Oxygène et réanimation?

P Asfar et P Radermacher

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„For as a candle burns much faster indephlogisticated (oxygen-enriched) than in common air, so we might live out too fast, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve.“

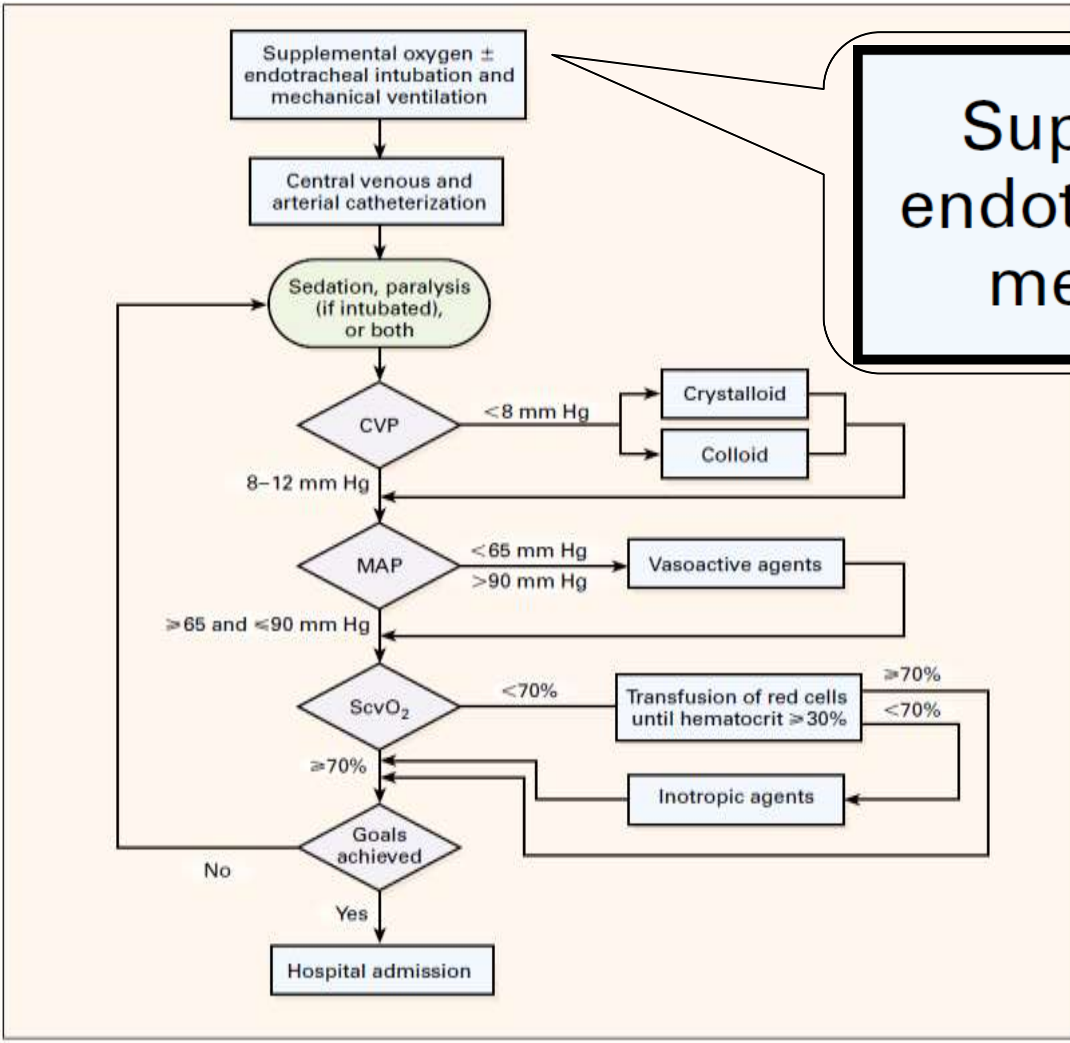
***In:*THE DISCOVERY OF OXYGEN, section 3:**
„Experiments and Observations on Different Kinds of Airs“

Joseph Priestley 1733- 1804

Weil MH & Shubin H: **The "VIP" approach to the bedside management of shock.**
JAMA 1969;207:337-40

"…v̲entilate (oxygen administration), i̲nfuse (fluid resuscitation), p̲ump (vasoactive drugs)..."

Give lots of oxygen? The *Rivers* trial!



Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Rivers et al 2001;345:1368

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

Circulatory Shock

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

VENTILATORY SUPPORT

The administration of oxygen should be started immediately to increase oxygen delivery and prevent pulmonary hypertension. Pulse oximetry is often unreliable as a result of peripheral vasoconstriction, and precise determination of oxygen requirements will often require blood gas monitoring.

N Engl J Med 2013;369:1726-34.

*<u>Hypo</u>*xia promotes inflammation, hence….

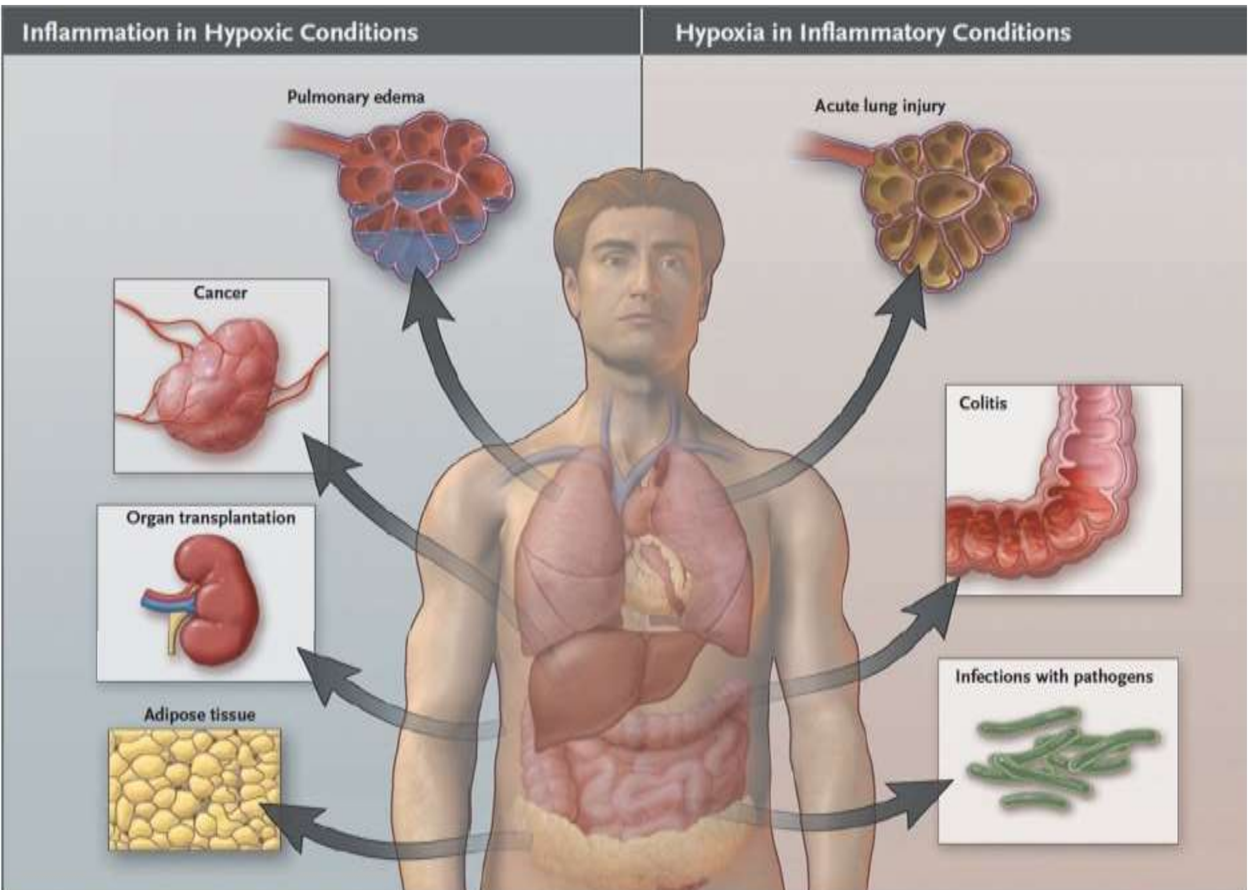


Figure 1. Links between Hypoxia and Inflammation.
Shown is an overview of clinical conditions characterized primarily by tissue hypoxia that causes inflammatory changes (left) and inflammatory diseases leading to tissue hypoxia (right).

