SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

MODENA MICU INTENSIVE CARE UNIT 2

UNIVERSITAS STUDIORUM MUTINENSIS ET REGIENSIS
1175
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Ipossia o iperossia
Quale è peggiore ?

slides and discussion
girardis.massimo@unimo.it

Disclosures

None conflict of interest related to this lecture/issue

I trust in PHYSIOLOGY & EBM,
but the latter is more 'voluble', particularly in these days

OTHER POTENTIAL CONFLICT of INTEREST
Unrestricted grants, lectures, advisory boards, etc.

Astra Zeneca
Baxter
Biotest
Eli-Lilly
CSL-Behring
Kedrion
Masimo
MSD
Novartis
NovoNordisk
Orion Pharma
Thermofisher

O_2 therapy in critically ill patients: **STATE of ART**

- → Oxygen is a 'drug' essential for human life; tissue hypoxia *(uncertain the level)* cause organ dysfunction
- → Oxygen is the most widely prescribed therapy in critically ill patients to prevent and/or correct hypoxemia
- → The use of supplemental oxygen therapy is recommended in numerous clinical practice guidelines but specific limits for the PaO_2 (or SaO_2) maximum levels are not provided
- → ICU patients spend substantial periods in hyperoxemia that is rarely corrected *(de Graff et al, Intensive Care Med 2011; Suzuki et al, J Crit Care 2013)*
- → Mild hyperoxemia is considered safe and useful since it may provide a safety buffer.
- → Many healthcare professionals believed that oxygen had little or no harm in critically ill patients

O_2 therapy in critically ill patients: **Current Guidelines**

thebmj
Cite this as: *BMJ* 2018;363:k4169
doi: 10.1136/bmj.k4169
RAPID RECOMMENDATIONS

Oxygen therapy for acutely ill medical patients: a clinical practice guideline

Reed A C Siemieniuk,[1] Derek K Chu,[2] Lisa Ha-Yeon Kim,[2] Maria-Rosa Güell-Rous,[3] Waleed Alhazzani,[1 2] Paola M Soccal,[4 5] Paul J Karanicolas,[6] Pauline D Farhoumand,[7] Jillian L K Siemieniuk,[8] Imran Satia,[2] Elvis M Irusen,[9] Marwan M. Refaat,[10] J. Stephen Mikita,[11] Maureen Smith,[12] Dian N Cohen,[13] Per O Vandvik,[14] Thomas Agoritsas,[17 15] Lyubov Lytvyn,[1] Gordon H Guyatt[1 2]

Table 1 | Current guidance on supplemental oxygen therapy

		Recommendations	
Organisation	Condition	Lower limit	Upper limit
AARC, 2002[8]	All patients in acute care facility	Provide oxygen if SaO_2 <90%	No upper limit
AHA/ASA, 2018[9]	Ischaemic stroke	Provide oxygen to maintain SaO_2 >94%	No upper limit
EAN, 2018[10]	Ischaemic stroke	Provide oxygen to maintain normoxia in patients with SaO_2 <95%. Routine use of O_2 is not recommended	None mentioned
AHA, 2013[11]	Myocardial infarction with ST elevation	Provide oxygen in patients with SaO_2 <90%, heart failure, or dyspnoea	No upper limit
ESC, 2017[12]	Myocardial infarction with ST elevation	Provide oxygen in patients with hypoxaemia (SaO_2 <90% or PaO_2 <60 mm Hg). Routine oxygen not recommended if SaO_2 ≥90%	No upper limit
ESC, 2015[13]	Myocardial infarction without ST elevation	Provide oxygen blood oxygen saturation <90% or respiratory distress.	No upper limit
BTS, 2017[14]	Acute medical conditions	Provide oxygen if SaO_2 <94% for most acutely ill patients; <88% for patients with hypercapnia	98% for most patients, 92% for patients with hypercapnia
TSANZ[15]	Acute medical conditions	Provide oxygen if SpO2 <92%	96% for most patients

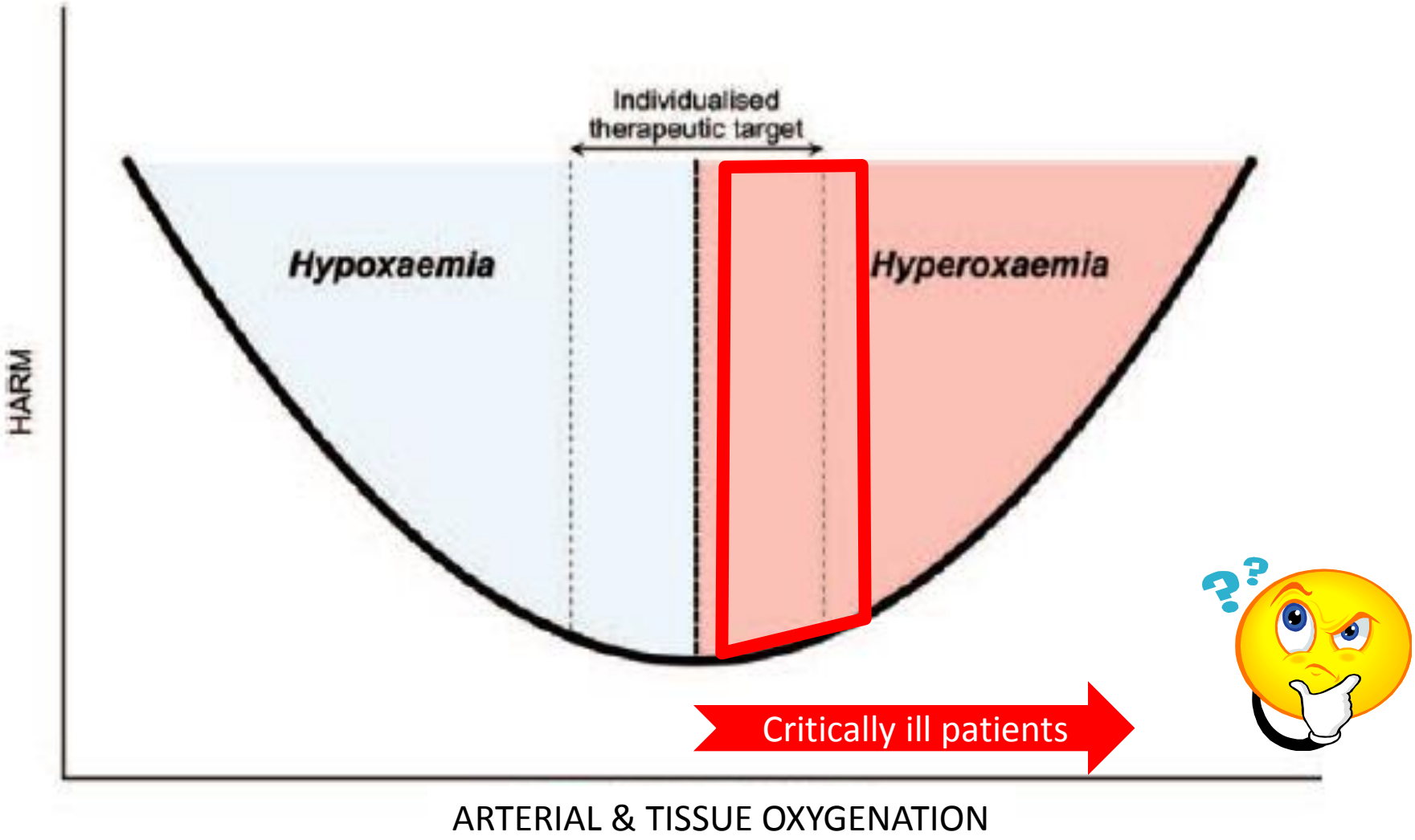
AARC=American Association for Respiratory Care; AHA=American Heart Association; ASA=American Stroke Association; EAN=European Academy of Neurology; ESC=European Society of Cardiology; BTS=British Thoracic Society; TSANZ=Thoracic Society of Australia and New Zealand.
SaO_2=oxygen saturation; PaO_2=partial pressure of oxygen; SpO_2=peripheral capillary oxygen saturation

O_2 therapy in critically ill patients
Pathophysiology

Oxygen Therapy in Critical Illness: Precise Control of Arterial Oxygenation and Permissive Hypoxemia*

(*Crit Care Med* 2013; 41:423–432)

Daniel Stuart Martin, BSc, MBChB, PhD, FRCA, FFICM[1,2];
Michael Patrick William Grocott, MBBS, MD, FRCA, FRCP, FFICM[1,3,4]



PaO2 and mortality

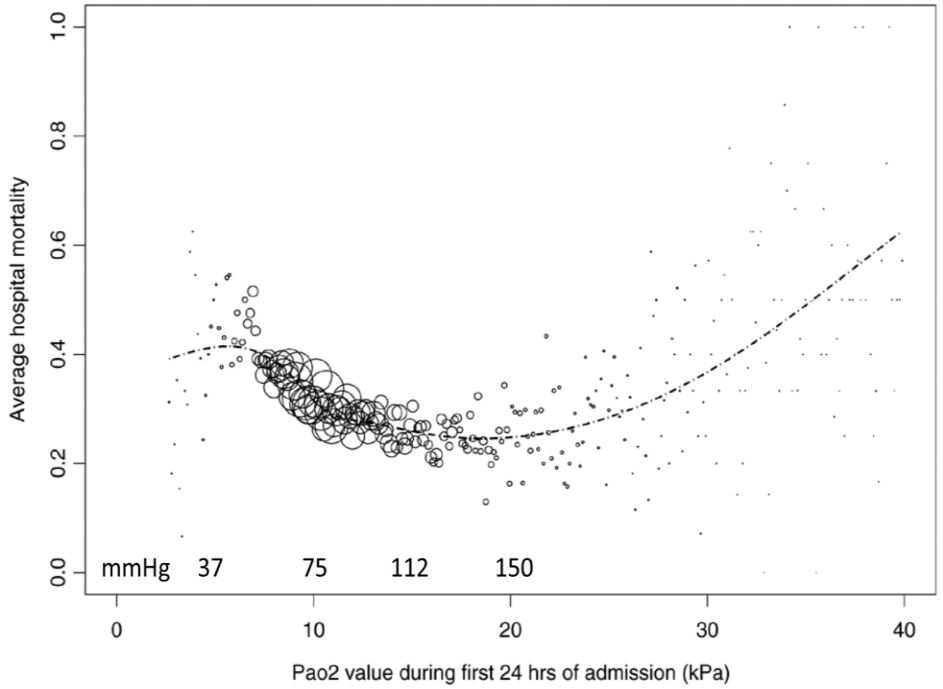
Research
Open Access

Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients

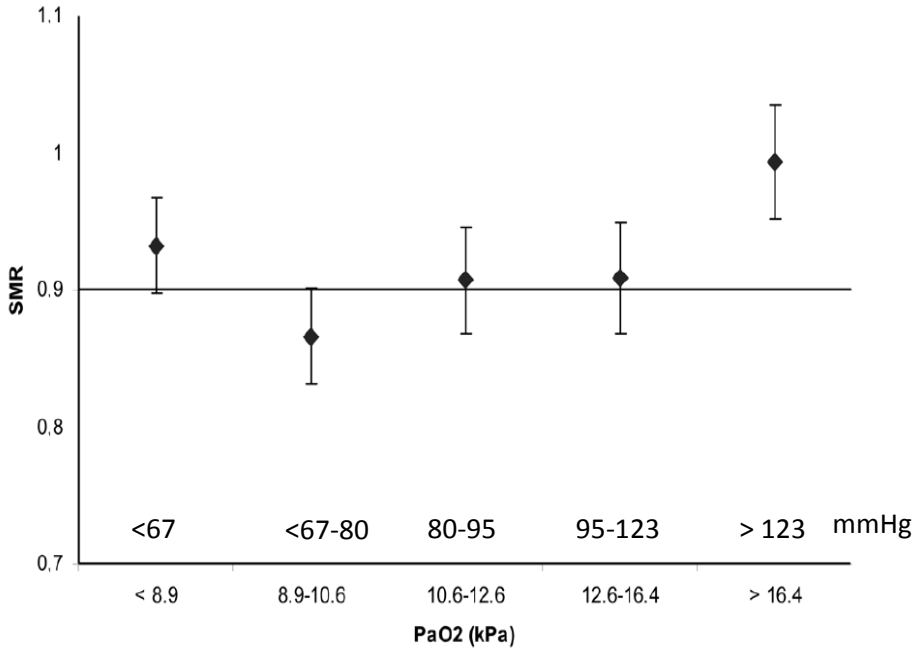
Evert de Jonge[1], Linda Peelen[2,3], Peter J Keijzers[4], Hans Joore[4], Dylan de Lange[4], Peter HJ van der Voort[5], Robert J Bosman[5], Ruud AL de Waal[6], Ronald Wesselink[7] and Nicolette F de Keizer[2]

@ Retrospective study
@ PaO2 and FiO2 first 24 h after admission
@ 36,307 consecutive patients mechanically ventilated , 50 Dutch ICUs

Interestingly, apart from FiO_2 values, there was also a U-shaped association between achieved arterial oxygen tension (PaO_2) during the first 24 h after ICU admission and mortality with higher mortality in patients with either a very low or high PaO_2. That mortality is higher in patients with very low PaO_2 is not unexpected and possibly related to ischaemia or to selection of the sickest patients. However, mortality was also higher in patients with highest PaO_2 values, suggesting the possibility of systemic oxygen toxicity.



In-hospital mortality by partial oxygen pressure (PaO_2) (kPa). Values were taken from blood gas analysis with lowest PaO_2/fraction of oxygen in inspired air (FiO_2) ratio in the first 24 h after intensive care unit (ICU) admission. The sizes of the circles represent the number of patients with the same PaO_2 value. The curve represents the predicted mortality using the logistic regression equation in which the PaO_2 value was incorporated using a spline function.

