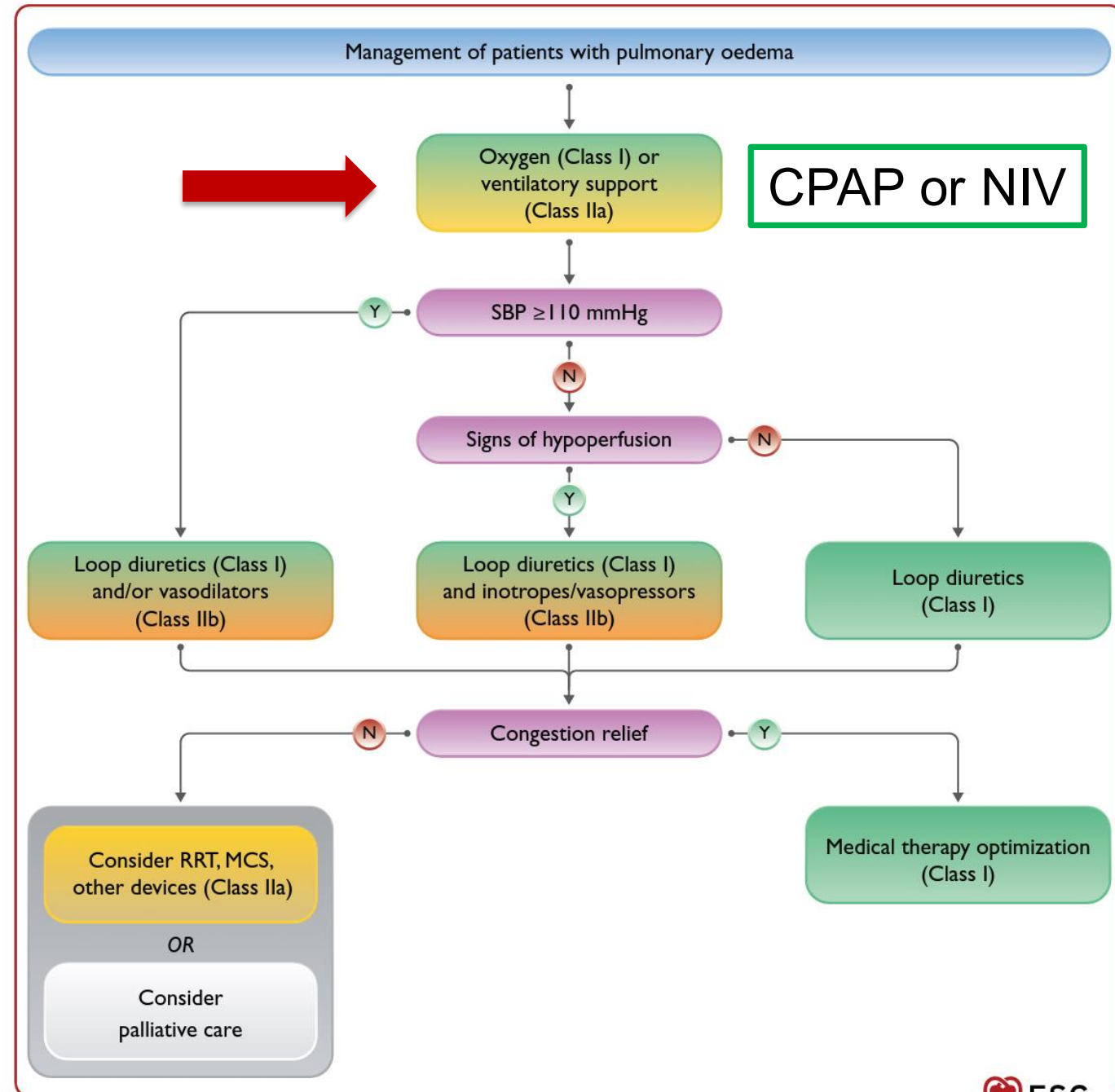
Recommendation Table 3 — Recommendations for the initial management of patients with acute coronary syndrome

Recommendations	Class ^a	Level ^b
Hypoxia		
Oxygen is recommended in patients with hypoxaemia (SaO ₂ <90%).	I	C
Routine oxygen is not recommended in patients without hypoxaemia (SaO ₂ >90%). ^{148,172}	III	A
Symptoms		
Intravenous opioids should be considered to relieve pain.	IIa	C
A mild tranquilizer should be considered in very anxious patients.	IIa	C
Intravenous beta-blockers		
Intravenous beta-blockers (preferably metoprolol) should be considered at the time of presentation in patients undergoing PPCI with no signs of acute heart failure, an SBP >120 mmHg, and no other contraindications. ^{163–167,169}	IIa	A

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



In **AHF** patients **oxygen** should not be used routinely in non-hypoxaemic patients, as it causes vasoconstriction and a reduction in cardiac output



Effects on the Brain



Hyperoxia

- Cerebral vasoconstriction
- Reduced CBF and metabolic dysfunction
- neuronal damage and neurological impairment