„…Taken together, these clincial studies indicate that hypoxia promotes inflammation…"

„…We stress that in the case of inflamed tissue, hypoxia is not a bystander but instead can influence the environment of the itssue by regulating oxygen-dependent gene epxression…"

(Eltzschig & Carmeliet: Hypoxia and inflammation. NEJM 2011;364:656)

BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 17 1947

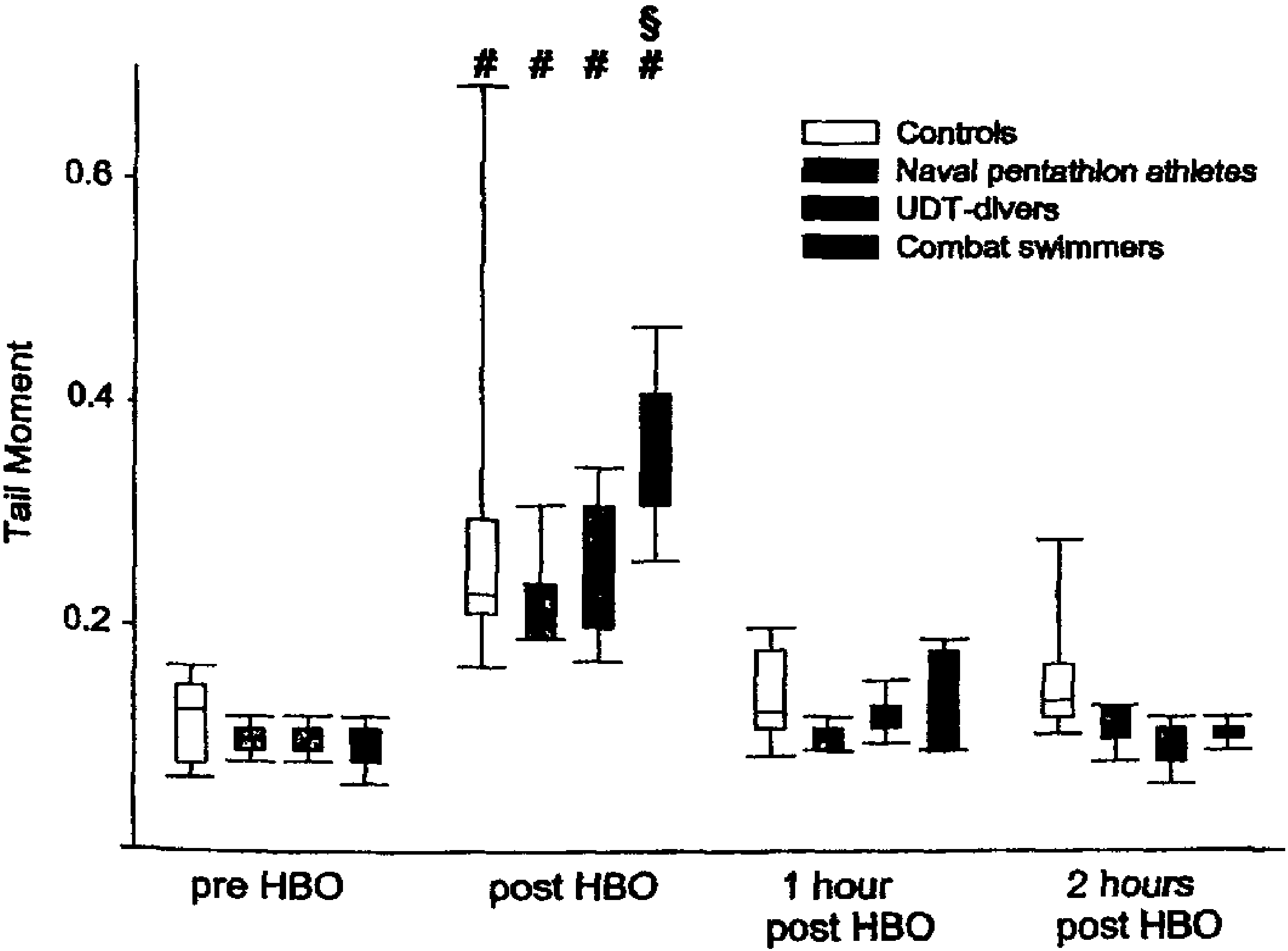
OXYGEN POISONING IN MAN

BY

KENNETH W. DONALD, D.S.C., M.D., M.R.C.P.

TABLE I.—*Oxygen Poisoning at 90 ft. (27.4 m.) in the Dry in 36 Subjects in Order of Performance*

Exposure (mins.)	Symptoms	Exposure (mins.)	Symptoms
96	Prolonged dazzle; severe spasmodic vomiting	18	Vertigo and severe lip-twitching
67	Severe lip-twitching	18	Vertigo + +; epigastric aura
62	Euphoria and lip-twitching	17	Lip-twitching
62	Nausea and vertigo; arm twitch	17	Lip-twitching; spasmodic respiration
54½	Severe lip-twitching	17	Lip-twitching; spasmodic respiration
51	Dazzle and lip-twitching	16½	Slight lip-twitching
50½	Blubbering of lips; fell asleep	16	Severe lip-twitching; spasmodic respiration
50½	Dazed and lip-twitching	15½	Inspiratory predominance; lip-twitching and syncope
34½	Nausea, vertigo, lip-twitching	15	Nausea, syncope, and confusion
33	Convulsed	14	Lip-twitching
32	,,	12½	,,
32	Severe lip-twitching	9	Dazed and lip-twitching; paraesthesiae
30	Convulsed	9	Lip-twitching and vertigo
26½	,,	7½	Severe lip-twitching
25½	Drowsiness and lip-twitching	7	"Diaphragmatic spasm"
24½	Severe lip-twitching	6	Severe nausea
23	Lip-twitching; epigastric aura	6	Severe lip-twitching
20½	Lip-twitching; twitch L. arm; amnesia		
19½	Convulsed		

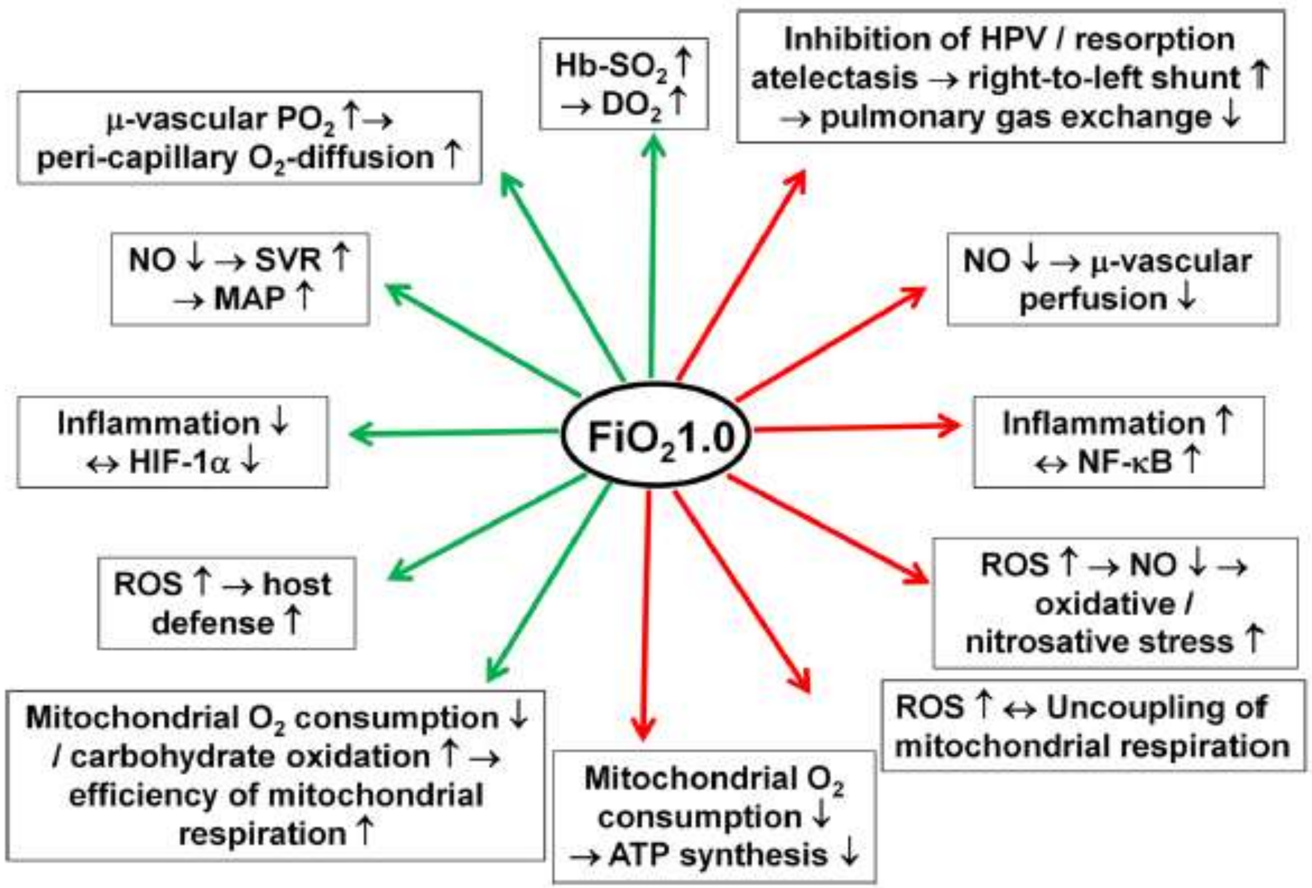

§
# # # #
Controls
Naval pentathlon athletes
UDT-divers
Combat swimmers
Tail Moment
0.6
0.4
0.2
pre HBO
post HBO
1 hour post HBO
2 hours post HBO