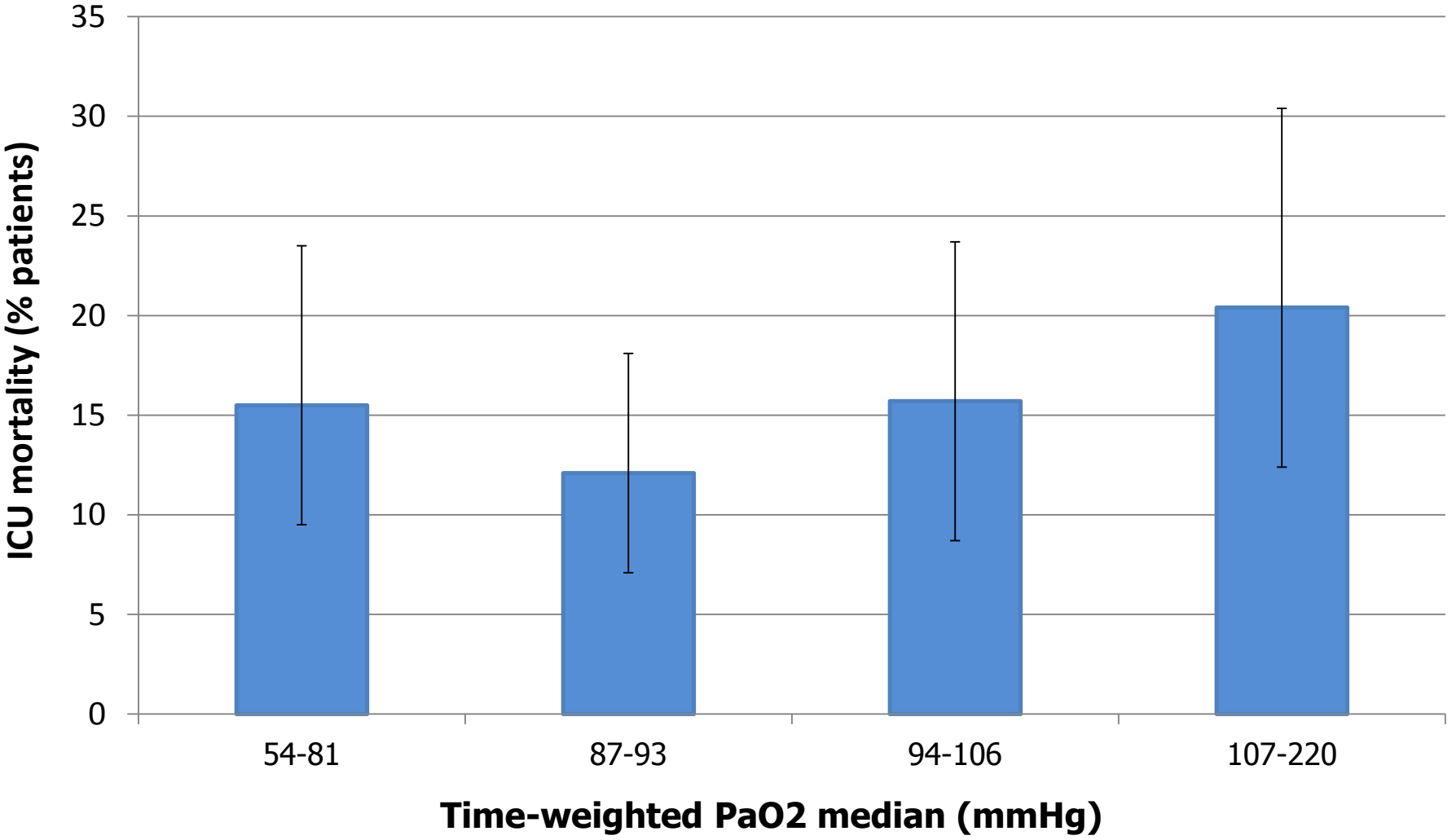


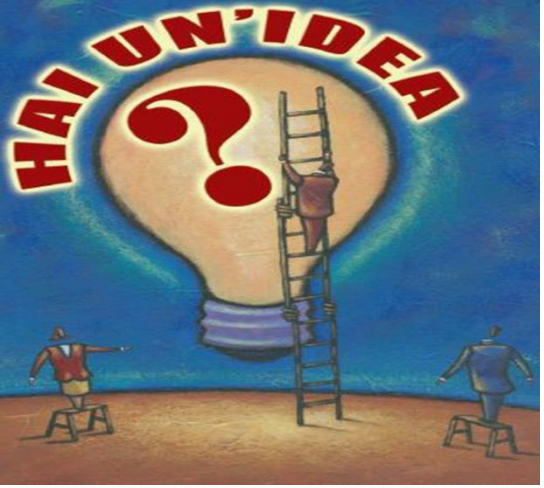
(PaO_2) (kPa). PaO_2 values were taken from blood gas analysis with lowest PaO_2/fraction of oxygen in inspired air (FiO_2) ratio in the first 24 h after intensive care unit (ICU) admission. PaO_2 values are categorised as quintiles. Error bars represent 95% confidence intervals.

Oxygen-ICU trial

PaO2 and mortality

Quartile distribution





QUALE TRIGGER ?
(in pazienti critici)

Intensive Care Med (2002) 28:369–375
DOI 10.1007/s00134-001-1205-2

CONFERENCE REPORT

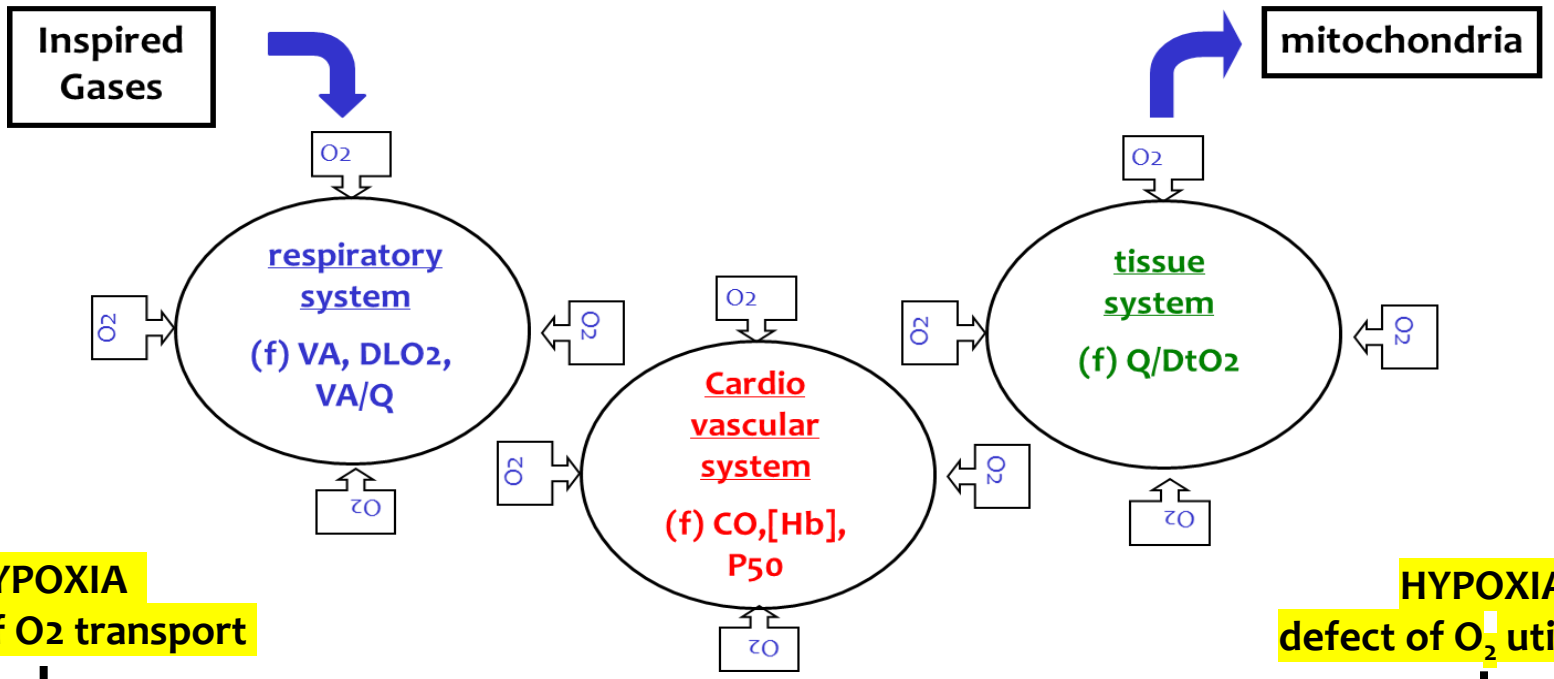
M. P. Fink
T. W. Evans

Mechanisms of organ dysfunction in critical illness: report from a Round Table Conference held in Brussels

IPOSSIA TISSUTALE è il principale fattore che determina **DISFUNZIONE D'ORGANO** nel paziente critico

IPOSSIA TISSUTALE può essere causata da un inefficienza di ciascuno dei sistemi coinvolti nel trasporto/utilizzo di O_2. Quindi ogni sistema coinvolto nel trasporto di O_2 (i.e. respiratorio, cardiovascolare, tissutale, cellulare) deve essere attentamente monitorato. **(CASCATA RESPIRATORIA)**

from HYPOXIA to ORGAN DYSFUNCTION



HYPOXIA
defect of O2 transport

HYPOXIA
defect of O_2 utilization

HYPOXIA

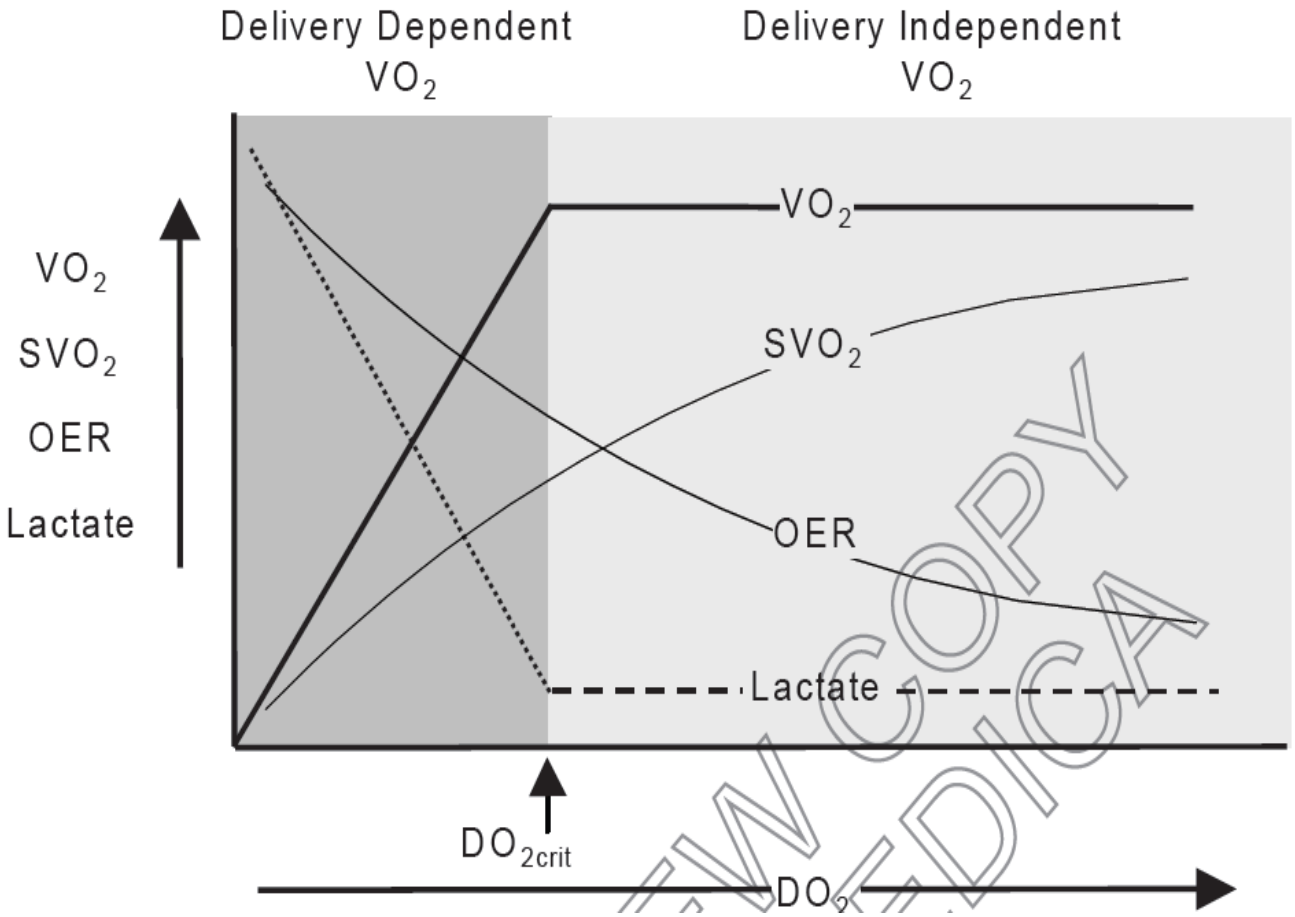
↓

Derangement in cellular energy metabolism

↓

CELLULAR/ORGAN DYSFUNCTION

ABC of O2 TRANSPORT
Oxygen delivery & Uptake



Oxygenation:

Volume & Time

(flow)

or

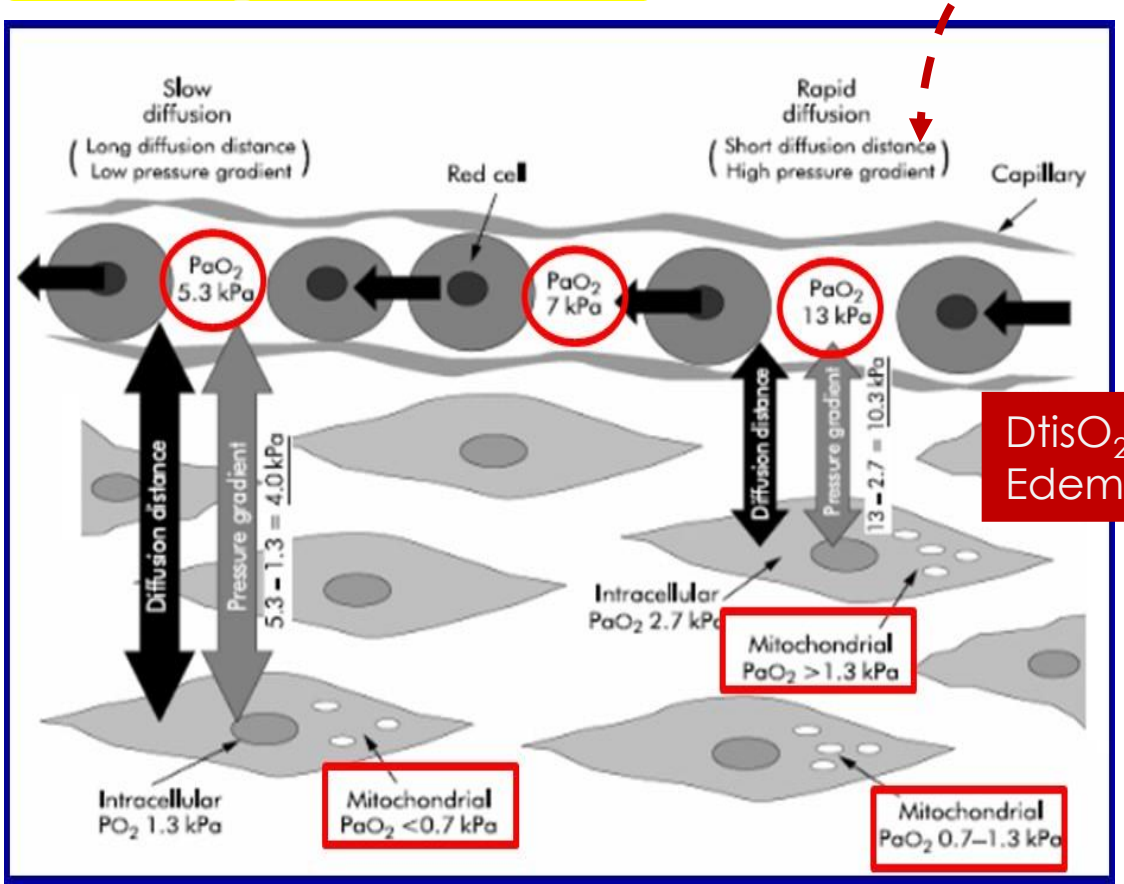
pressure gradients ?