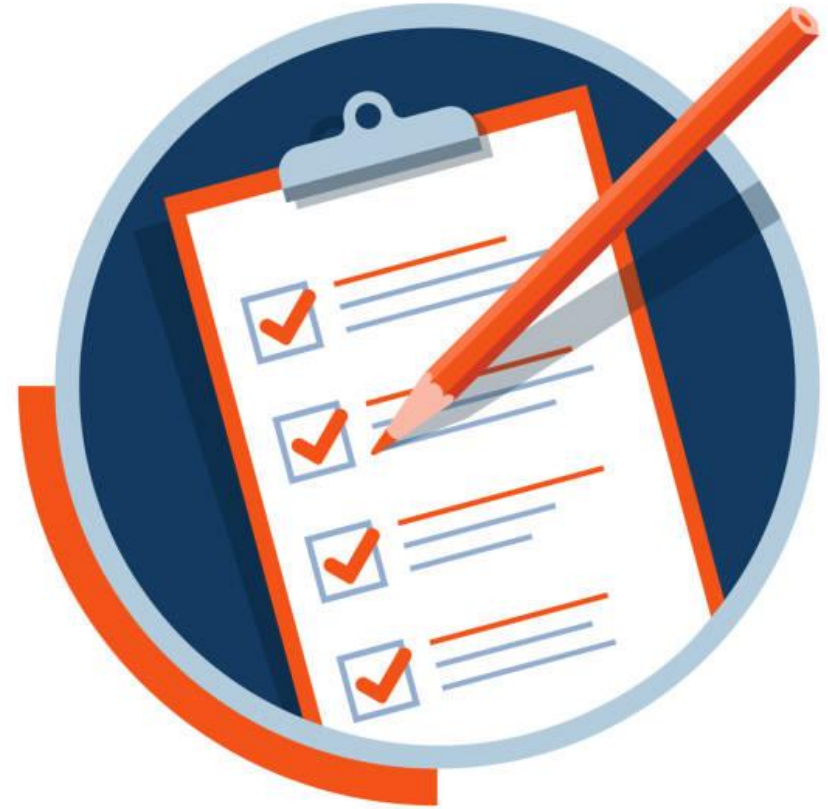
EAN Guidelines/CME Article | [Free Access](#)

**European Academy of Neurology and European Stroke
Organization consensus statement and practical guidance for
pre-hospital management of stroke**

Routine use of O₂ is not recommended
In patients with SpO₂ <95% the administration of O₂ titrated to
maintain normoxia is recommended.

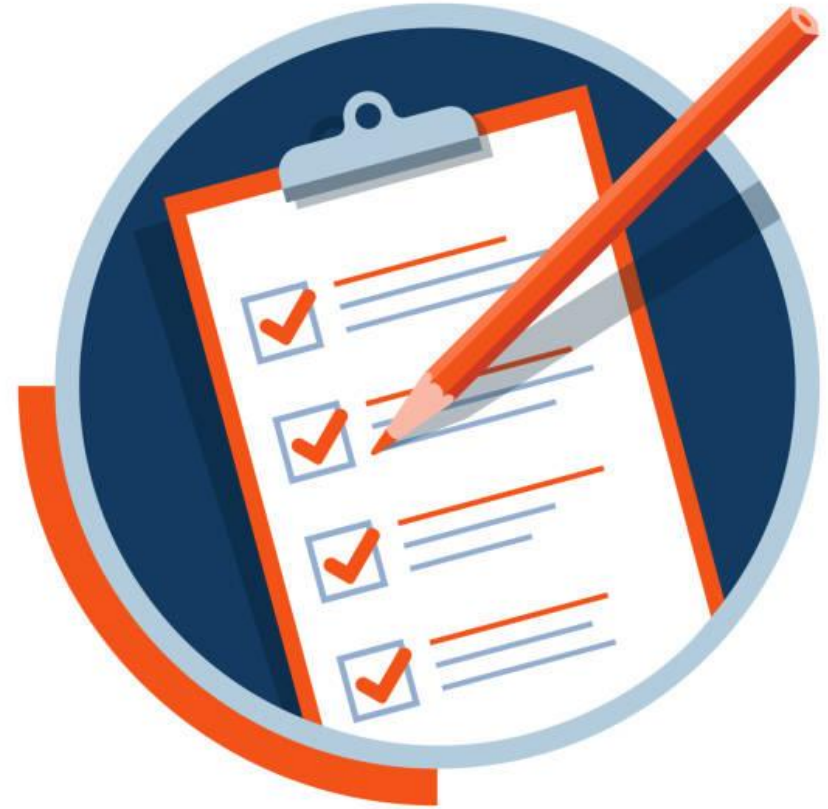
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ICU Patients





Oxygen in the critically ill: friend or foe?

Elisa Damiani^a, Abele Donati^a, and Massimo Girardis^b

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit

The Oxygen-ICU Randomized Clinical Trial

Massimo Girardis, MD; Stefano Busani, MD; Elisa Damiani, MD; Abele Donati, MD; Laura Rinaldi, MD; Andrea Marudi, MD; Andrea Morelli, MD; Massimo Antonelli, MD; Mervyn Singer, MD, FRCA