Intensive Care Med
DOI 10.1007/s00134-015-3670-z

UNDERSTANDING THE DISEASE

Pierre Asfar
Mervyn Singer
Peter Radermacher

Understanding the benefits and harms of oxygen therapy



- Oxygen and cardio-vascular changes

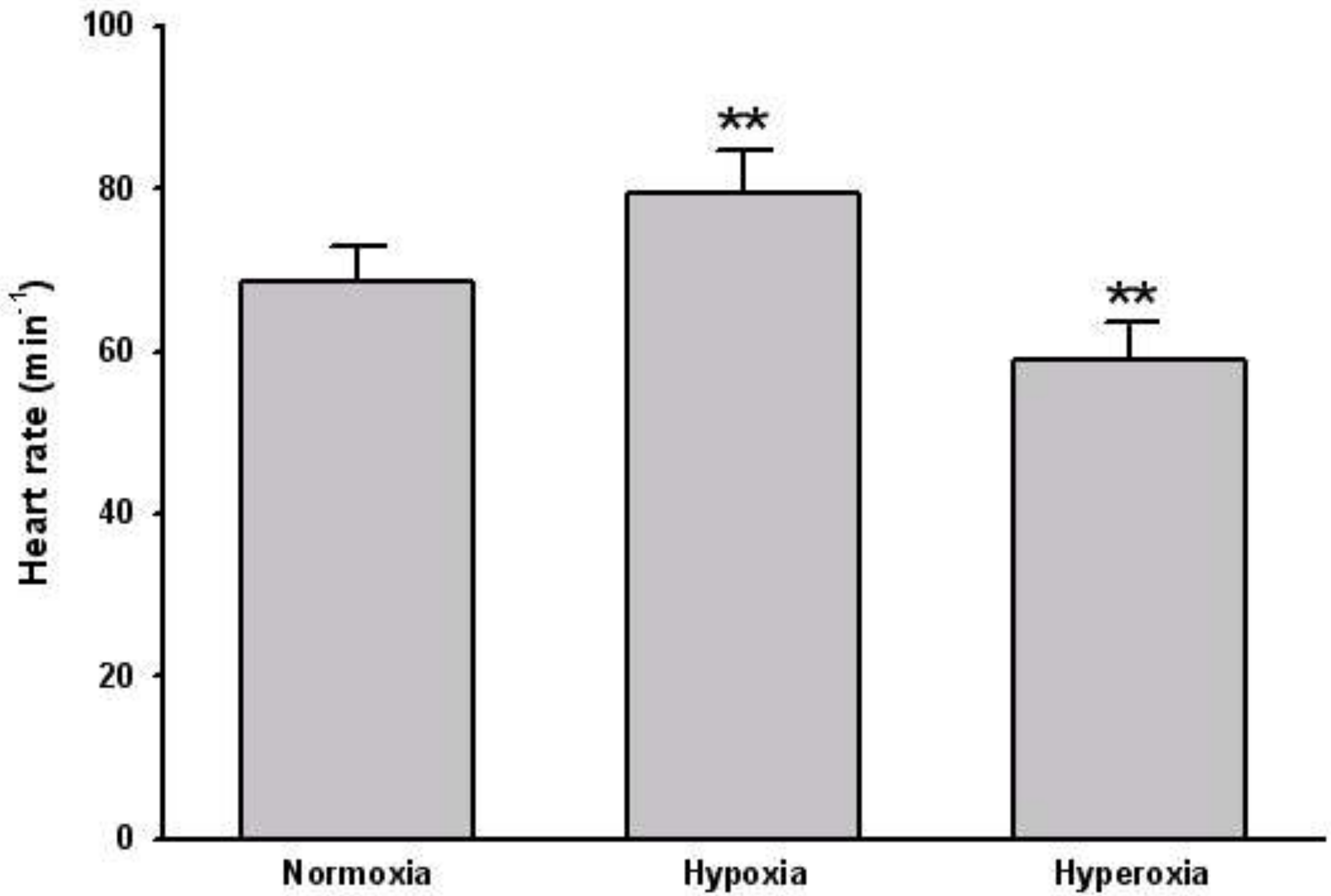
Research

Open Access

Influence of oxygen tension on myocardial performance. Evaluation by tissue Doppler imaging

Ole Frøbert*[1,2], Jacob Moesgaard[1], Egon Toft[3], Steen Hvitfeldt Poulsen[4] and Peter Søgaard[1]

Cardiovasc ultrasounds 2004;2:22



CHEST ONLINE

Effect of Hyperoxia on Left Ventricular Function and Filling Pressures in Patients With and Without Congestive Heart Failure*

Susanna Mak, Eduardo R. Azevedo, Peter P. Liu and Gary E. Newton

Chest 2001;120;467-473

Table 2—*Effect of Hyperoxia on Hemodynamics and Cardiac Function in Patients With CHF**

Variables	Control	Hyperoxia	Recovery
Heart rate, beats/min	73 ± 3	72 ± 3	74 ± 4
FAsys, mm Hg	139 ± 7	140 ± 7	138 ± 9
FAdiast, mm Hg	69 ± 3	72 ± 2	70 ± 3
RAP, mm Hg	8 ± 1	9 ± 1	9 ± 1
PAsys, mm Hg	40 ± 3	40 ± 4	41 ± 4
PAdiast, mm Hg	18 ± 2	19 ± 2	20 ± 2
PVR, dyne · s · cm^{-5}	185 ± 24	214 ± 45	239 ± 50
Cardiac output, L/min	4.6 ± 0.4	4.1 ± 0.3†	4.3 ± 0.3
SV, mL/beat	64 ± 6	57 ± 5†	58 ± 5†
SVR, dyne · s · cm^{-5}	1,626 ± 148	1,901 ± 181†	1,715 ± 177
CSBF, mL/min	94 ± 6	72 ± 8†	84 ± 6
LVEDP, mm Hg	21 ± 3	25 ± 3†	25 ± 3†
LVSP, mm Hg	123 ± 6	128 ± 6	128 ± 8
+dP/dt, mm Hg/s	1,050 ± 84	1,020 ± 79	1,021 ± 80
τ_L, ms	60 ± 3	67 ± 4†	68 ± 3†
$\tau_{1/2}$, ms	46 ± 1	49 ± 2†	49 ± 2†