WHICH HYPOXIA IN WELL RESUSCITATED SEPTIC PATIENTS ?

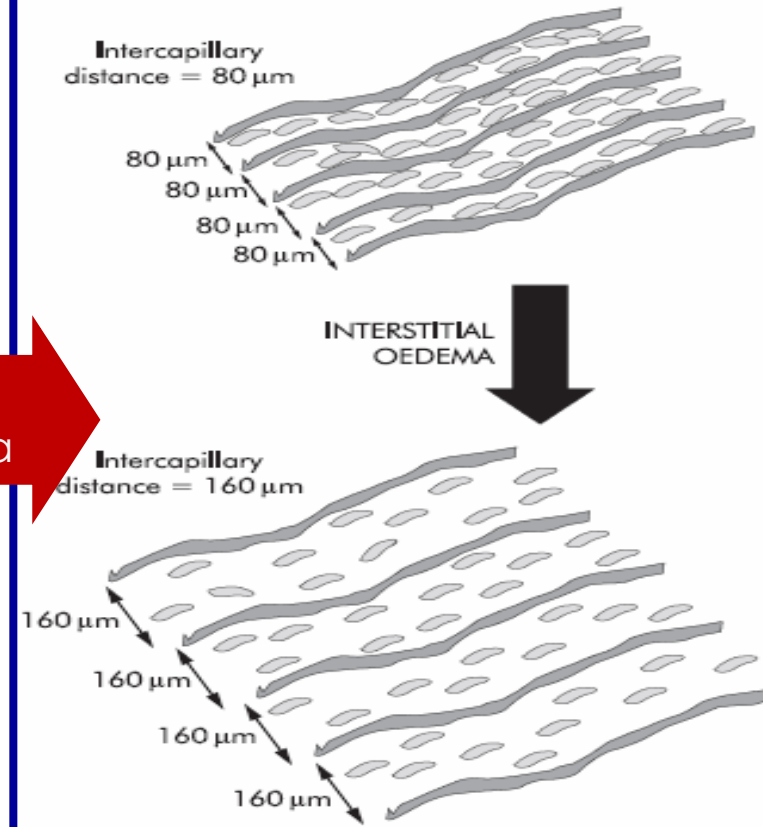
Edema

edema is not benign: the accumulation of parenchymal and interstitial fluid could impair organ function by increasing the distance required for the diffusion of oxygen and by compromising microvascular perfusion because of increased interstitial pressure. It is no coincidence that a well-

	physiological mechanisms	Clinical measurements
Circulatory System	Q, [Hb], curva diss. Hb	Q, [Hb], DO_2
Tissue		SvO_2; O_2ext; Lab
Microcirculation	Qtis; DtisO2	
Cell	Enzymes activity	



DtisO2
Edema



MITOCHONDRIAL METABOLIC SHUTDOWN

REVIEW

Critical illness and flat batteries

Mervyn Singer

Singer *Critical Care* 2017, **21**(Suppl 3):309
DOI 10.1186/s13054-017-1913-9

@ Tissue hypoxia, especially before adequate resuscitation.
@ Prolonged inflammation with excessive production of mediators (ROS,RNS)
@ Decreased turnover of healthy and functional mitochondria (biogenesis)
@ Uncoupled respiration with production of heat and ROS

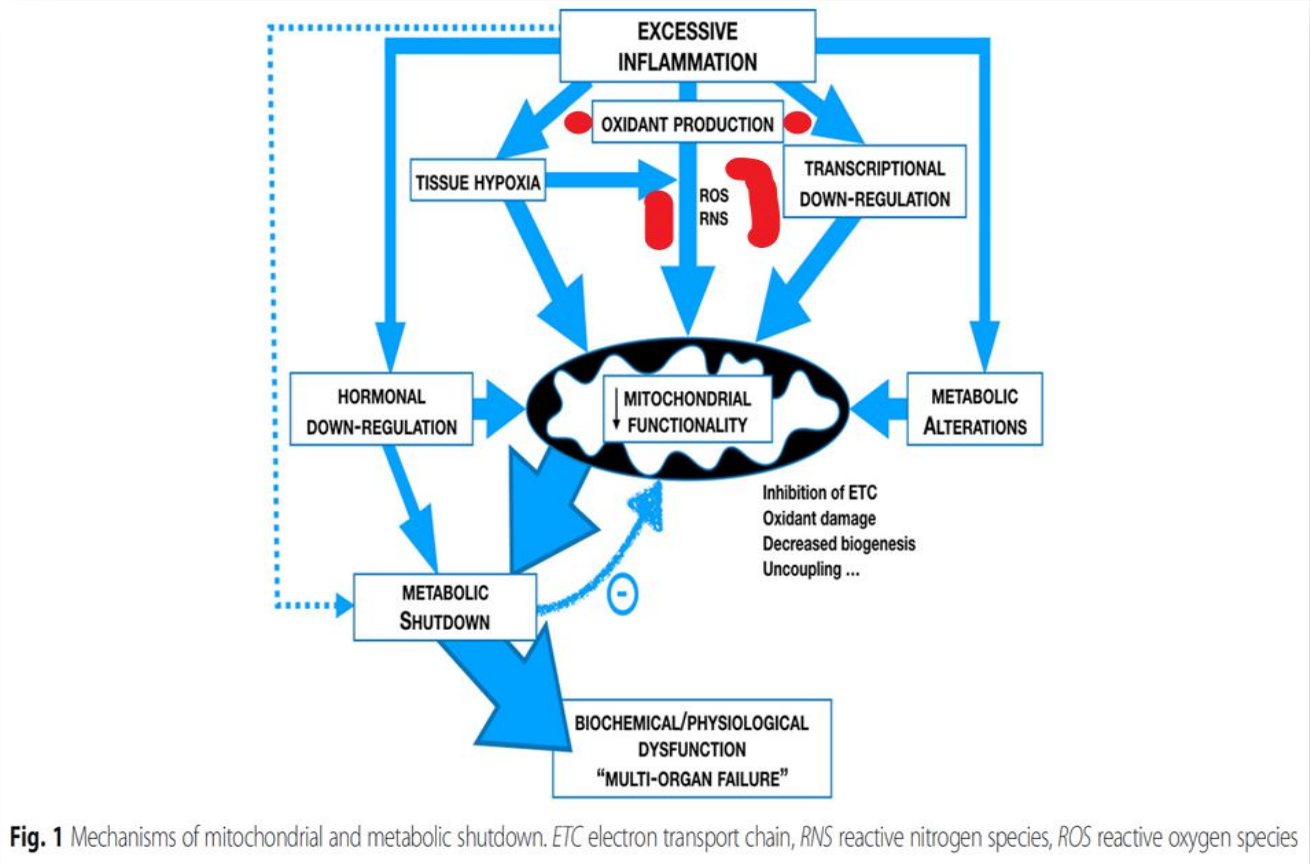


Fig. 1 Mechanisms of mitochondrial and metabolic shutdown. *ETC* electron transport chain, *RNS* reactive nitrogen species, *ROS* reactive oxygen species

MITOCHONDRIAL METABOLIC SHUTDOWN

@ Reactive Oxygen Species (ROS): includes molecules with an unpaired electron (free radicals) as super-oxide anion and hydrogen peroxide (strong oxidizing agents)

@ Reactive Nitrogen Species (RNS) : Nitric oxide reaction with super-oxide is rapid with Per-oxynitrite production

Table 1
Selected examples of reactive oxygen and nitrogen species

Reactive oxygen species	
$O_2^{\cdot-}$	Superoxide anion
H_2O_2	Hydrogen peroxide
$^{\cdot}OH$	Hydroxyl radical
HOCl	Hypochlorous acid
LOOH	Lipid peroxides
$^{\cdot}RO_2$	Peroxyl
$^{\cdot}HO_2$	Hydroperoxyl
$^{\cdot}RO$	Alkoxyl
ROOH	Hydroperoxide
Reactive nitrogen species	
NO_2^-	Nitrite
NO_3^-	Nitrate
$NO_2^{\cdot}$	Nitrogen dioxide
$ONOO^-$	Peroxynitrite
$ONOOCO_2^-$	Nitrosoperoxocarboxylate
3-NO_2-tyr	3-Nitrotyrosyl residues
RSNO	S-Nitrosothiols
Nitrosyl-haeme	Nitrosyl-haeme
LOONO	Lipid peroxynitrites
HNO_2	Nitrous oxide
NO_2^+	Nitronium cation
NO^+	Nitrosyl cation
ROONO	Alkyl peroxynitrite

@ ROS have essential roles in cell signalling and their activity is normally tightly regulated by a collaborative interacting network of antioxidants.

@ Several endogenous antioxidant systems exist within mitochondria to protect against damage by ROS (combination of enzyme and non-enzyme pathways): manganese superoxide dismutase (MnSOD), the glutathione system (GSH-GPx) are the most important

TABLE 1: Summary of antioxidants and their effects.

Antioxidant	Mechanism of action
GPx	H_2O_2 to H_2O
SOD	O_2^- to O_2
CAT	H_2O_2 to H_2O and O_2
GSH	Antioxidant scavenger, DNA repair, cofactor for enzymes
AA	Acts against oxidation of lipids, proteins, and DNA
α-Tocopherol	Scavenger for lipid peroxidation products

GPx: glutathione peroxidase; SOD: superoxide dismutase; CAT: catalase; GSH: glutathione; AA: ascorbic acid.

MITOCHONDRIAL METABOLIC SHUTDOWN

Oxidative stress and mitochondrial dysfunction in sepsis

H. F. Galley*

OXIDATIVE STRESS-INDUCED MITOCHONDRIAL DAMAGE

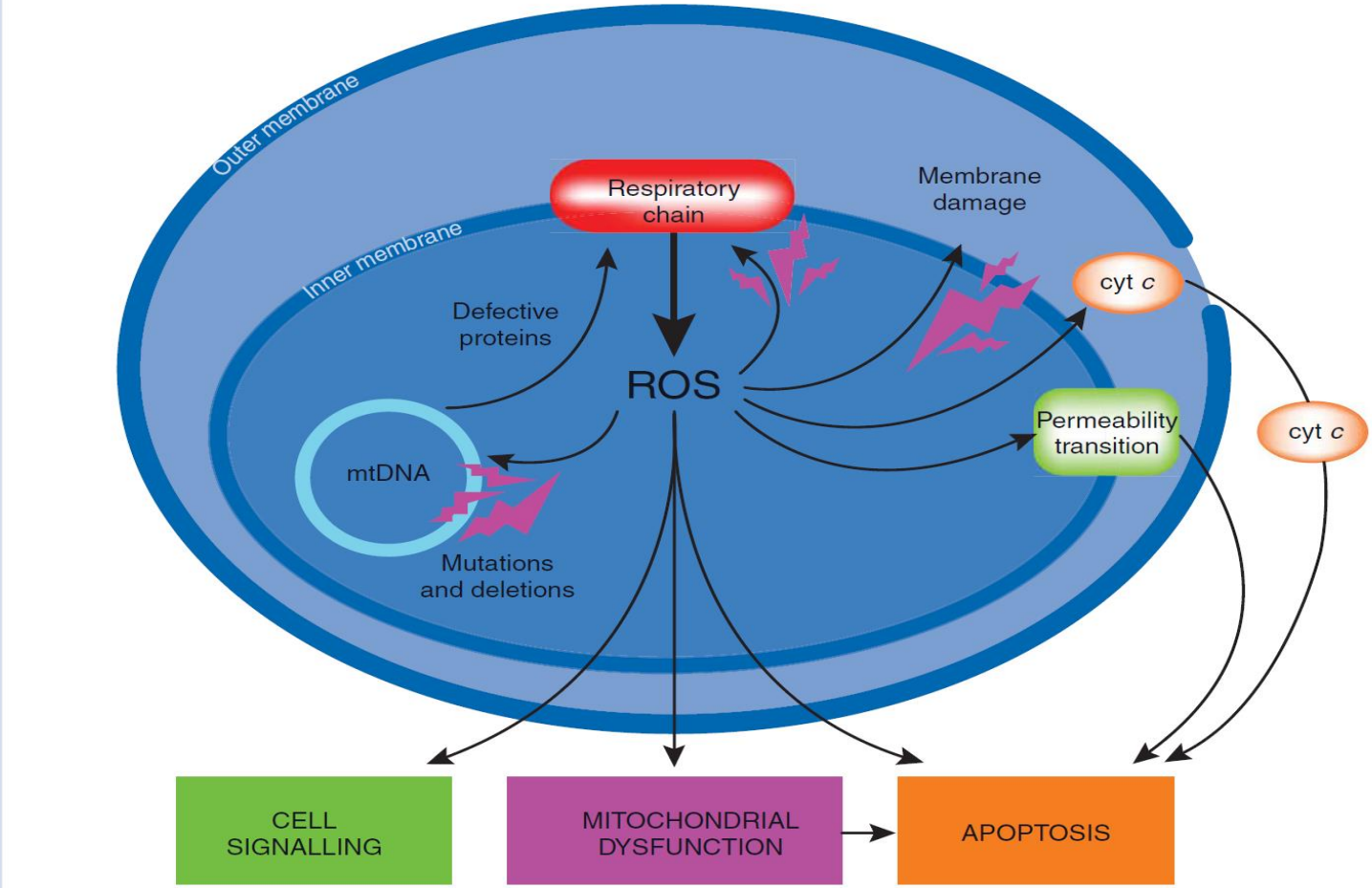


Fig 2 Overview of mitochondrial ROS production. ROS production within mitochondria can lead to oxidative damage to mitochondrial proteins, membranes, and mtDNA. Mitochondrial oxidative damage leads to the release of cytochrome *c* (cyt *c*) into the cytosol resulting in apoptosis. Increased permeability makes the inner membrane permeable to small molecules. Mitochondrial ROS are also important in cell signalling pathways which modulate several cellular functions. Figure reproduced with permission, from Murphy MP (2009).[2]

MITOCHONDRIAL METABOLIC SHUTDOWN

REVIEW

Critical illness and flat batteries

Mervyn Singer

Singer *Critical Care* 2017, **21**(Suppl 3):309
DOI 10.1186/s13054-017-1913-9

The beginning of the end ?