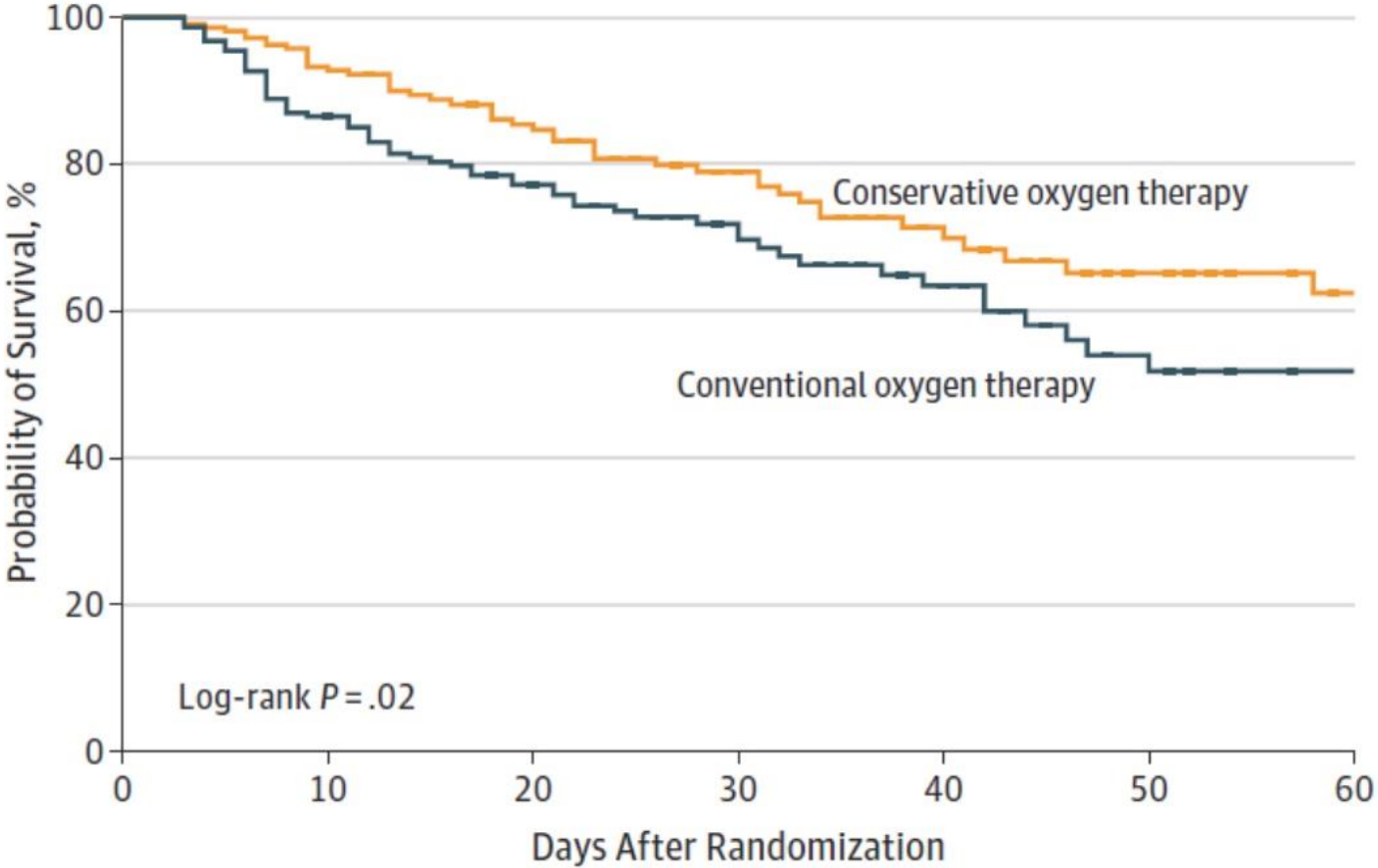
RESULTS A total of 434 patients (median age, 64 years; 188 [43.3%] women) received conventional (n = 218) or conservative (n = 216) oxygen therapy and were included in the modified intent-to-treat analysis. Daily time-weighted PaO₂ averages during the ICU stay were significantly higher (*P* < .001) in the conventional group (median PaO₂, 102 mm Hg [IQR, 88-116]) vs the conservative group (median PaO₂, 87 mm Hg [IQR, 79-97]). Mortality was lower in the conservative oxygen therapy group. The conservative group had fewer episodes of shock, liver failure, and bacteremia.

	Oxygen Therapy, No. (%)		Absolute Risk Reduction (95% CI)	P Value
	Conservative (n = 216)	Conventional (n = 218)		
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017-0.150)	.01
Secondary outcomes				
Shock	8 (3.7)	23 (10.6)	0.068 (0.020-0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008-0.088)	.02
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000-0.090)	.049

Conventional:
PaO2 up to 150 and 97%<SpO2>100%

Conservative:
PaO2 between 70 and100 or 94%<SpO2 >98%

Figure 2. Probability of Survival From Study Inclusion (Day 0) Through Day 60 for Patients in the Conservative and Conventional Oxygen Strategy Groups



8,6%

No. at risk							
Conservative oxygen therapy	216	201	188	181	173	170	169
Conventional oxygen therapy	218	189	172	163	158	152	152

Higher versus lower fractions of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit (Review)



**Cochrane
Library**

Cochrane Database of Systematic Reviews

Klitgaard TL, Schjørring OL, Nielsen FM, Meyhoff CS, Perner A, Wetterslev J, Rasmussen BS, Barbateskovic M

19 RCTs (10,385 participants)

Authors' conclusions

In adult ICU patients, it is still not possible to draw clear conclusions about the effects of higher versus lower oxygenation strategies on all-cause mortality, SAEs, quality of life, lung injuries, myocardial infarction, stroke, and sepsis at maximum follow-up. This is due to low or very low-certainty evidence.

QUESTION Does targeting a PaO_2 of 60 mm Hg vs 90 mm Hg affect the number of days alive without life support in patients in the intensive care unit (ICU) with COVID-19 and severe hypoxemia?

CONCLUSION A PaO_2 target of 60 mm Hg vs 90 mm Hg resulted in more days alive without life support in ICU patients with COVID-19 and severe hypoxemia.