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
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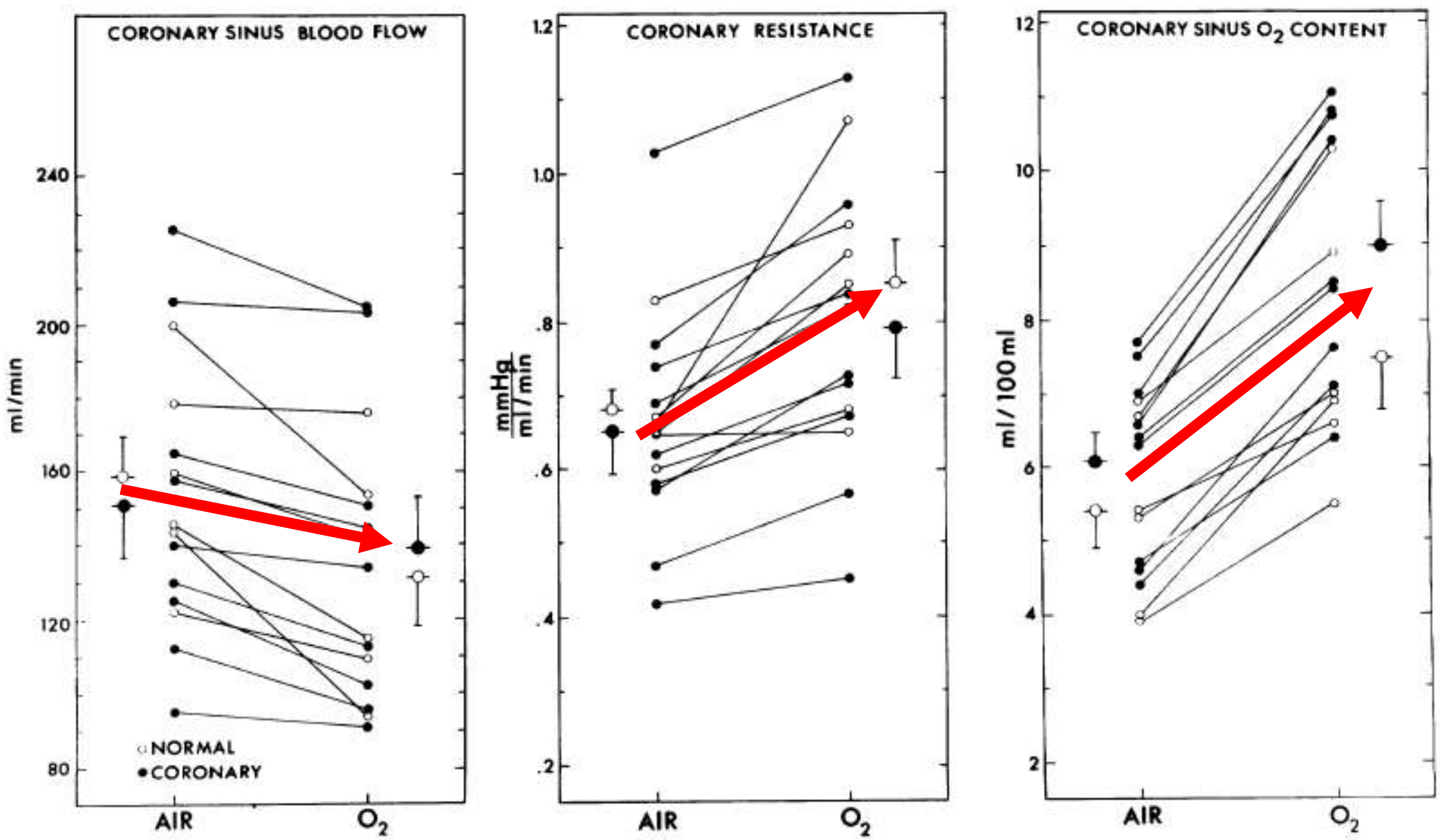
Coronary Hemodynamics and Myocardial Oxygen Metabolism during Oxygen Breathing in Patients with and without Coronary Artery Disease

WILLIAM GANZ, ROBERTO DONOSO, HAROLD MARCUS and H. J.C. SWAN

Circulation 1972;45:763-768



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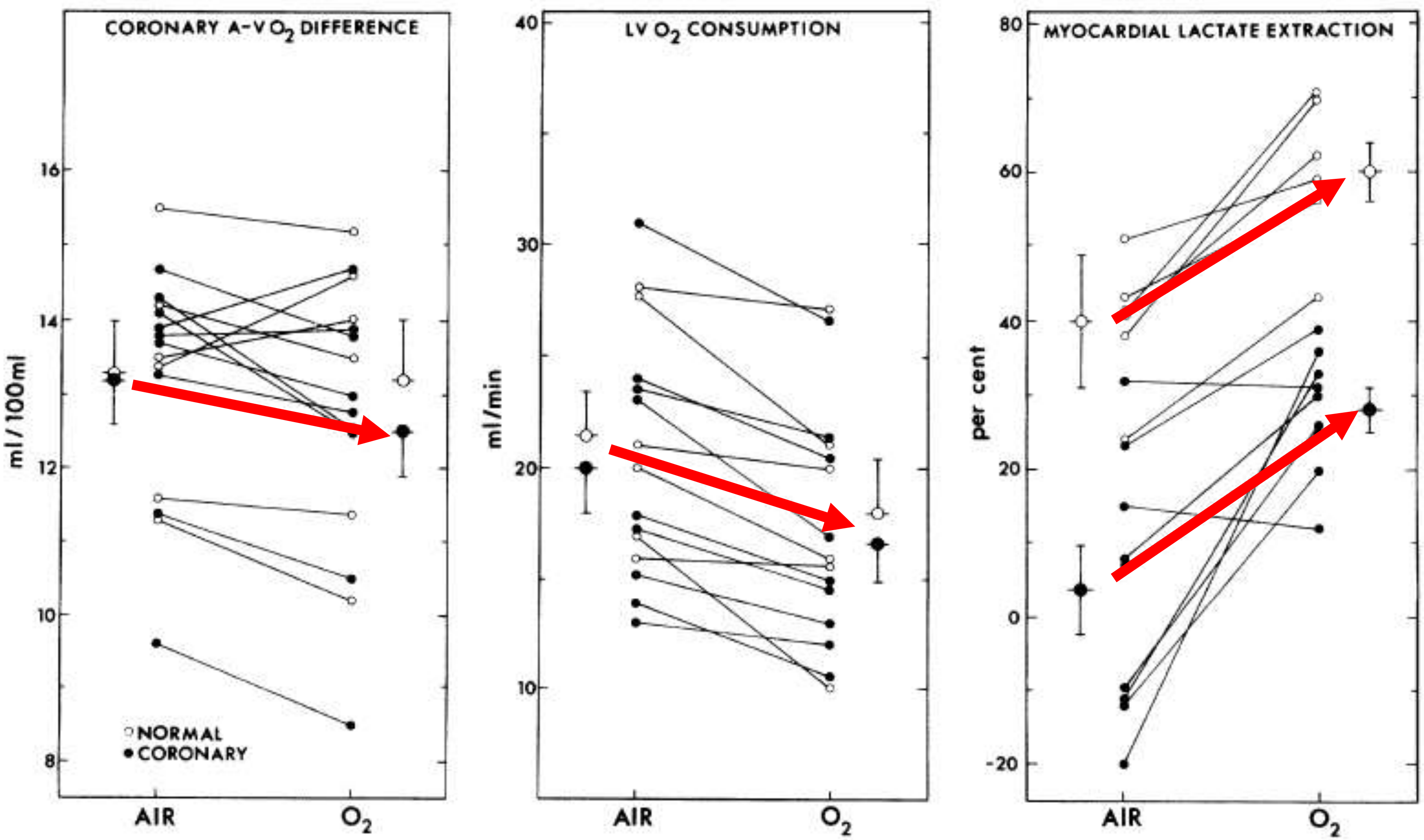


The „*window of opportunity*“

Horvat…Swan, Ganz: **Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency.** ***Circulation 1972;45:837***

Pt	HR (beats/min)		Angina present	
	Air	O_2	Air	O_2
1	125	125	Yes	No
2	130	130	Yes	No
3	160	160	Yes	No
4	105	105	Yes	No
5	158	158	Yes	No
6	135	135	Yes	No
7	145	145	Yes	No
8	120	120	Yes	Yes
9	153	153	Yes	Yes
10	125	125	Yes	No
11	114	114	Yes	No

CHEST®

Official publication of the American College of Chest Physicians

CHEST ONLINE

Reversible decrease of oxygen consumption by hyperoxia.