Mitochondrial shutdown is the clue of irreversible cells apoptosis and death

An adaptive response to prolonged stress to survive ?

Key to survival is to downregulate cellular metabolic rate to new hypometabolic steady states (balances the ATP demand and ATP supply pathway)

MAXIMAL EFFORT FOR EARLY RESTORING

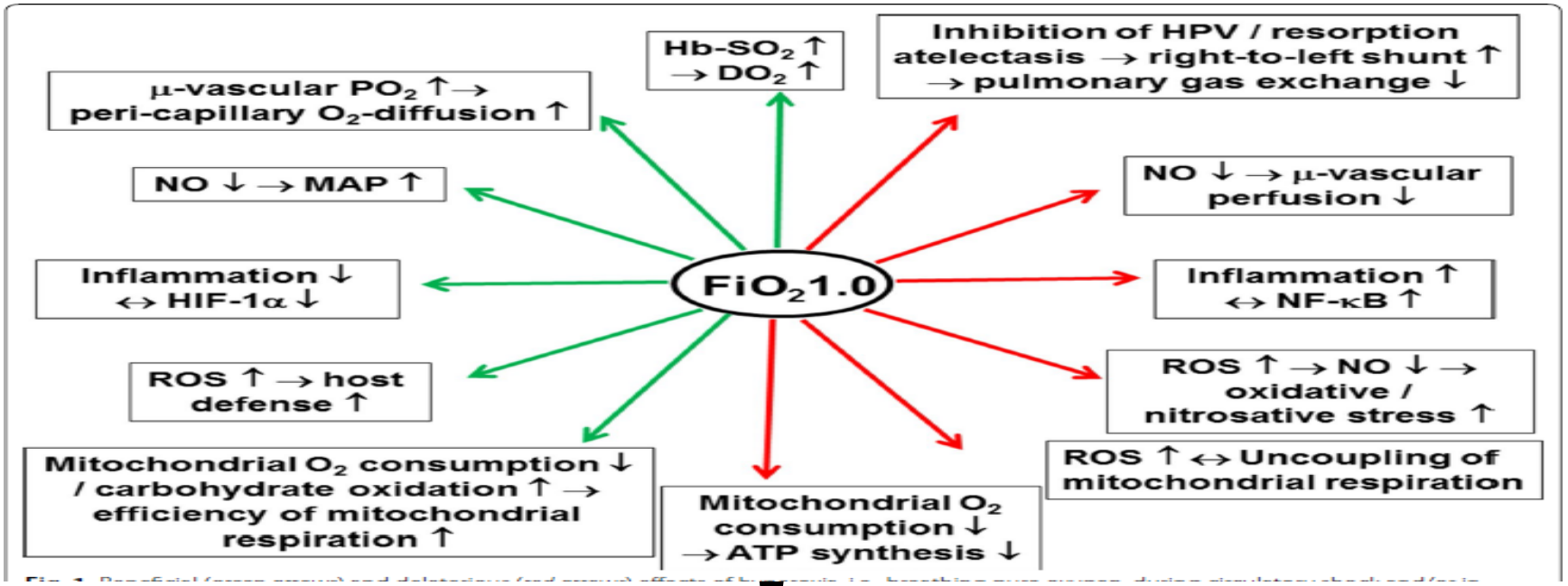
PERMISSIVE HYPOMETABOLIC STATE

Hyperoxemia: Possibile Effects in Critically ill Patients

REVIEW Open Access

Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update

Hafner et al. Ann. Intensive Care (2015) 5:42



BENEFICIAL

- Prevention of tissue hypoxia
- Vasoconstriction
- Reduction of inflammation

DETRIMENTAL

- *Pulmonary effects (hyperoxia)*
- Microcirculation impairment
- Immune-paralysis

Depend on

- duration and dose of O2 exposure (lung and blood)
- concomitant conditions (ARDS, endothelial dysfunction, bacteremia)

O_2 therapy in critically ill patients: **Which evidence ?**

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Lancet 2018; 391: 1693–705

Derek K Chu†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani*

@ 25 RCTs with 16037 adult critically ill patients (median 137 patients/RCT); 18 low risk of bias

@ 8 RCTs Cerebral Stroke; 6 RCTs Myocardial Infarction ; 3 RCTs Emergency Surgery, 2 RCTs Cardiac arrest; 2 RCTs mixed ICU patients; 2 Sepsis; 1 TBI; 1 limb ischemia

@ Not included hypoxic and chronic respiratory

@ Liberal : median FiO2 0,52 (0,28-1,00); Conservative: median FiO2 0,21 (0,21-0,50)

@ Duration of O2 therapy: median 8 H (1-144)

@ 8 RCTs with mechanical ventilation

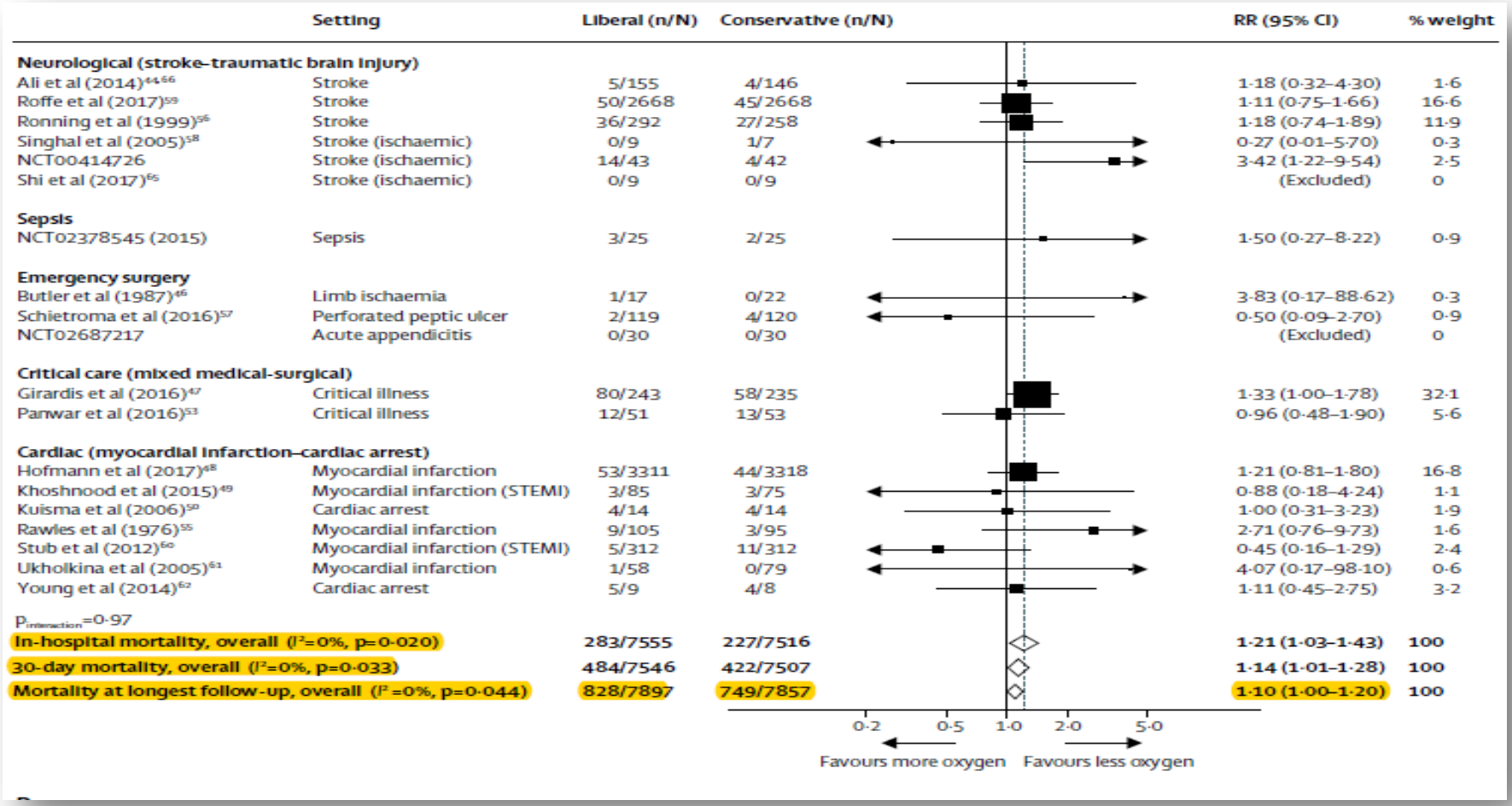
@ Follow up median 3 months (14 days-12 months)

O_2 therapy in critically ill patients: **Which evidence ?**

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

Lancet 2018; 391: 1693–705

Derek K Chu*†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani



	Setting	Liberal (n/N)	Conservative (n/N)	RR (95% CI)	% weight
Neurological (stroke–traumatic brain injury)					
Ali et al (2014)[44,66]	Stroke	5/155	4/146	1·18 (0·32–4·30)	1·6
Roffe et al (2017)[59]	Stroke	50/2668	45/2668	1·11 (0·75–1·66)	16·6
Ronning et al (1999)[56]	Stroke	36/292	27/258	1·18 (0·74–1·89)	11·9
Singhal et al (2005)[58]	Stroke (ischaemic)	0/9	1/7	0·27 (0·01–5·70)	0·3
NCT00414726	Stroke (ischaemic)	14/43	4/42	3·42 (1·22–9·54)	2·5
Shi et al (2017)[65]	Stroke (ischaemic)	0/9	0/9	(Excluded)	0
Sepsis					
NCT02378545 (2015)	Sepsis	3/25	2/25	1·50 (0·27–8·22)	0·9
Emergency surgery					
Butler et al (1987)[46]	Limb ischaemia	1/17	0/22	3·83 (0·17–88·62)	0·3
Schietroma et al (2016)[57]	Perforated peptic ulcer	2/119	4/120	0·50 (0·09–2·70)	0·9
NCT02687217	Acute appendicitis	0/30	0/30	(Excluded)	0
Critical care (mixed medical-surgical)					
Girardis et al (2016)[47]	Critical illness	80/243	58/235	1·33 (1·00–1·78)	32·1
Panwar et al (2016)[53]	Critical illness	12/51	13/53	0·96 (0·48–1·90)	5·6
Cardiac (myocardial infarction–cardiac arrest)					
Hofmann et al (2017)[48]	Myocardial infarction	53/3311	44/3318	1·21 (0·81–1·80)	16·8
Khoshnood et al (2015)[49]	Myocardial infarction (STEMI)	3/85	3/75	0·88 (0·18–4·24)	1·1
Kuisma et al (2006)[50]	Cardiac arrest	4/14	4/14	1·00 (0·31–3·23)	1·9
Rawles et al (1976)[55]	Myocardial infarction	9/105	3/95	2·71 (0·76–9·73)	1·6
Stub et al (2012)[60]	Myocardial infarction (STEMI)	5/312	11/312	0·45 (0·16–1·29)	2·4
Ukholkina et al (2005)[61]	Myocardial infarction	1/58	0/79	4·07 (0·17–98·10)	0·6
Young et al (2014)[62]	Cardiac arrest	5/9	4/8	1·11 (0·45–2·75)	3·2
$p_{interaction}$=0·97					
In-hospital mortality, overall (I^2=0%, p=0·020)		283/7555	227/7516	**1·21 (1·03–1·43)**	100
30-day mortality, overall (I^2=0%, p=0·033)		484/7546	422/7507	**1·14 (1·01–1·28)**	100
Mortality at longest follow-up, overall (I^2=0%, p=0·044)		828/7897	749/7857	**1·10 (1·00–1·20)**	100

@ The magnitude of absolute risk increase in mortality with liberal oxygen therapy varied across the study populations.

@ Liberal oxygen supplementation increased the absolute risk in-hospital mortality by 1·1% (95% CI 0·2–2·2), 30-day mortality by 1·4% (0·1–2·7), and mortality at longest-follow-up by 1·2% (0–2·4). (Sepsis + 0,25% (0-0,5%))

O_2 therapy in critically ill patients: **Which evidence ?**

Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis Lancet 2018; 391: 1693–705

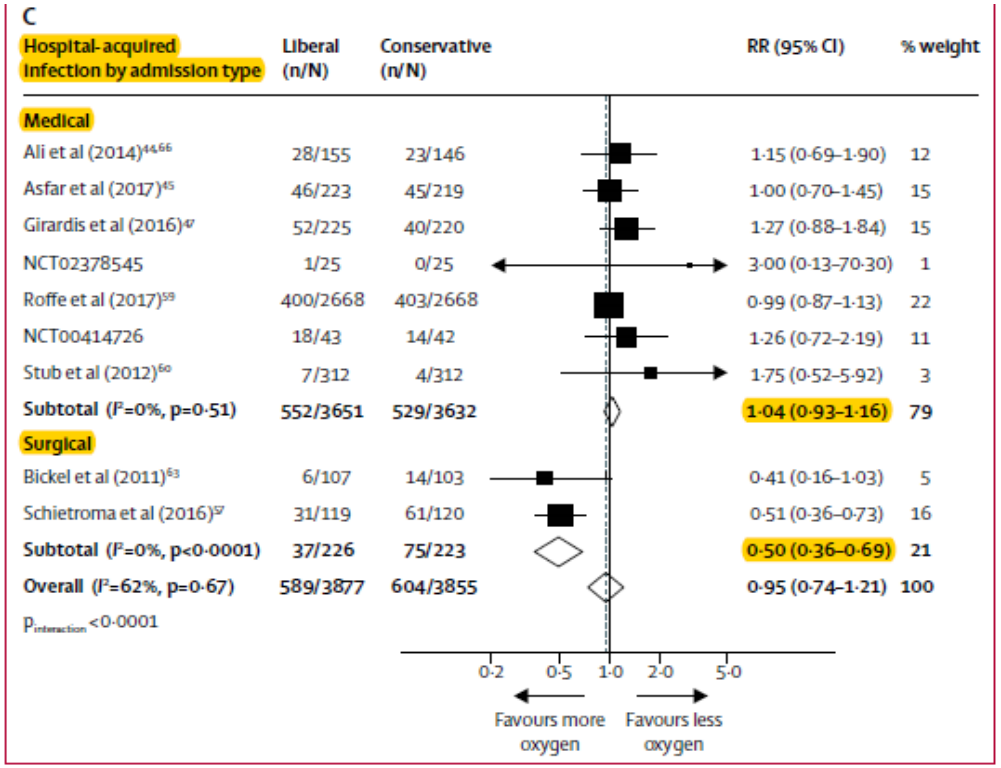
Derek K Chu*†, Lisa H-Y Kim*†, Paul J Young, Nima Zamiri, Saleh A Almenawer, Roman Jaeschke, Wojciech Szczeklik, Holger J Schünemann, John D Neary, Waleed Alhazzani

CONCLUSIONS

High-quality evidence that LIBERAL OXYGEN therapy:

@ Increased the relative risk of in-hospital mortality and mortality at 30 days and at longest follow-up

@ without any significant improvement in other patient-important outcomes, such as disability, risk of hospital-acquired pneumonia, risk of hospital-acquired infections, or length of hospital stay. These findings are distinct from the widespread view that liberal oxygen therapy for acute illnesses is harmless.