© AMA

POPULATION



495 Men 231 Women

Adults in the ICU with COVID-19, receiving at least 10 L/min of oxygen or mechanical ventilation

Median age: 66 years

LOCATIONS

11
ICUs in Europe



INTERVENTION

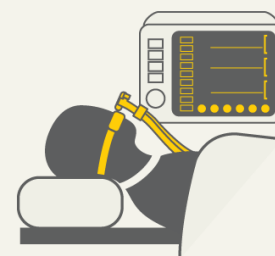


Lower oxygenation target

Supplemental oxygen
targeting a PaO_2 of 60 mm Hg

Higher oxygenation target

Supplemental oxygen
targeting a PaO_2 of 90 mm Hg



PRIMARY OUTCOME

Number of days alive without life support
(mechanical ventilation, circulatory support,
or kidney replacement therapy) at 90 days

FINDINGS

Median days alive without life support

Lower oxygenation target

80 (IQR, 9-89)

Higher oxygenation target

72 (IQR, 2-88)

The findings were statistically significant:

Between-group difference,
 $P = .009$ by van Elteren test

Supplemental bootstrapped adjusted mean difference,
5.8 days (95% CI, 0.2 to 11.5)

QUESTION Does reducing oxygen to a peripheral oxygen saturation (SpO₂) target of 90% reduce 90-day all-cause mortality in adult patients receiving supplemental oxygen in the intensive care unit?

CONCLUSION The findings do not support an approach of reducing oxygen exposure by targeting an SpO₂ of 90% in mechanically ventilated adults receiving oxygen while in an intensive care unit (ICU).

POPULATION



16 500 Patients

Adult patients (≥18 years) receiving mechanical ventilation and supplemental oxygen