K Reinhart, F Bloos, F König, D Bredle and L Hannemann

Chest 1991;99;690-694

	Baseline $FIO_2 < 0.4$, 0 min	Hyperoxia $FIO_2 = 1.0$ 30 min	60 min	90 min	Recovery $FIO_2 < 0.4$, 120 min
PaO_2, mm Hg	113±3†	402±106	407±100	393±100†	99±25
$P\bar{v}O_2$, mm Hg	40±4†	52±7	51±7	51±6†	41±4
SaO_2, %	97±2†	99±1	99±1	99±1†	96±2
$S\bar{v}O_2$, %	72±9†	83±8§	80±9	81±10†	72±7
CaO_2, ml/dl	14.5±1.8†	15.7±2.0	15.8±2.0	15.6±2.2†	14.4±1.9
$C\bar{v}O_2$, ml/dl	10.4±1.8†	12.1±1.9	11.8±2.0	11.9±2.4†	10.8±2.1
CaO_2-$C\bar{v}O_2$, ml/dl	4.0±1.4†	3.5±1.1†	3.9±1.2	3.7±1.4	3.7±0.9
O_2 er, %	27.4±9.0†	22.5±6.6‡	25.1±7.5	24.0±8.6†	25.8±7.4
O_2 delivery, $ml \cdot min^{-1} \cdot m^{-2}$	581±175	619±166	606±192	609±201	627±191
$\dot{V}O_2$, $ml \cdot min^{-1} \cdot m^{-2}$	149±34‡	134±33	141±31	135±34§	151±30
pH, arterial	7.41±0.05†	7.39±0.05	7.38±0.05	7.38±0.06§	7.40±0.05
pH, venous	7.40±0.05	7.39±0.05	7.39±0.06	7.39±0.06	7.39±0.06
$PaCO_2$, mm Hg	35±6	35±5	35±6	36±5	35±5
$PvCO_2$, mm Hg	37±6	38±6	40±7	39±7	39±7

Hyperoxia and Blood flow

Farquhar et al: **Systemic review of the effect of hyperoxia on coronary blood flow. *Am Heart J 2009;158:371***

" … Hyperoxia from high-oxygen concentration therapy causes a marked reduction in coronary blood flow… AND myocardial oxygen consumption…"

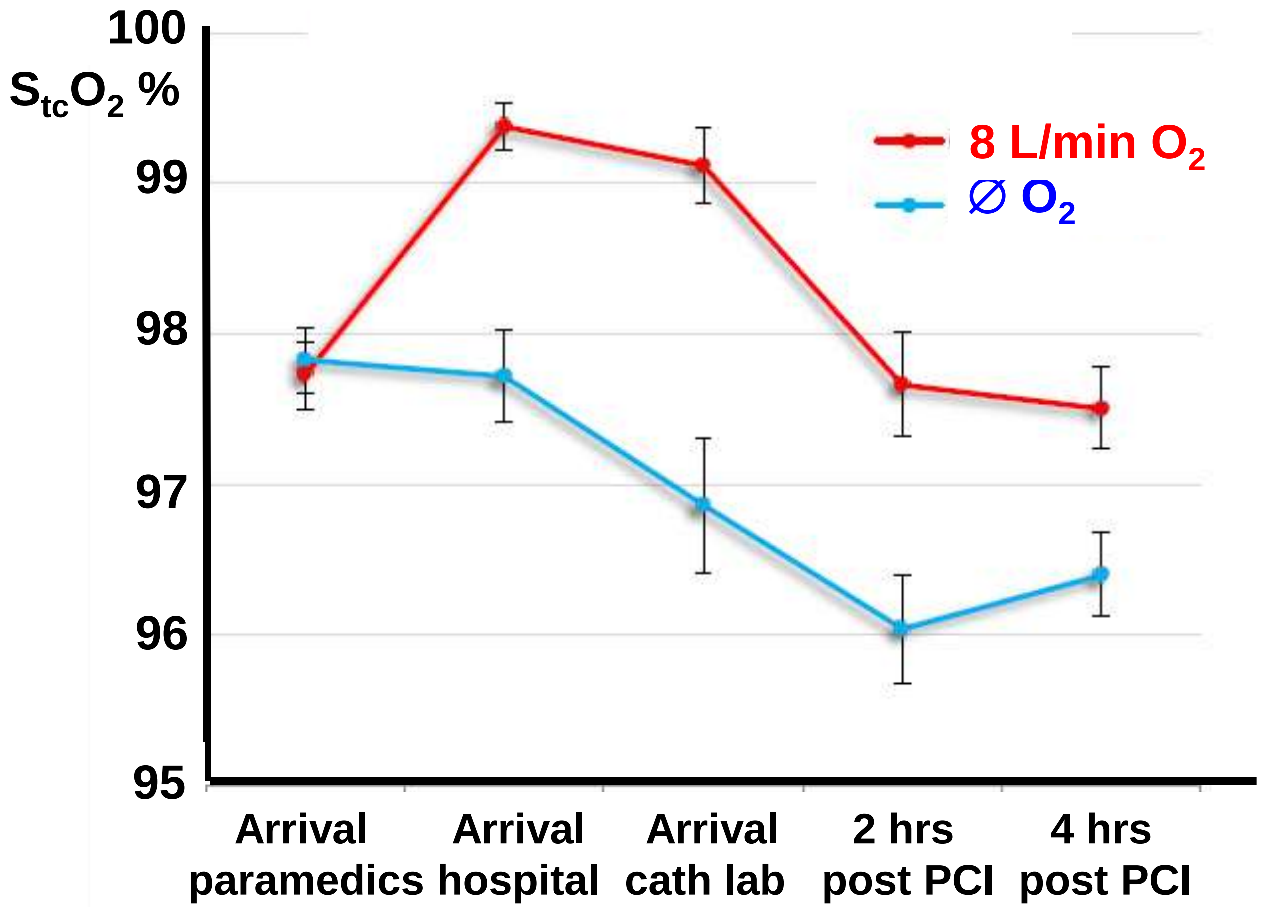
Hyperoxia and acute myocardial ischemia

Hyperoxia and AMI

Stub et al:

Air versus oxygen in ST-segment-elevation myocardial infarction.

Circulation 2015;131:2143-50



Hyperoxia and AMI

Stub et al:

Air versus oxygen in ST-segment-elevation myocardial infarction.

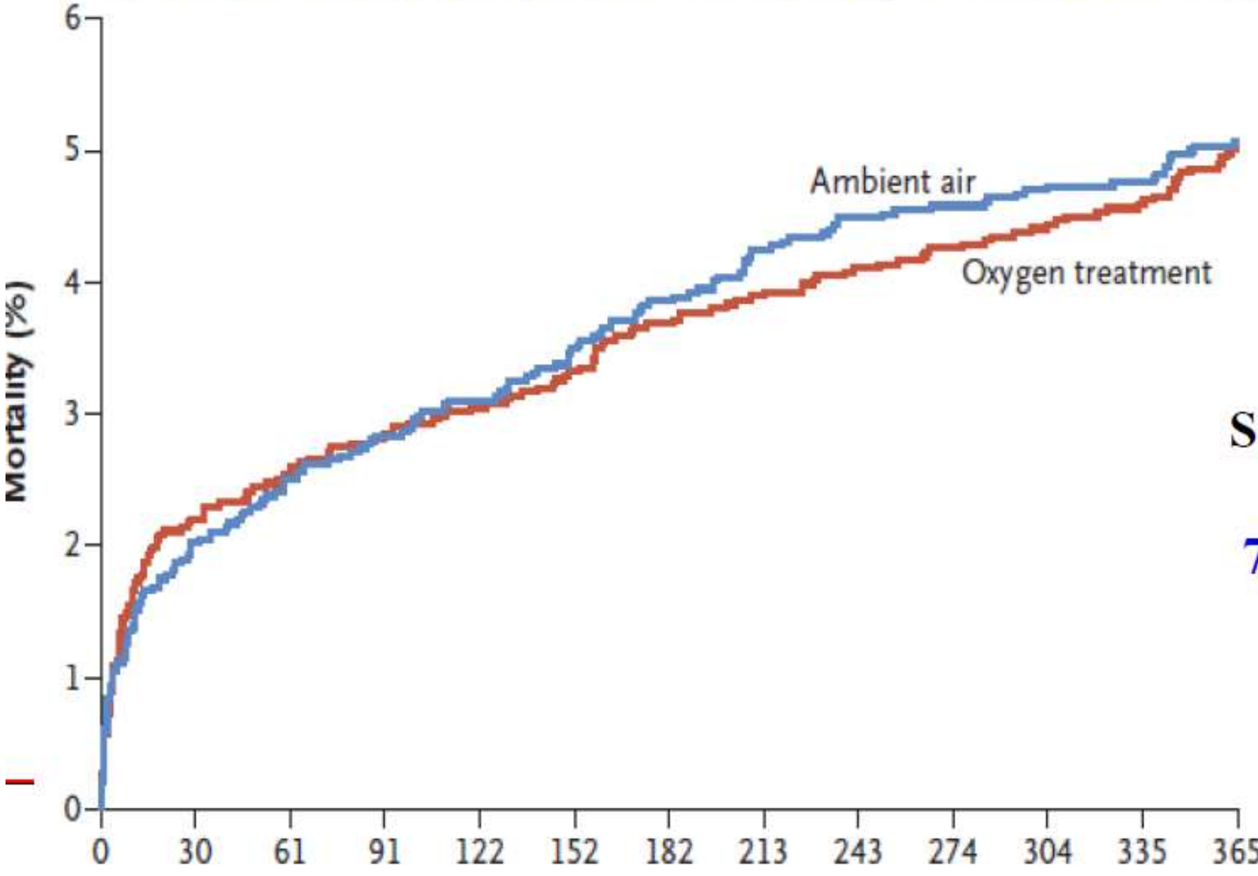
Circulation 2015;131:2143-50

	Hyperoxia	Normoxia	P-value
Mean peak CPK [U/L]	1948 (1721-2205)	1543 (1348-1776)	0.01
Peak troponin [micg/L]	57 (48-69)	48 (40-58)	0.18
Arrhythmia [%]	40	31	0.05
Recurrent MI (at hospital discharge) [%]	5.5	0.9	< 0.01
Infarct size @ 6 mo	20 (10-30)	13 (5-24)	0.04
Mortality [%]	1.8	4.5	0.11