SURGICAL SITE INFECTION
SURGICAL PATIENTS

O_2 therapy septic shock: **Which evidence ?**

Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial

Lancet Respir Med 2017

Pierre Asfar, Frédérique Schortgen, Julie Boisramé-Helms, Julien Charpentier, Emmanuel Guérot, Bruno Megarbane, David Grimaldi, Fabien Grelon,

@ RCT in 22 ICUs, 442 patients with septic shock + mechanical ventilation

@ 4 groups treatment (stratified for ARDS)

a) OXYGEN: FiO2 at 1·0 (hyperoxia) or FiO2 target SpO2 of 88–95% (normoxia) during the first 24 h;

b) FLUID: 280 mL boluses of 3·0% (hypertonic) saline or 0·9% (isotonic) saline for fluid resuscitation during the first 72 h

@ MORTALITY at day-28: Normoxia 35% vs Hyperoxia 43% (p = 0,12); Isotonic 37% vs Hypertonic 42%

@ ADVERSE EVENT

a) Significant difference (p=0,02) in the overall incidence of serious adverse events

b) In the hyperoxia group the number of patients with intensive care unit-acquired weakness (24 [11%] vs 13 [6%]; p=0·06) and atelectasis (26 [12%] vs 13 [6%]; p=0·04) were doubled than the normoxia group.

c) no statistical difference for serious adverse events between the two saline groups (p=0·23)

Implications of all the available evidence

The findings of HYPER2S concerning ventilation with 100% oxygen are consistent with the most recent meta-analyses, showing that very high arterial oxygen partial pressures are associated with an increased risk of mortality.

The findings of HYPER2S concerning hypertonic saline are consistent with previous trials in patients with trauma resuscitation, showing that hypertonic fluid resuscitation does not improve outcome. Taken together, these findings do not support the use of hyperoxia or hypertonic saline during the early management of patients with septic shock.

O_2 therapy
MYOCARDIAL INFARCTION

Oxygen Therapy in Patients with Acute Myocardial Infarction: A Systemic Review and Meta-Analysis

Ahmed Abuzaid, MD,[a] Carly Fabrizio, DO,[a] Kevin Felpel, MD,[a] Haitham S. Al Ashry, MD,[b] Pragya Ranjan, MD,[a] Ayman Elbadawi, MD,[c] Ahmed H. Mohamed, MD,[c] Kirolos Barssoum, MD,[c] Islam Y. Elgendy, MD[d]

The American Journal of Medicine (2018)

@ 7 studies : 3842 patients with oxygen therapy and 3860 patients without oxygen therapy.

@ Oxygen compared with the no - oxygen did not decrease

i. all-cause mortality (RR, 0.99; 95% CI, 0.81-1.21; P = .43
ii. recurrent ischemia or myocardial infarction (RR, 1.19; 95% CI, 0.95-1.48; P = .75),
iii. heart failure (RR, 0.94; 95% CI, 0.61-1.45; P = .35)
iv. occurrence of arrhythmia (RR, 1.01; 95% CI, 0.85-1.2; P = .23).

Table 1 Showing Risk of Bias of Randomized Trials by Cochrane Risk Assessment Tool

	Rawles et al[20]	Wilson et al[21]	Ukholkina et al[22]	Ranchord et al[23]	Stub et al[24]	Khoshnood et al[25]	Hofmann et al[12]
Random sequence generation (selection bias)	?	?	?	+	+	+	+
Allocation concealment (selection bias)	+	+	?	+	+	+	+
Blinding of (performance bias and detection bias)	+	+	+	+	+	+	+
Baseline characteristics	?	+	-	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	-	-	-	-	+
Selective reporting (reporting bias)	+	?	-	-	-	+	+
Other sources of bias	+	+	-	-	?	-	+

+ = Low risk of bias; - = Risk of bias; ? = Unclear.

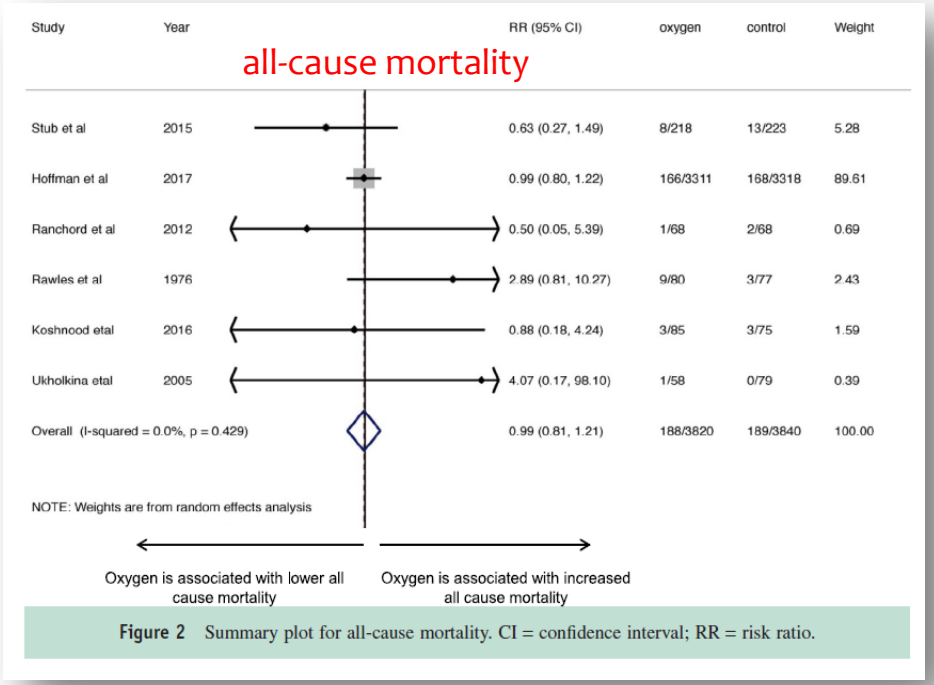


Figure 2 Summary plot for all-cause mortality. CI = confidence interval; RR = risk ratio.

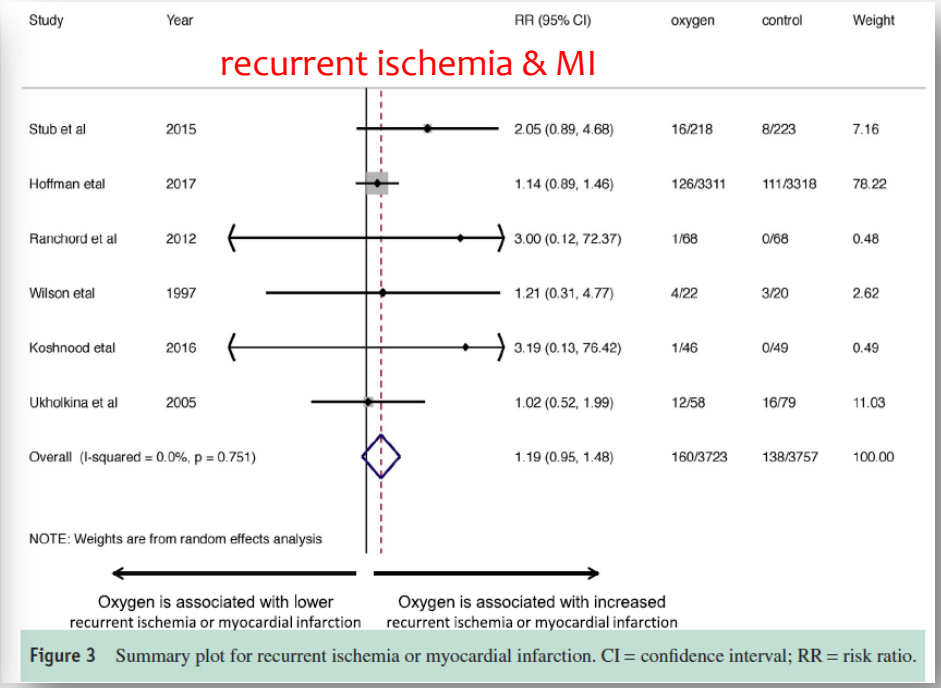


Figure 3 Summary plot for recurrent ischemia or myocardial infarction. CI = confidence interval; RR = risk ratio.