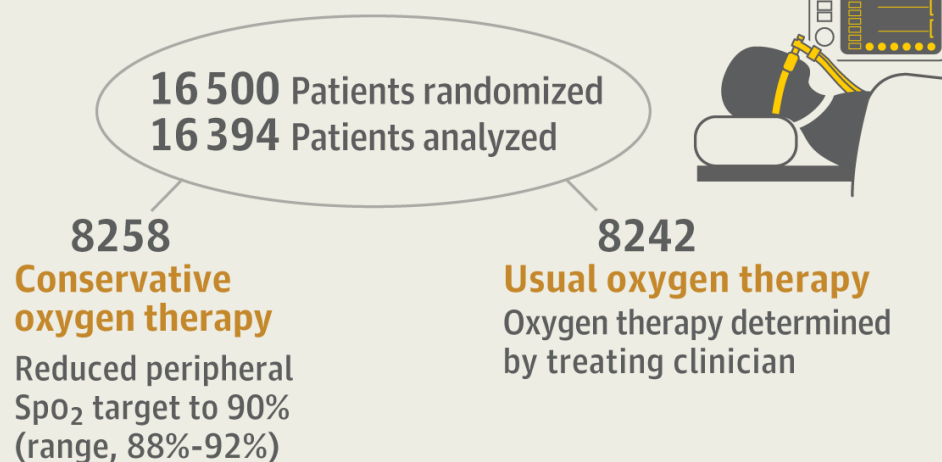
Mean age: **60** years

LOCATIONS

97
ICUs in the UK



INTERVENTION



PRIMARY OUTCOME

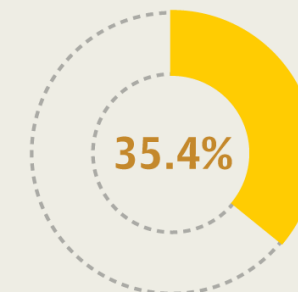
All-cause mortality at 90 days

FINDINGS

All-cause mortality at 90 days

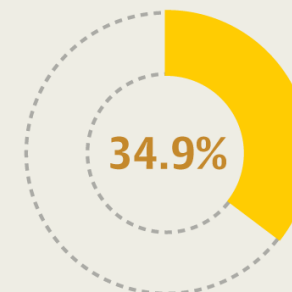
Conservative oxygen therapy

2908 patients



Usual oxygen therapy

2858 patients



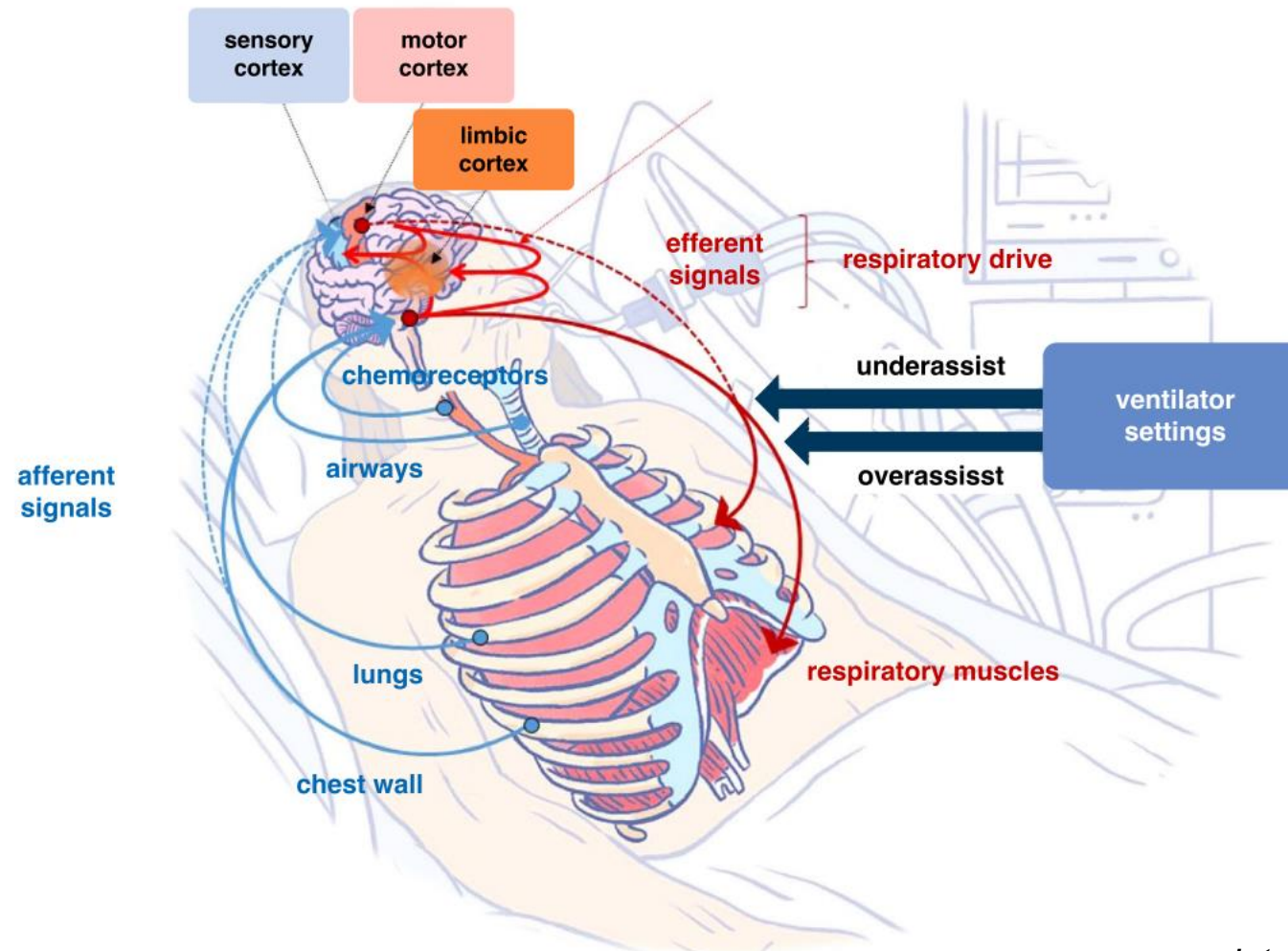
After adjustment for prespecified baseline variables, the risk difference was

0.7 percentage points

(95% CI, -0.7 to 2.0; P = .28)



Dyspnoea in acutely ill mechanically ventilated adult patients: an ERS/ESICM statement



Clinical Question 4: What Nonpharmacologic Interventions Provide Palliation of Dyspnea?

Recommendation 4.1. Airflow interventions such as directing a fan at the cheek (trigeminal nerve distribution) should be offered (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 4.2. Standard supplemental oxygen should be available for patients with hypoxemia who are experiencing dyspnea (ie, $\text{SpO}_2 \leq 90\%$ on room air) (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 4.3. Supplemental oxygen is not recommended when $\text{SpO}_2 > 90\%$ (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).



HYPEROXIA



- COPD: hypercapnia (*Haldane effect*)
- absorption atelectasis (*Lorrain Smith effect*)
- bronchopulmonary dysplasia (*BPD*)
- hyperoxic acute lung injury (*HALI*)
- lung inflammatory edema

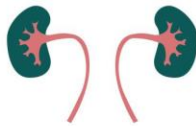


- ↓ heart rate
- ↓ cardiac output



nervous system

- activation of parasympathetic nervous system
- *Paul Bert effect*



kindey

- CKD
- AKI



vascular system

- ↑ systemic vascular resistance
- ↓ NO bioavailability



- retinopathy of prematurity (*ROP*)

$\text{FIO}_2 > 0.21$

Hyperoxaemia (i.e. arterial $\text{PaO}_2 > 100 \text{ mmHg}$)

Hyperoxia (increased tissue O_2 concentration)

ROS formation

Discomfort!!!

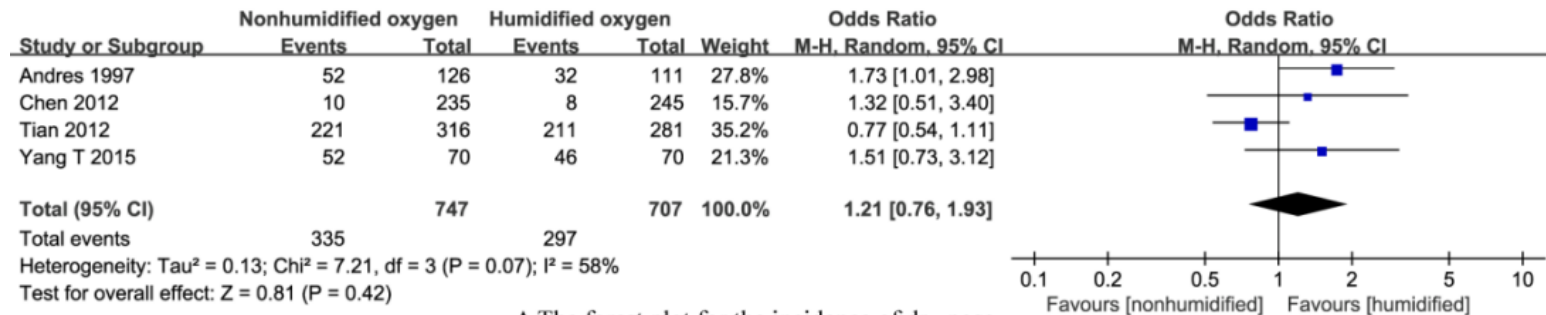


Is Humidified Better than Non-humidified Low Flow Oxygen Therapy?