Hyperoxia and AMI

Hofmann et al:
Oxygen therapy in suspected acute myocardial infarction.
NEJM 2017;377:1240-9

6226 patients, symptoms < 6 h, $SO_2 \geq$ 90%, Air *vs.* 6 L/min O_2 over 6-12 h



Supplemental O_2 due to hypoxemia:
7.7 *vs.* 1.9 % (p<0.001)

Oxygène et poumon

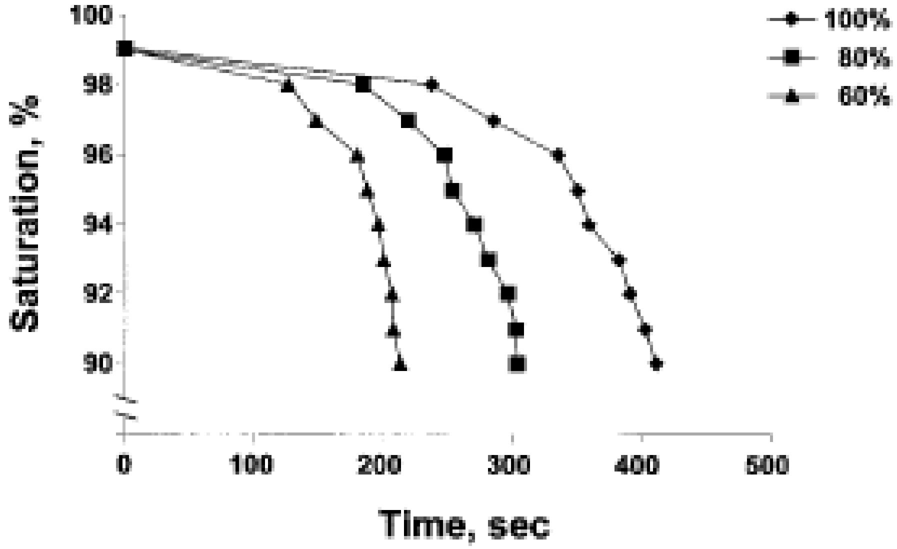
Exposition de cobayes à l'oxygène: mort par OAP.

Antoine Lavoisier 1743-1794

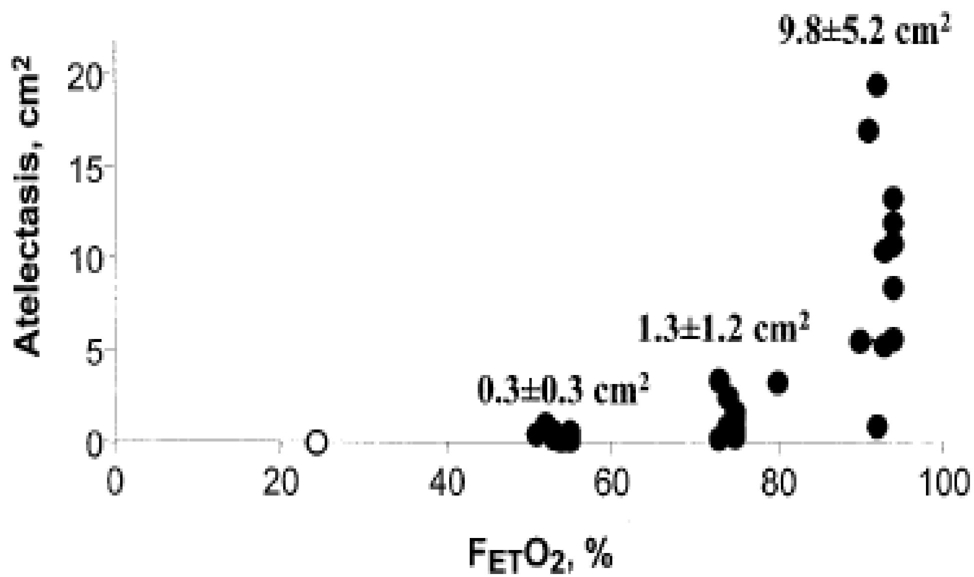
Anesthesiology 2003; 98:28–33

Optimal Oxygen Concentration during Induction of General Anesthesia

Lennart Edmark, M.D., D.E.A.A., Kamelia Kostova-Aherdan, M.D.,† Mats Enlund, M.D., Ph.D.,‡ Göran Hedenstierna, M.D., Ph.D.§*



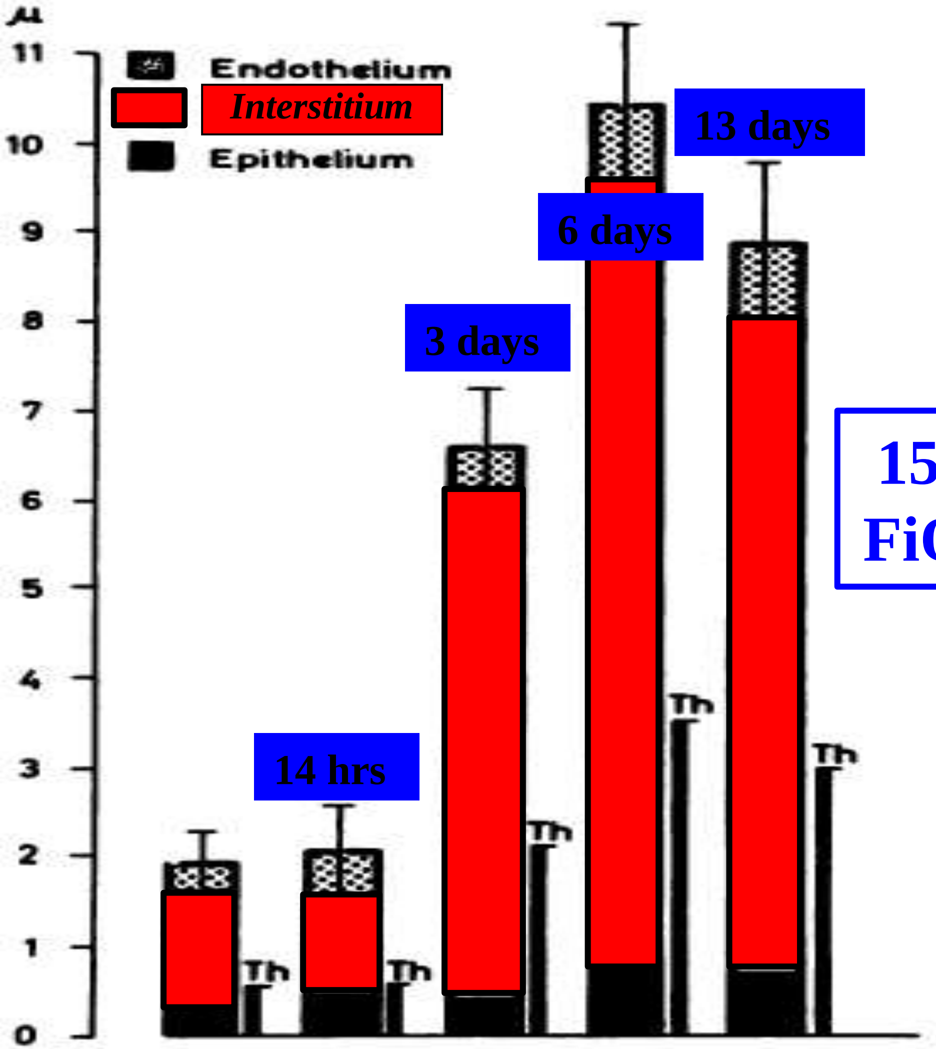
5 minutes O2 puis apnée
jusqu'à saturation 90%



Hyperoxia and Lungs

Kapanci et al: Oxygen pneumonitis in man. *Chest 1972;62:162*

Gould et al: Oxygen pneumonitis in man. *Lab Invest 1972;26:499*



15 mechanically ventilated patients

FiO_2 60 – 100 %, 14 hours – 30 days

Hyperoxia and Lungs

- **100% O_2 over 25 h: modest reduction of vital capacity, symptoms of tracheitis at 6 h**

  Comroe et al. JAMA 1945

- **100% O_2 over 6-12 h, A-aDO_2, Compliance, extravascular lung water unchanged**

  De Water et al. N Eng J Med 1970

- **100% O_2 over 6 h, symptoms of tracheitis**

  Sackner et al. Ann Intern Med 1975

- **95% O_2 over 17 h, increased albumin levels in BAL fluid**

  Davis et al. N Eng J Med 1983

- **100 vs. 30% O_2 over 8 h, normal bronchoscopy**

  Kotani et al. Anesthesiology 2000

Hyperoxia and Lungs

R. Branson (University of Cincinnati) at the 50th Respiratory Care Journal Conference, San Francisco, April13-14, 2012:

„…oxygen toxicity is like Bigfoot: everybody's heard about it, but nobody's ever seen it….“

Discussion in:

Kallet & Matthay:
Hyperoxic acute lung injury.
Respir Care 2013;58:123-41

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Hyperoxia and Lungs

Elmer et al:

Exposure to high concentrations of inspired oxygen does not worsen lung injury after cardicc arrest.