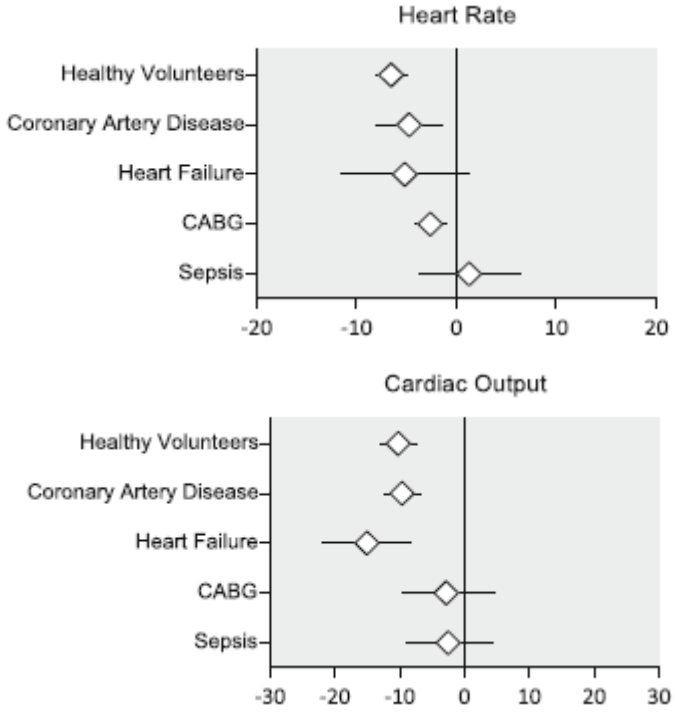
Hyperoxemia in Septic Patients

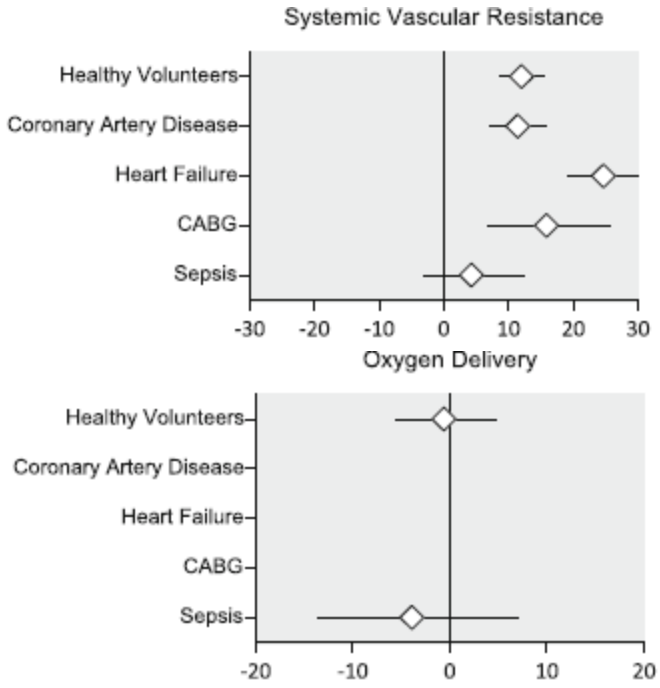
CARDIOVASCULAR EFFECTS

REVIEW Open Access

Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis

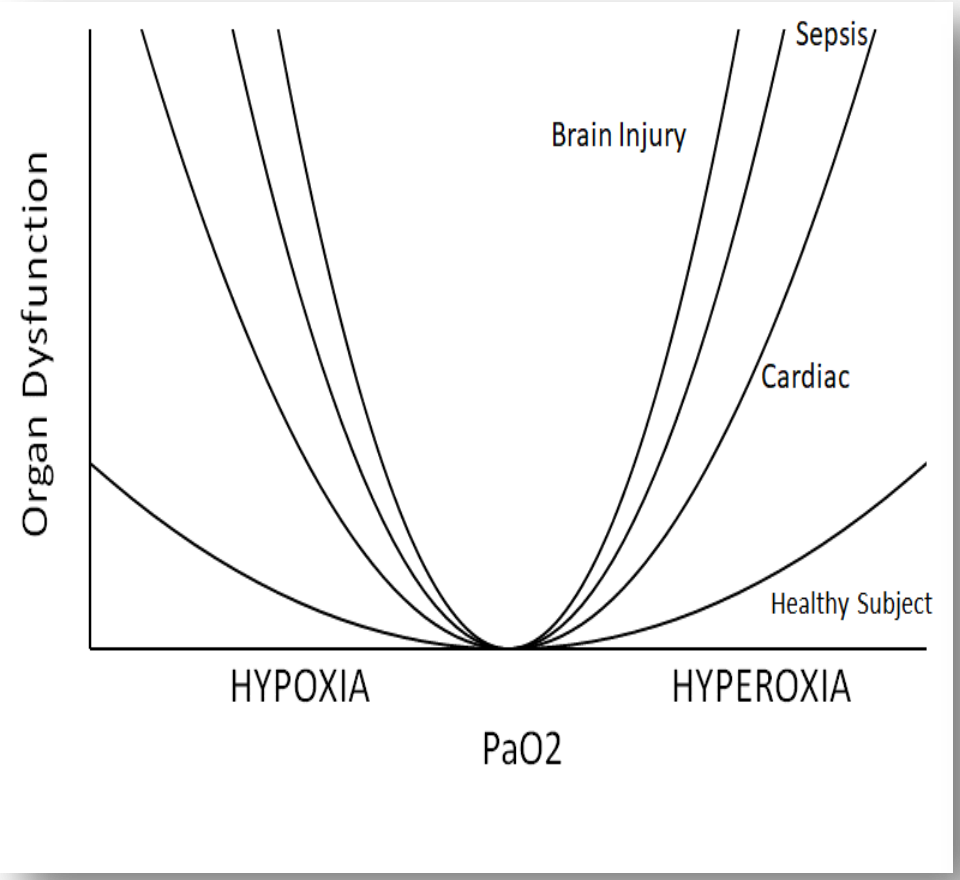
Smit et al. Critical Care (2018) 22:45



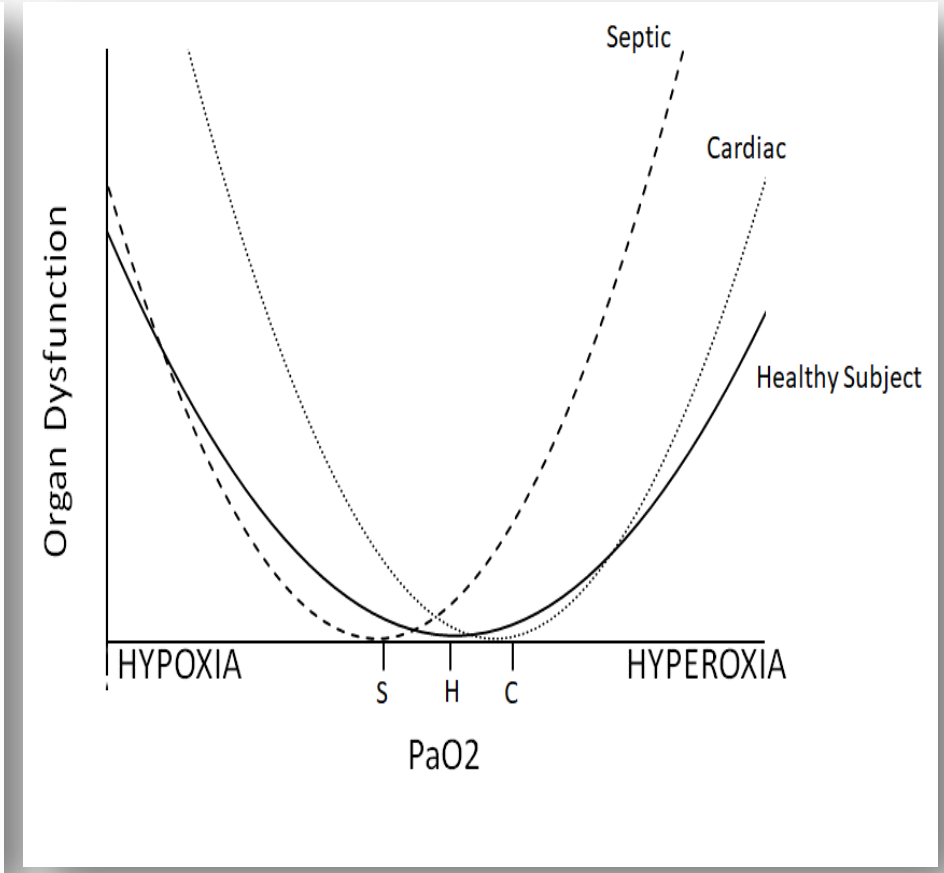


Conclusions: Hyperoxia may considerably decrease cardiac output and increase systemic vascular resistance, but effects differ between patient categories. Heart failure patients were the most sensitive while no hemodynamic effects were seen in septic patients. There is currently no evidence supporting the notion that oxygen supplementation increases oxygen delivery.

Appropriate & Personalized Oxygenation



Equal threshold for best benefit , variable susceptibility to HYPO-HYPER



Variable threshold for best benefit , variable susceptibility to HYPO-HYPER

Which is the appropriate level of Arterial PO2 in critically ill patients ?

ONGOING RCTs on OXYGEN THERAPY in CRITICALLY ILL PATIENTS

EDITORIAL

What's new in oxygen therapy?

Massimo Girardis[1], Waleed Alhazzani[2,3] and Bodil Steen Rasmussen[4,5*]

Intensive Care Med
https://doi.org/10.1007/s00134-019-05619-9

Table 1 How conservative is the oxygenation targets in the ICU trials?

RCTs	Status	Number of patients recruited	Inclusion criteria	Oxygen target(s) in the conservative group
Girardis [9]	Terminated after an unplanned interim analysis	434 out of 660	Expected length of stay in the ICU of 72 h	SpO_2 up to 98% PaO_2 70–100 mmHg
Asfar [10]	Terminated after a planned interim analysis	442 out of 800	Mechanical ventilation and septic shock	SpO_2 up to 97%
Panwar [11]	Completed	103	Mechanical ventilation	SpO_2 up to 92%
ICU-ROX (ACTRN12615000957594)	Completed but no results reported yet	1000	Mechanical ventilation	SpO_2 91–96%
LOCO2 (NCT02713451)	Active, not recruiting	205 out of 850	ARDS according to the Berlin definition	PaO_2 55–70 mmHg SpO_2 88–92%
HOT-ICU (NCT03174002)	Recruiting	1504 out of 2928	FiO_2 at least 0.50 or at least 10 L per minute in an open system	PaO_2 60 mmHg
ICU-Conservative O2 trial (EUDRACT 2018-002525-35)	Starts recruiting in May 2019	Expected 1000	Mechanical ventilation and expected length of stay in the ICU of 72 h	SpO_2 up to 98% PaO_2 70–100 mmHg

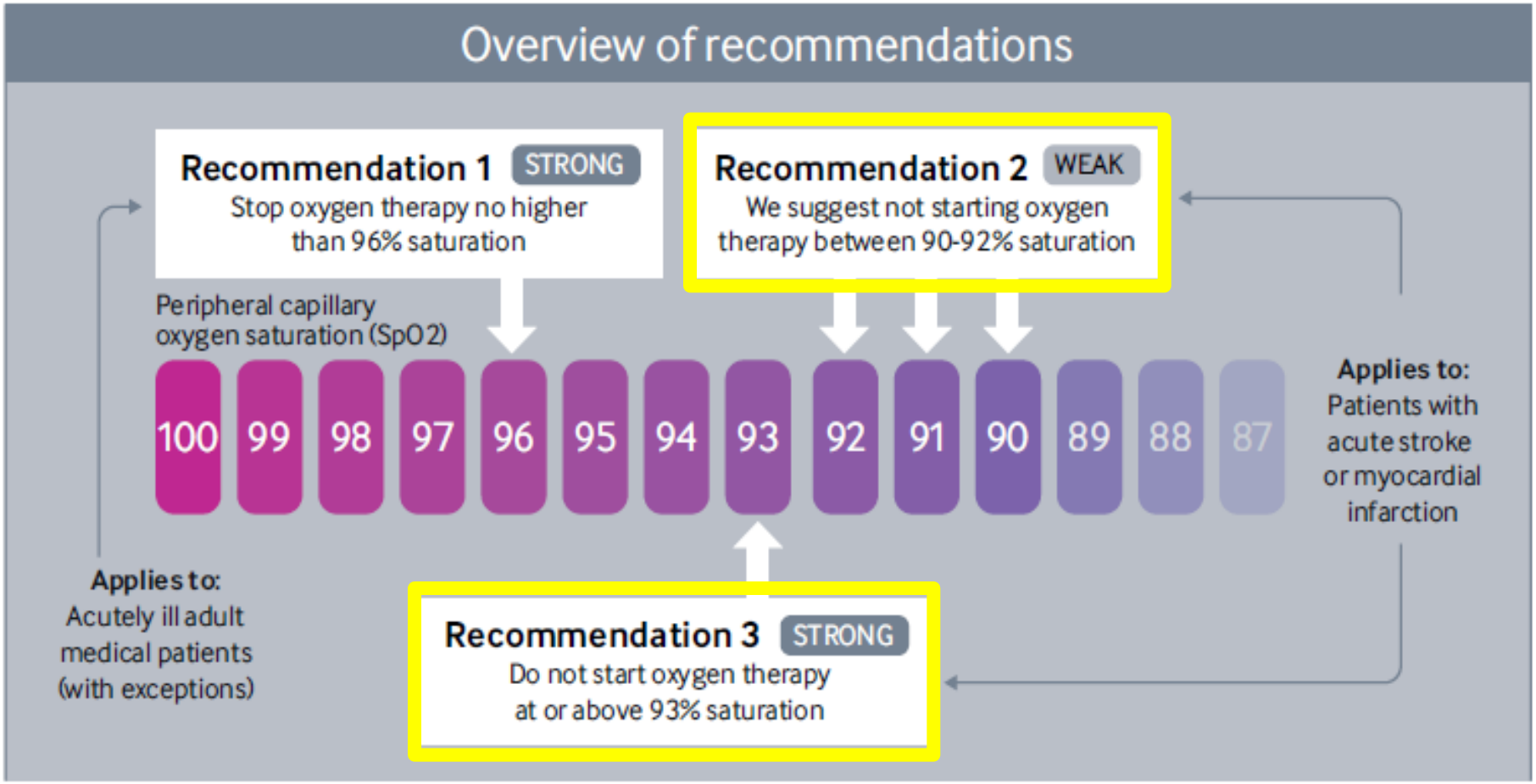
ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *PaO_2* partial pressure of arterial oxygen, *SpO_2* peripheral oxygen saturation

TAKE HOME PICTURE

the bmj
Cite this as: *BMJ* 2018;363:k4169
doi: 10.1136/bmj.k4169
RAPID RECOMMENDATIONS

Oxygen therapy for acutely ill medical patients: a clinical practice guideline

Reed A C Siemieniuk,[1] Derek K Chu,[2] Lisa Ha-Yeon Kim,[2] Maria-Rosa Güell-Rous,[3] Waleed Alhazzani,[1 2] Paola M Soccal,[4 5] Paul J Karanicolas,[6] Pauline D Farhoumand,[7] Jillian L K Siemieniuk,[8] Imran Satia,[2] Elvis M Irusen,[9] Marwan M. Refaat,[10] J. Stephen Mikita,[11] Maureen Smith,[12] Dian N Cohen,[13] Per O Vandvik,[14] Thomas Agoritsas,[17 15] Lyubov Lytvyn,[1] Gordon H Guyatt[1 2]



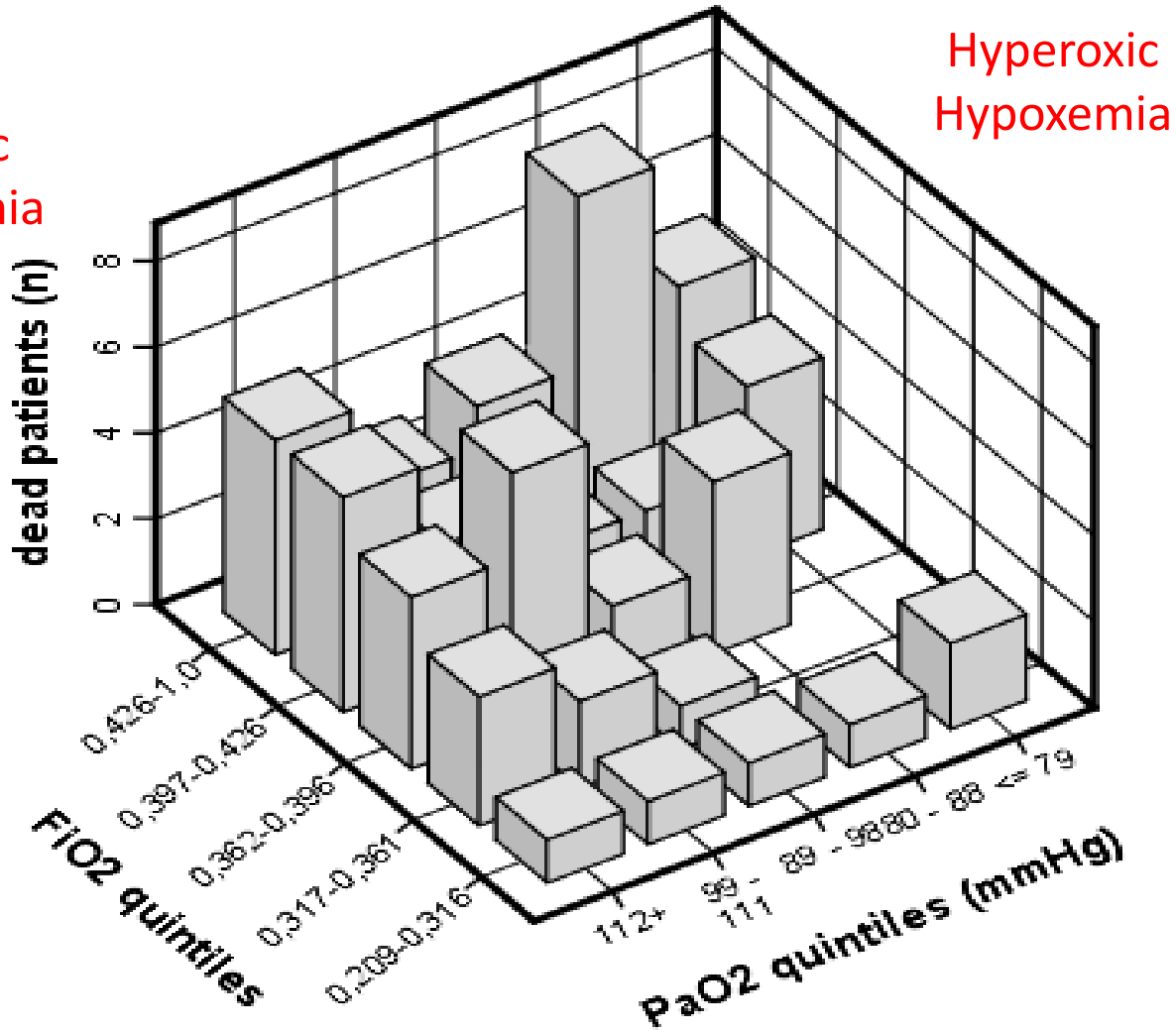
Oxygen-ICU trial

PaO2&FiO2 and mortality

ICU mortality (all patients)