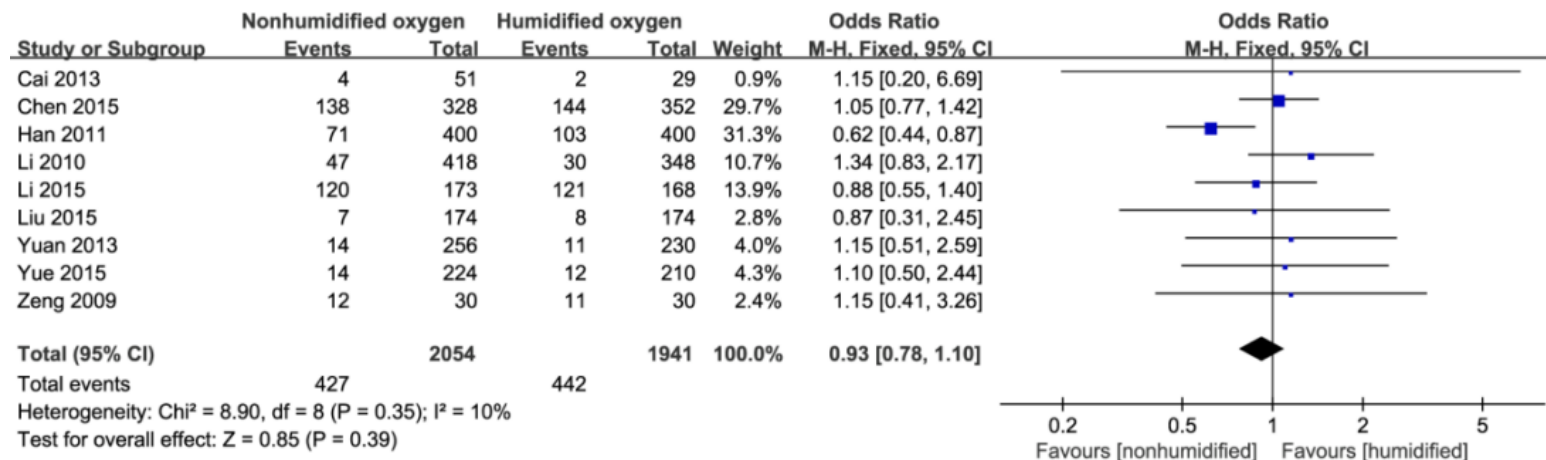
A Systematic Review and Meta -Analysis



Dry nose



A The forest plot for the incidence of dry nose

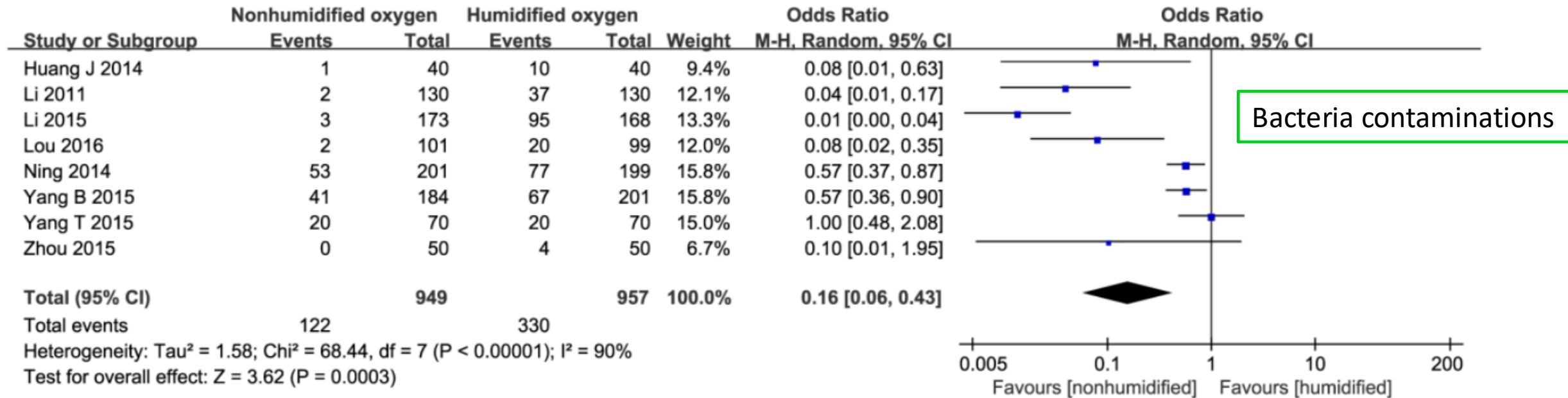


B The forest plot for the incidence of dry nose and throat

Dry nose and throat

Is Humidified Better than Non-humidified Low Flow Oxygen Therapy?