Crit Care 2015;19:105

"…Higher exposure to inhaled oxygen in the first *24 hours after cardiac arrest* was *not associated with deterioration in gas exchange or pulmonary compliance*… but ….*decreased survival and worse neurological outcome*."

- Oxygen and infection

Oxygen as an Antibiotic

The Effect of Inspired Oxygen on Infection

David R. Knighton, MD; Betty Halliday; Thomas K. Hunt, MD

• Granulocytes' in vitro bactericidal capacity for certain bacteria depends on an adequate environmental oxygen supply. Oxygen available to granulocytes in infected tissue is decreased by local conditions and can be altered significantly by small changes in its inspired concentration. We modified Burke's and Miles' bacteria-injection model in animals to test the effect of breathing 12%, 21%, and 45% oxygen on the size of lesions produced by intradermal injections of *Escherichia coli*. Moderately increased inspired oxygen concentrations (fraction of inspired oxygen [FIO_2]) significantly decreased the size and number of necrotic lesions, whereas hypoxia increased both. Increasing FIO_2 to 45% after three and 24 hours of hypoxia also significantly decreased lesion size. Suppression of infection by moderate hyperoxia is comparable with that reported by Burke after timely, adequate doses of type-specific antibiotics.

(*Arch Surg* 1984;119:199-204)

Schietroma et al: **Prevention of anastomotic leakage after total gastrectomy with perioperative supplemental oxygen administration: A prospective randomized, double-blind, controlled, single-center trial.** ***Ann Surg Oncol 2013;20:1594-90***

171 Patients, FiO_2 30 vs. 80 %

FiO2	Anastomotic leackage %	
30 %	20	$p < 0.05$
80 %	9	OR 0.61 (0.40-0.95)

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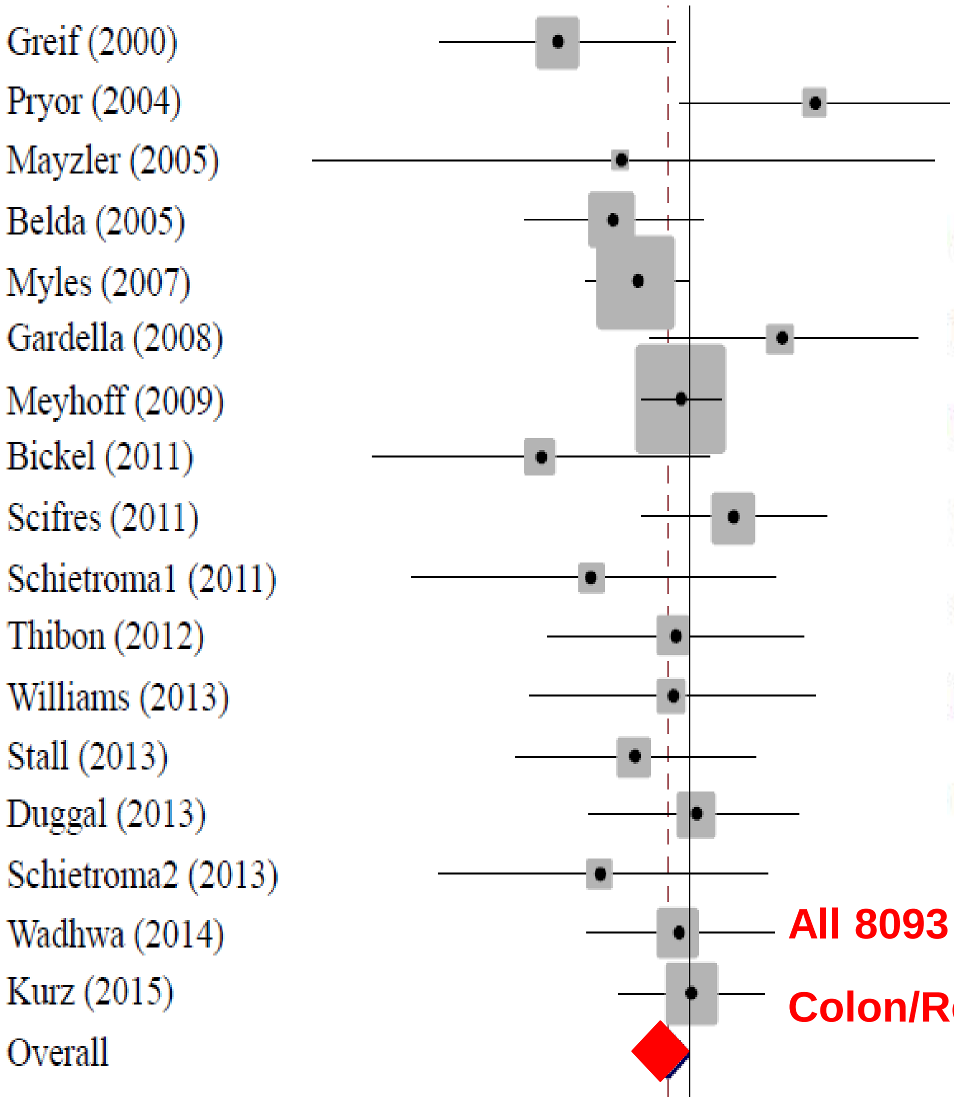
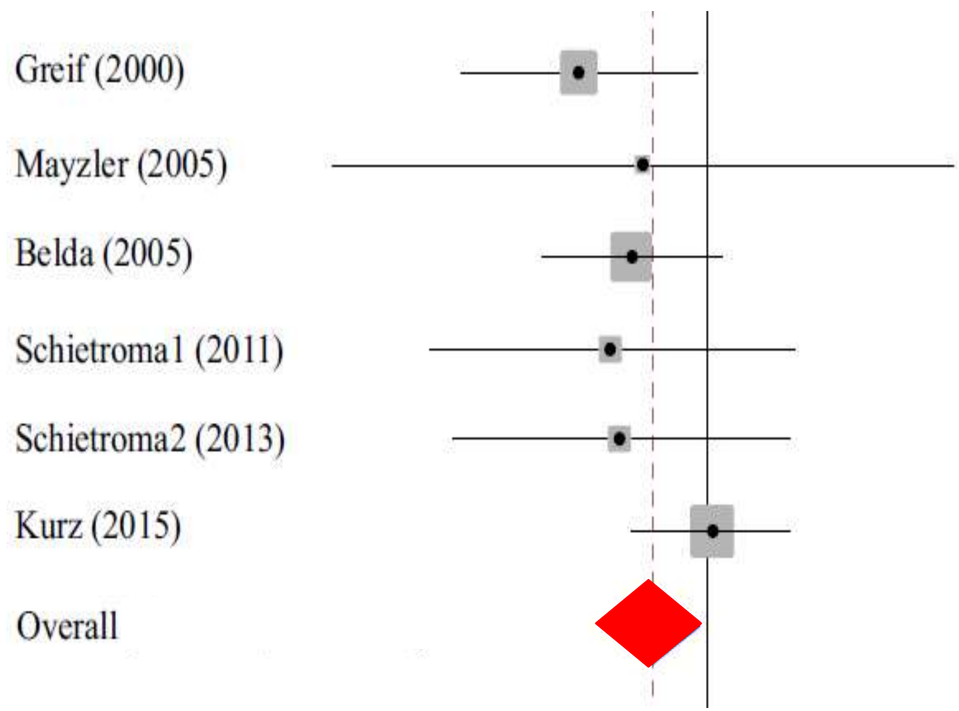
Yang et al: Effect of intra-operative high inspired oxygen concentration on surgical site infection: a meta-analysis of randomized controlled trials. *J Hospital Inf 2016;93:329*



Meta-Analysis from 17 RCT!