Hyperoxic Hyperoxemia

Hyperoxic Hypoxemia



O_2 therapy in critically ill patients: **Pathophysiology**

Bench-to-bedside review: the effects of hyperoxia during critical illness

Helmerhorst *et al. Critical Care* (2015) 19:284

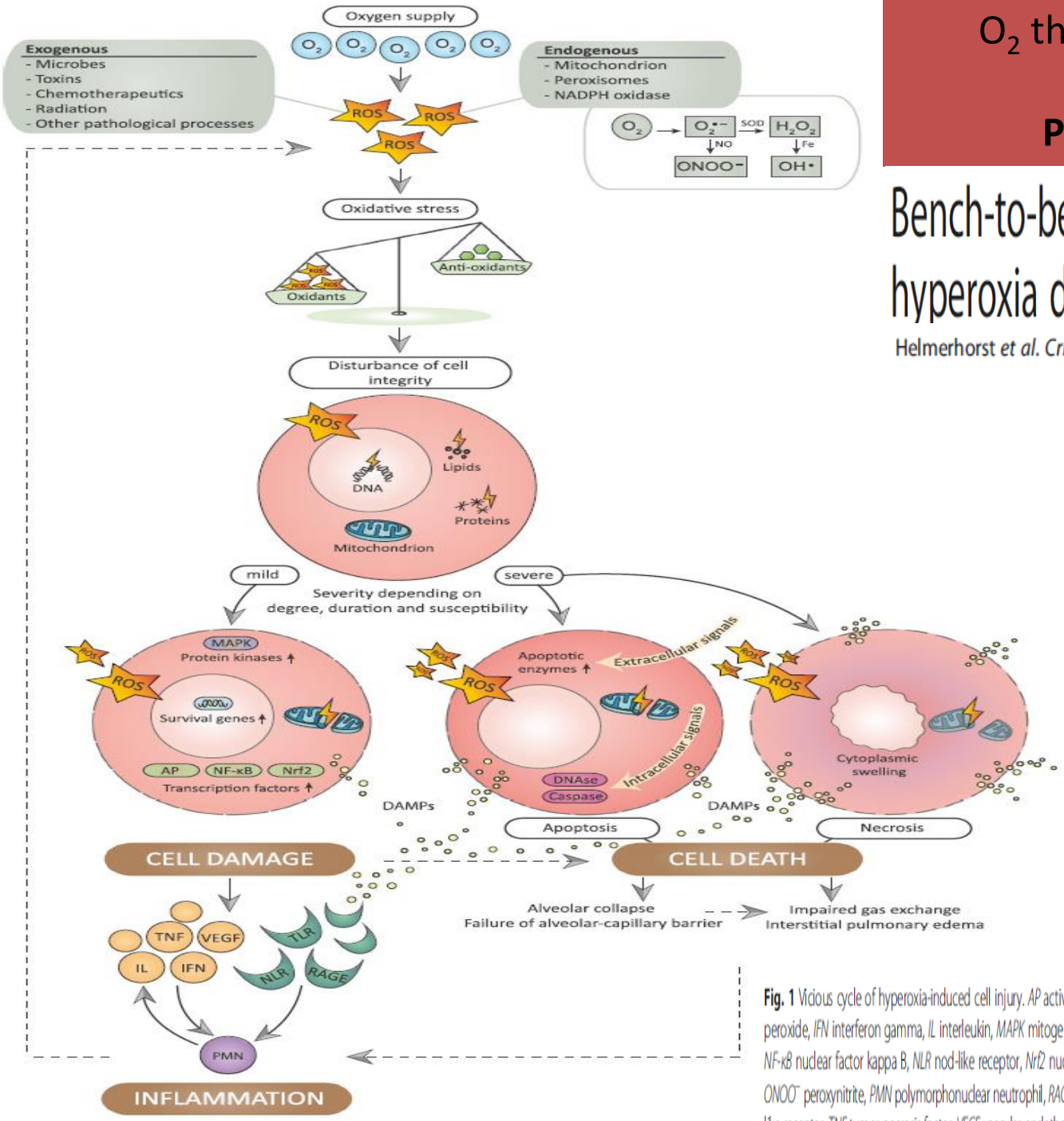


Fig. 1 Vicious cycle of hyperoxia-induced cell injury. *AP* activator protein, *DAMP* damage-associated molecular pattern molecules, H_2O_2 hydrogen peroxide, *IFN* interferon gamma, *IL* interleukin, *MAPK* mitogen-activated protein kinase, *NADPH* nicotinamide adenine dinucleotide phosphate, *NF-κB* nuclear factor kappa B, *NLR* nod-like receptor, *Nrf2* nuclear factor-2 erythroid related factor-2, O_2 oxygen, O_2^- superoxide, *OH* hydroxyl radical, $ONOO^-$ peroxynitrite, *PMN* polymorphonuclear neutrophil, *RAGE* receptor for advanced glycation end products, *ROS* reactive oxygen species, *TLR* Toll-like receptor, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor

MITOCHONDRIAL METABOLIC SHUTDOWN

@ Inner membrane: large surface area, impermeable with enzymes involved in oxidative phosphorylation

@ ATP production (energy) takes place via a flow of electrons passed along the 5 molecular complexes of the electron transport chain. The electron transfer results in reciprocal transfer of protons, creating the mitochondrial membrane potential.

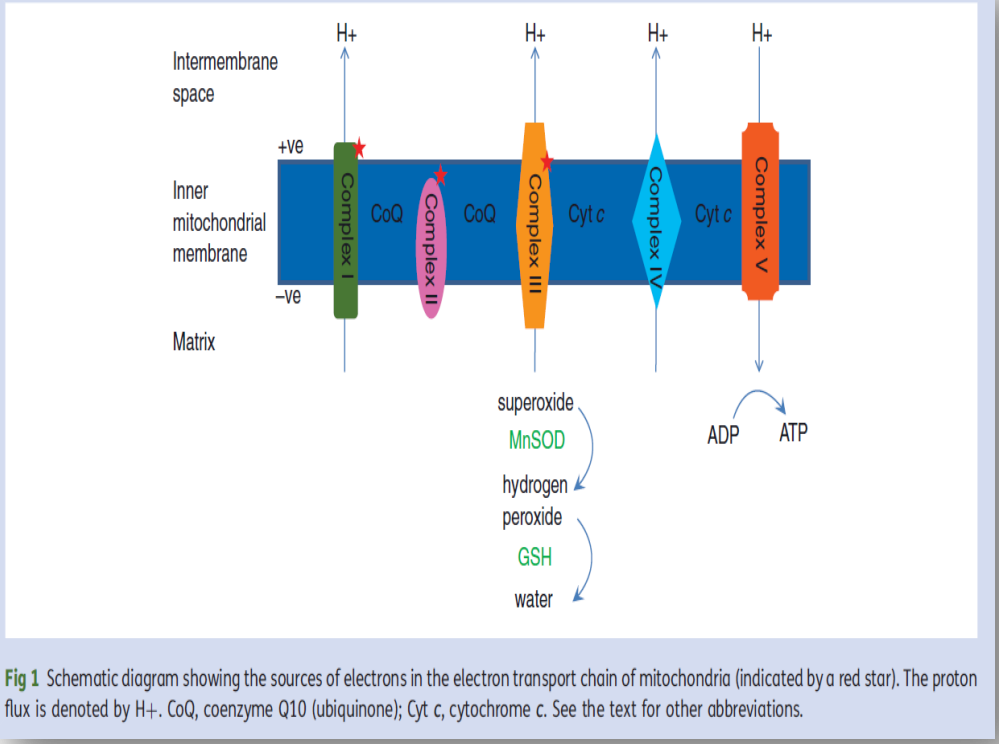


Fig 1 Schematic diagram showing the sources of electrons in the electron transport chain of mitochondria (indicated by a red star). The proton flux is denoted by H+. CoQ, coenzyme Q10 (ubiquinone); Cyt *c*, cytochrome *c*. See the text for other abbreviations.

@ Reactive oxygen species (ROS) are by-products of the incomplete four-electron reduction of molecular O2 to water (final electron acceptor). Around 1% of O2 is converted to ROS in physiological conditions

@ A proportion of the proton gradient created by electron transfer is dissipated and 'lost' as heat. Amount of oxygen utilised by uncoupled respiration is uncertain, varies from 15% in heart to 50% in skeletal muscle

@ Respiratory chain can produce (sepsis) NO (iNOS ?) and other nitric oxide by-products called reactive nitrogen species (RNS).

TISSUE HYPOXIA

REVIEW ARTICLE

Optimising organ perfusion in the high-risk surgical patient and ICU patient: a narrative review

Thomas Parker, David Brealey, Alex Dyson and Mervyn Singer*

Br J Anaesth. 2019 May 2

@ Inadequate organ perfusion/oxygenation with resultant tissue HYPOXIA represents a common pathway to poor outcomes in both surgical and ICU patient groups.

@ An initial increase in VO2 is characteristic of the stress response after a surgical insult. Failure to meet this increased demand, with consequent development of a conceptual tissue OXYGEN DEBT, is detrimental

@ Increased incidence of complications, organ failure, and death correlate with an increasing severity and duration of tissue hypoxia

@ Standard haemodynamic measures (HR and BP) are poor markers of early tissue hypoperfusion. Global blood flow monitoring gives more indication of the adequacy of tissue perfusion but does not offer detail at the tissue level (microcirculatory perturbations, variability in blood flow and hypoxia susceptibility of particular organs)

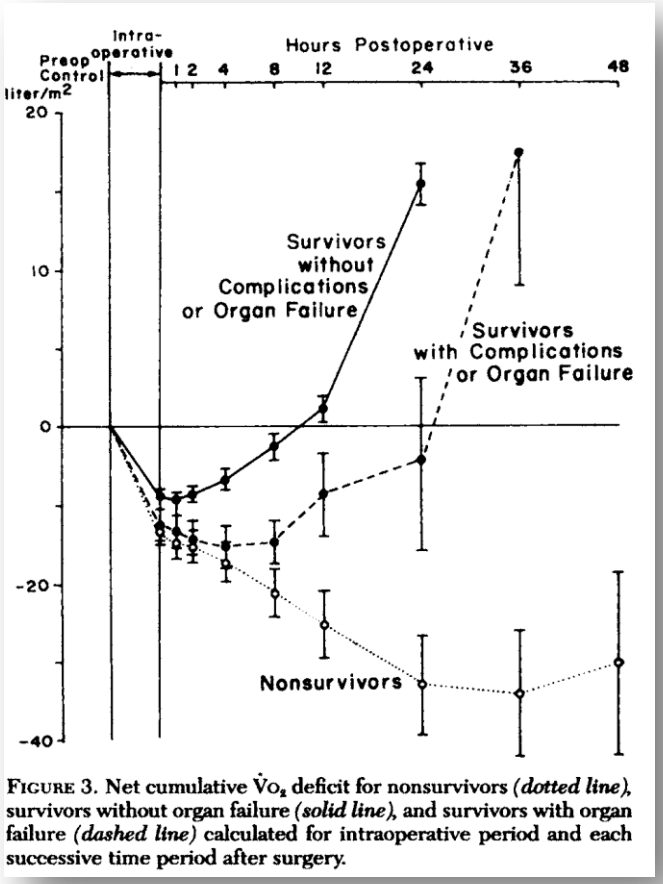


FIGURE 3. Net cumulative $\dot{V}O_2$ deficit for nonsurvivors (*dotted line*), survivors without organ failure (*solid line*), and survivors with organ failure (*dashed line*) calculated for intraoperative period and each successive time period after surgery.

@ How best to identify and respond to such perfusion abnormalities and any associated oxygen supply/demand mismatch remains unresolved both in the operating theatre and on the ICU.

ABC of O_2 TRANSPORT

	PHYSIOLOGICAL MECHANISMS	CLINICAL ASSESSMENT
RESPIRATORY SYSTEM	V_A, V_A/Q, D_LO_2	$P(A\text{-}a)O_2$, PaO_2/FiO_2
CIRCULATORY SYSTEM	Q, [Hb], diss. curve Hb	Q, [Hb], DaO_2, $P(v\text{-}a)CO_2$
TISSUE		SvO_2; O_2ext; La_b
Microcirculation	Qtis; DtisO2	
Cellular level	Enzyme Activity	

$$CxO2 = [Hb]*K1*SxO2 + K2*PxO2$$

$$DxO2 = Q* CxO2 = Q * (([Hb]*K1*SxO2 + K2*PxO2)$$

$$VO2 = Q * (Ca\text{-}Cv)O2 = DaO2\text{-}DvO2 \approx Q * (Sa\text{-}Sv)O2$$

K1 = 1,34 mlO2* (100 ml * g)$^{-1}$

K2 = 0,003 mlO2* (100 ml * mmHg)$^{-1}$

ΔHb 1g/100ml *Δ PaO2 10 mmHg^{-1} = 45

$$O2ext = VO2/DaO2 = (Ca\text{-}Cv)O2 / CaO2 \approx (Sa\text{-}Sv)O2/SaO2$$

$$SvO_2 = SaO_2 - (VO_2 / (Q*K1*[Hb])^{-1})$$

CYTOPATHIC HYPOXIA
Mitochondrial Uncoupling

Review
BURNS 43 (2017) 471–485
Oxidative stress in sepsis: Pathophysiological implications justifying antioxidant co-therapy

OXIDATIVE STRESS-INDUCED MITOCHONDRIAL DAMAGE: PREVENTION and/or THERAPY ?

GENERAL ANTIOXIDANTS

@ Selenium
@ Vit C
@ N-Acetylcysteine
@ NOS Inhibitors.
@ Melatonin

MITOCHONDRIAL ANTIOXIDANTS

@ MitoQ consists of the antioxidant ubiquinone (or co-enzyme Q10) attached to a lipophilic triphenylphosphonium
@ MitoVitE is a form of tocopherol (vitamin E) attached to lipophilic triphenylphosphonium
@ Hemigramicidin-TEMPOL
@ Antioxidant peptides
@ Increasing endogenous mitochondrial antioxidants by glutathione N-acetyl-L-cysteine choline esters or genetic approach

O_2 therapy IN TRAUMA

Early exposure to hyperoxia and mortality in critically ill patients with severe traumatic injuries

Russell *et al. BMC Pulmonary Medicine* (2017) 17:29

@ 471 Critically ill patients with traumatic injuries (including TBI) undergoing invasive mechanical ventilation (prospective cohort of study on biomarkers in ALI)

@ Primary analysis was comparison of the highest PaO2 between hospital survivors and non-survivors.