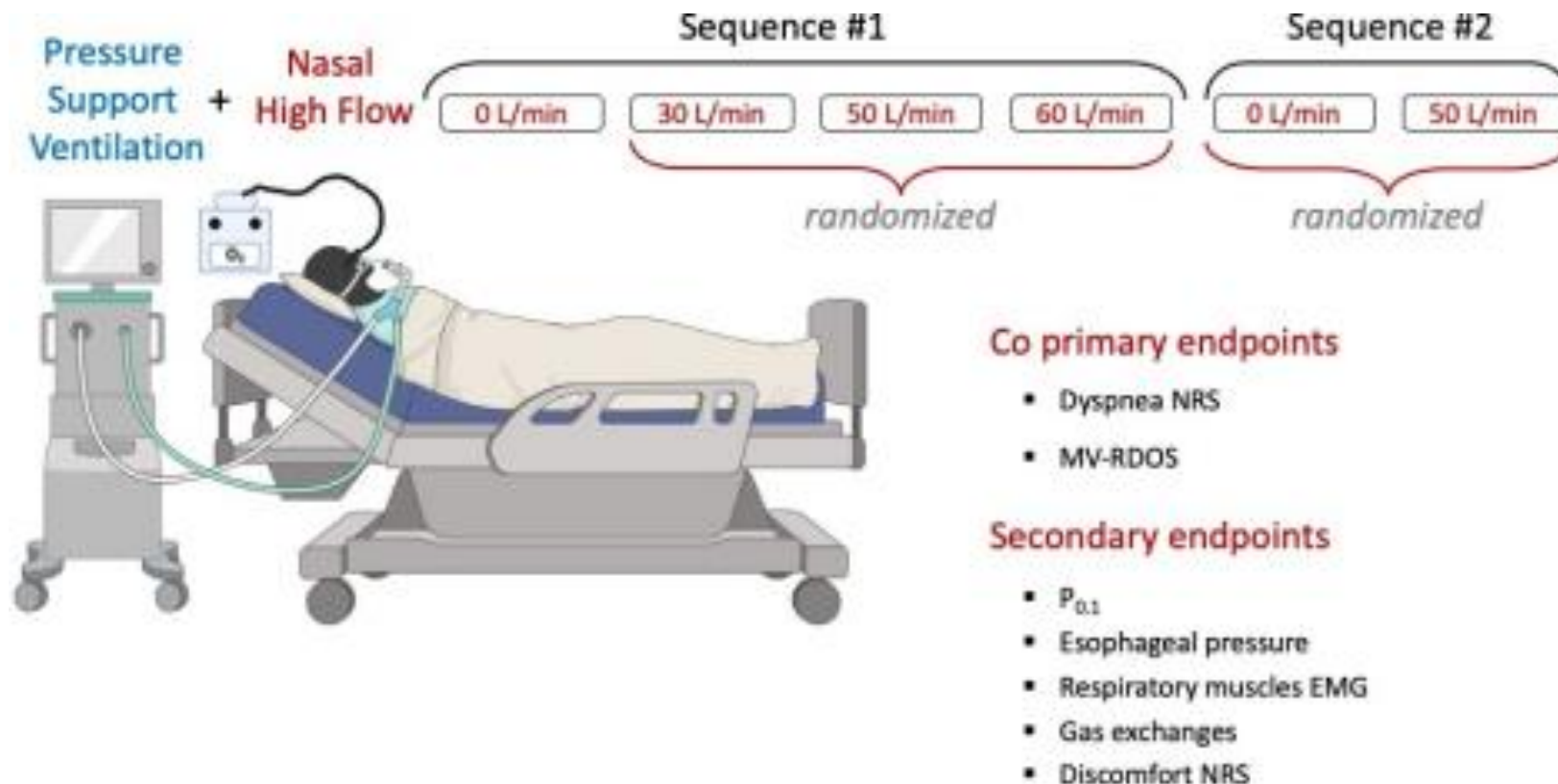
A Systematic Review and Meta-Analysis

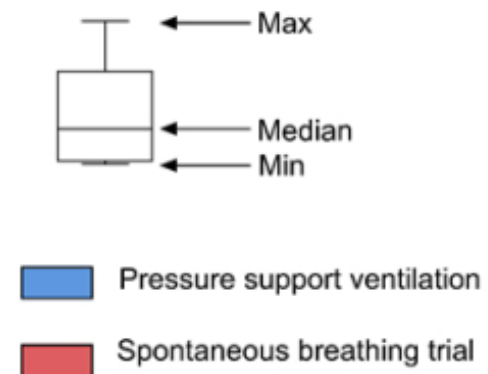
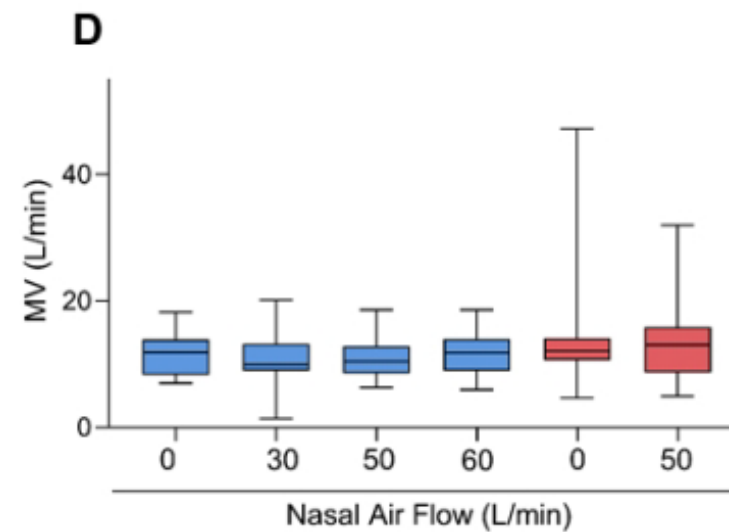
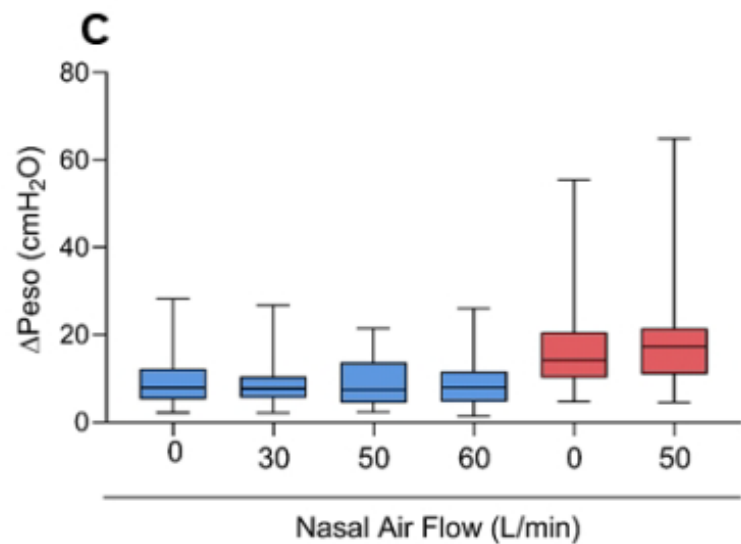
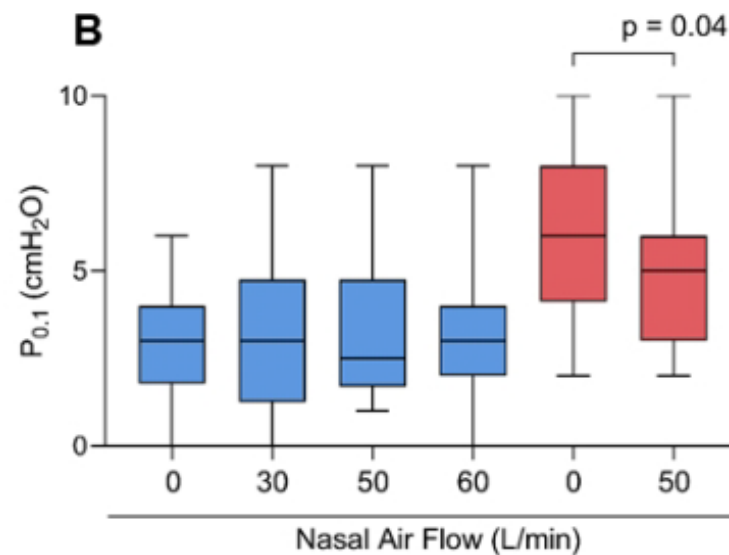
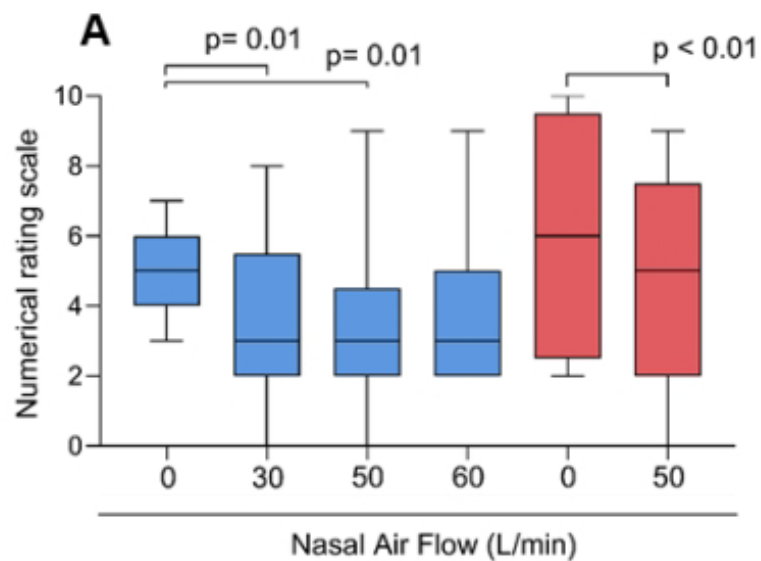


A The forest plot for bacteria contaminations of humidifier bottles

Nasal High Flow to Modulate Dyspnea in Orally Intubated Patients

Valentine Le Stang^{1 2}, Mélodie Graverot^{1 2}, Antoine Kimmoun^{3 4}, Marie-Cécile Niérat¹,
Maxens Decavèle^{1 2}, Thomas Similowski^{1 5}, Alexandre Demoule^{1 2}, Martin Dres^{1 2}





Conclusions

- Oxygen is one of the most ubiquitously used medical interventions in medicine
- Although oxygen supplementation is beneficial to support life in the clinic, excessive oxygen therapy has also been linked to multiple organ injuries (lung, heart, brain, etc)
- To date, no consensus has been reached regarding the clinical impact of hyperoxia and hyperoxemia, specifically in ICU patients. It is plausible that oxygen therapy has a differing effect according to patients' characteristics
- Don't forget palliation of dyspnea and comfort!!