Table 1 Baseline characteristics of 471 critically-Ill trauma patients included in the analysis

Characteristic	*N*	Overall	Survivors	Non-survivors	*p*-value
		n = 471	*n* = 422 (89.6%)	*n* = 49 (10.4%)	
Age (Years)	471	42 (27, 55)	41 (27, 54)	51 (43, 67)	<0.001
Men (n, %)	471	342 (73%)	308 (73%)	34 (69%)	0.59
Head Trauma (Yes)	471	266 (56%)	231 (55%)	35 (71%)	0.03
APACHE II score	471	25 (20, 28)	24 (20, 28)	28 (25, 31)	<0.001
Injury Severity Score	470	29 (18, 36)	29 (18, 36)	29 (20, 39)	0.37
Number of ABGs measured	471	3 (2, 5)	3 (2, 5)	3 (2, 6)	0.44
FiO_2 Associated with Maximum PaO_2	352	0.40 (0.40, 0.60)	0.40 (0.40, 0.60)	0.40 (0.40, 0.60)	0.56
Maximum PaO_2 (mmHg)	471	142 (103, 212)	141 (103, 212)	148 (105, 209)	0.82
GCS	471	11 (8, 15)	11 (9, 15)	3 (3, 9)	<0.001

Table 2 Logistic regression model for in-hospital mortality

Characteristic	Odds ratio	95% Confidence interval	*p*-value
Age (Increment of 5 years)	1.20	1.10–1.31	<0.001
Injury Severity Score (Increment of 5)	1.41	1.03–1.94	0.03
Number of ABGs Measured	1.05	0.91–1.22	0.49
FiO_2 at time of ABG (Increment of 10%)	0.94	0.77–1.15	0.54
Maximum PaO_2 (Increment of 1 fold)	1.27	0.72–2.25	0.41

Conclusions: In mechanically ventilated patients with severe traumatic injuries, hyperoxia in the first 24 hours of admission was not associated with increased risk of death or worsened neurological outcomes in a setting without brain tissue oxygenation monitoring.

O_2 therapy
MYOCARDIAL INFARCTION

Oxygen Therapy in Suspected Acute Myocardial Infarction

This article was published on August 28, 2017, at NEJM.org.

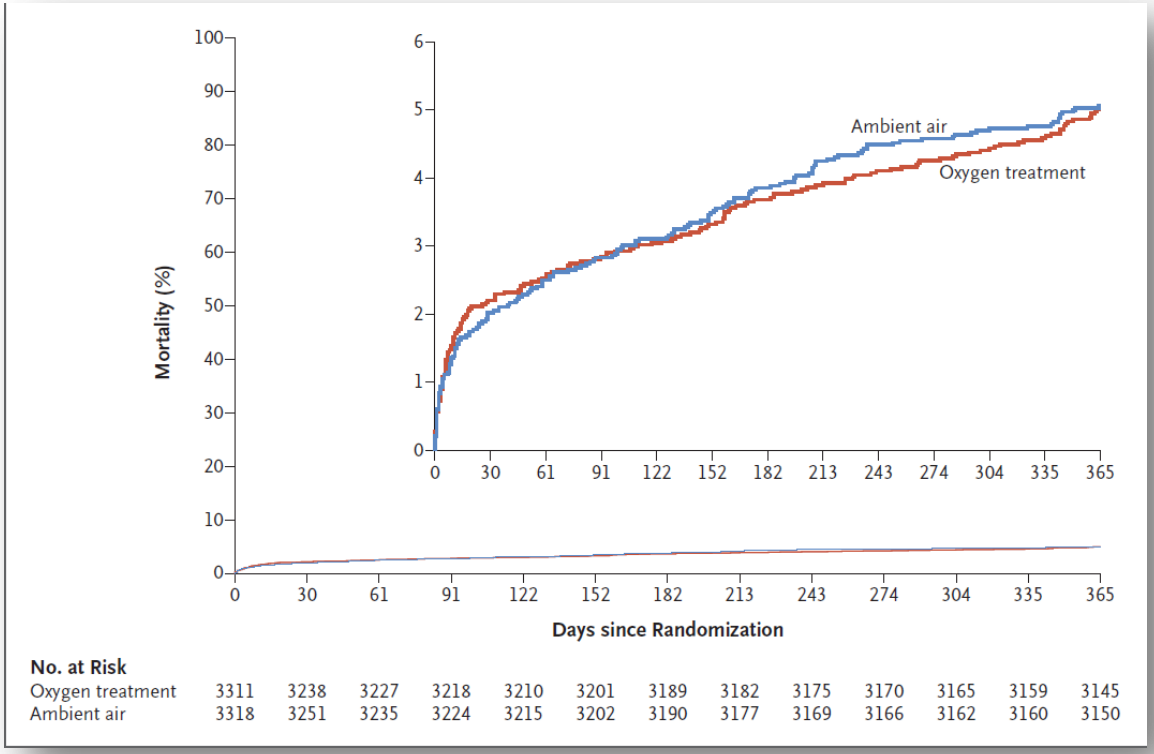
Robin Hofmann, M.D., Stefan K. James, M.D., Ph.D.,

@ Patients with suspected myocardial infarction and an oxygen saturation of 90% or higher were randomly assigned to receive either supplemental oxygen (6L O2) or ambient air.

@ Median duration of oxygen therapy 11.6 hours, median O2 saturation was 99% in oxygen group and 97% in ambient air group

@ Safety: hypoxemia in 62 patients (1.9%) in oxygen group and 254 patients (7.7%) in the ambient-air group.

@ Rehospitalization with myocardial infarction within 1 year occurred in 126 patients (3.8%) assigned to oxygen and in 111 patients (3.3%) assigned to ambient air (hazard ratio, 1.13; 95% CI, 0.88 to 1.46; P = 0.33).



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

The Oxygen-ICU Randomized Clinical Trial

JAMA Published online October 5, 2016

Massimo Girardis, MD; Stefano Busani, MD; Elisa Damiani, MD; Abele Donati, MD; Laura Rinaldi, MD; Andrea Marudi, MD;

Oxygen-ICU trial

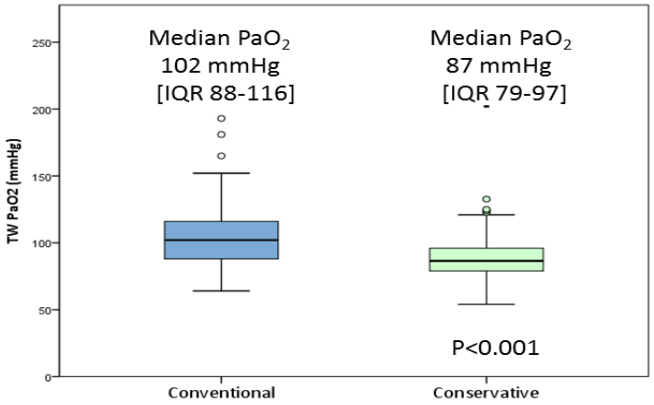
@ 434 patients with ICU lenght of stay > 72 hours

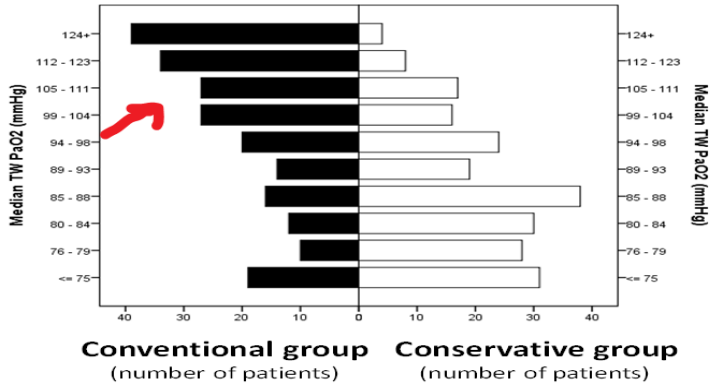
@ Randomly assigned:

SpO2 between **94% and 98%** with PaO_2 values between **70-100 mmHg** (conservative group)

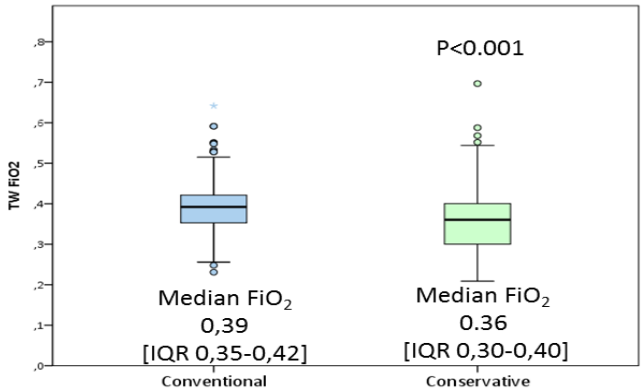
SpO2 between **97% and 100%** with PaO_2 values **up to 150 mmHg** (conventional control group).

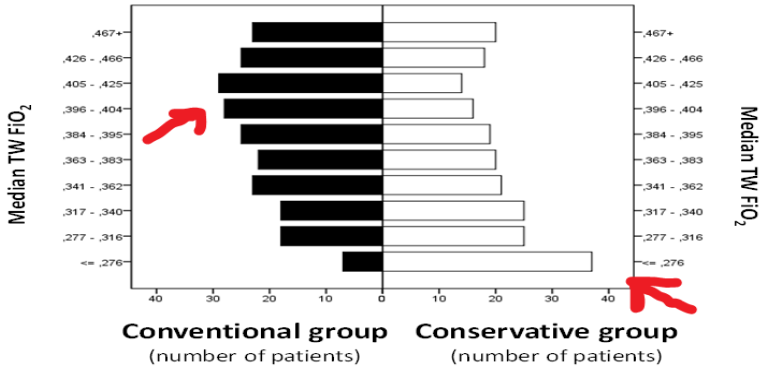
Time-weighted PaO_2: *average during ICU stay*





Time-weighted FiO_2: *average during ICU stay*





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

The Oxygen-ICU Randomized Clinical Trial

JAMA Published online October 5, 2016

Massimo Girardis, MD; Stefano Busani, MD; Elisa Damiani, MD; Abele Donati, MD; Laura Rinaldi, MD; Andrea Marudi, MD;

Oxygen-ICU trial

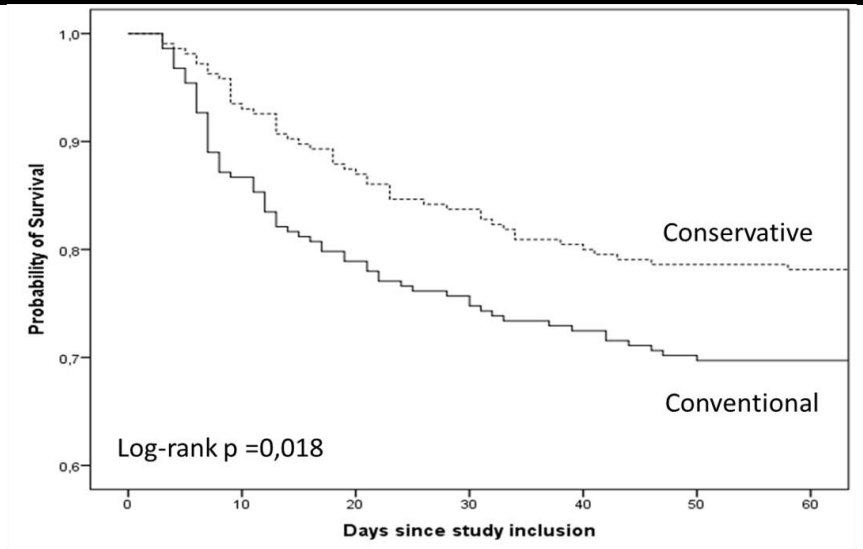
@ 434 patients with ICU lenght of stay > 72 hours

@ Randomly assigned: SpO2 between 94%-98% (conservative group) or between 97% - 100% (conventional control group).

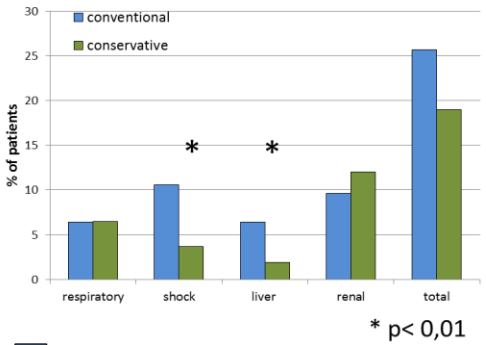
@ Time weighted PaO2: Conventional 102 mmHg (88-118); Conservative 87 mmHg (79-97)

PRIMARY OUTCOME	Conservative O2therapy N = 216	Conventional O2 therapy N = 218	P value	RR (95% CI)
ICU mortality, no. (%)	25/216 (11,6)	44/218 (20,2)	0,014	0,57 (0,37-0,90)

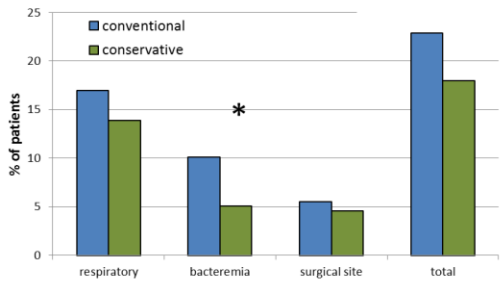
Probability of survival from study inclusion through day 60



New organ dysfunction during ICU stay



* p< 0,01



New documented infection during ICU stay

* p< 0,05

Which is the appropriate level of Arterial PO2 in critically ill patients ?

HYPEROXIA

PaO2 >100 mmHg

High level of PaO2 for avoiding tissue hypoxia

STRICT NORMOXIA

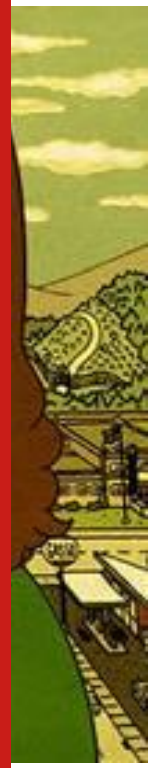
PaO2 60-100 mmHg

MILD HYPOXIA

PaO2 50-60 mmHg

Mild Hypoxia for reducing the harmful effects of reactive oxygen species

Which is the appropriate level of Arterial PO2 in critically ill patients ?



KEEP
CALM
and
USE
LESS OXYGEN

P
Hig
avoi

g
cing
of
ties

TAKE HOME PICTURE

Waiting for the publication of H2S trial (hyperoxia and hypertonic saline in sepsis)