All 8093 Patients: OR 0.89 (0.79-1.03, p=0.06)

Colon/Rectal 3081 Patients: OR 0.74 (0.57-0.94, p=0.02)

Cohen et al: Effect of intraoperative Hyperoxia on the incidence of surgical site infections: a meta-analysis. *BJA 2018*

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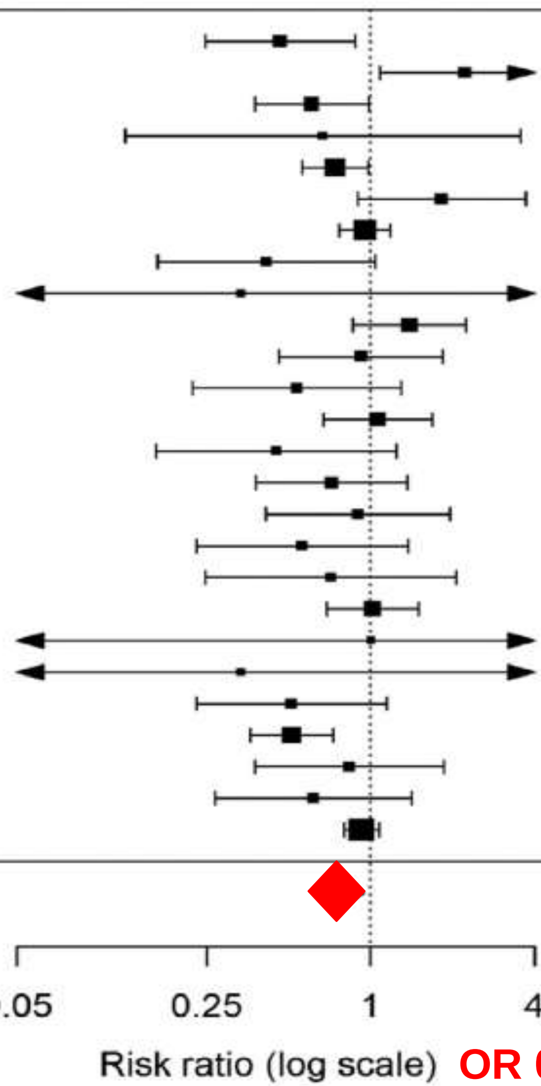
Author(s) and year	NO. SSI / Total no. High FiO_2	NO. SSI / Total no. Low FiO_2	Weight	Relative risk (95% CI)
Greif 2000	13/250	28/250	3.76%	0.46 (0.25, 0.88)
Pryor 2004	20/80	9/80	3.10%	2.22 (1.08, 4.58)
Belda 2005	22/148	35/143	5.39%	0.61 (0.38, 0.98)
Mayzler 2005	2/19	3/19	0.72%	0.67 (0.13, 3.55)
Myles 2007	77/997	106/1015	8.81%	0.74 (0.56, 0.98)
Gardella 2008	17/69	10/74	3.19%	1.82 (0.90, 3.70)
Meyhoff 2009	131/685	141/701	10.21%	0.95 (0.77, 1.18)
Bickel 2011	6/107	14/103	2.11%	0.41 (0.16, 1.03)
Golfam 2011	0/30	1/30	0.21%	0.33 (0.01, 7.87)
Scifres 2011	35/288	26/297	5.39%	1.39 (0.86, 2.25)
Thibon 2012	15/226	15/208	3.32%	0.92 (0.46, 1.84)
Chen 2013	5/30	19/61	2.25%	0.54 (0.22, 1.29)
Duggal 2013	34/416	32/415	5.63%	1.06 (0.67, 1.68)
Schietroma 2013	5/86	11/85	1.78%	0.45 (0.16, 1.24)
Stall 2013	14/119	19/116	3.70%	0.72 (0.38, 1.36)
Williams 2013	10/77	12/83	2.75%	0.90 (0.41, 1.96)
Schietroma 2014	6/40	11/41	2.20%	0.56 (0.23, 1.37)
Habib 2015	5/40	7/40	1.65%	0.71 (0.25, 2.06)
Kurz 2015	45/285	42/270	6.81%	1.02 (0.69, 1.49)
Wasnik 2015	0/32	0/32	0.14%	1.00 (0.02, 48.92)
Fariba 2016	0/61	1/61	0.21%	0.33 (0.01, 8.03)
Schietroma 2016a	7/42	14/43	2.64%	0.51 (0.23, 1.14)
Schietroma 2016b	31/119	61/120	7.45%	0.51 (0.36, 0.73)
Tajne 2016	10/120	12/120	2.64%	0.83 (0.37, 1.85)
Vallabha 2016	8/94	13/94	2.48%	0.62 (0.27, 1.42)
Kurz 2017	295/2896	314/2853	11.48%	0.93 (0.80, 1.08)
RE model (Q=42.7, df=25, *P*=0.015; I^2=41.4%)			100.00%	0.81 (0.70, 0.94)



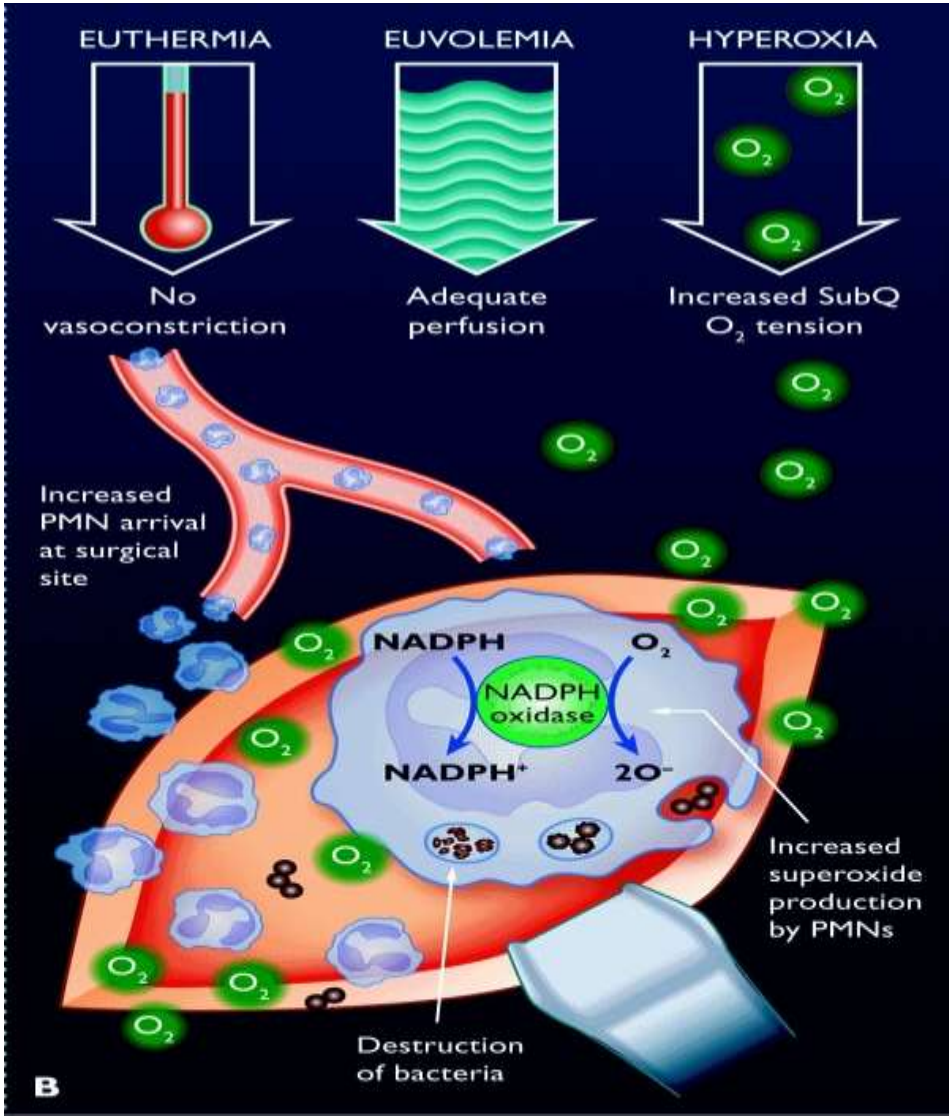
Meta-Analysis of 26 RCT including 14.710 patients!

OR 0.81 (0.70-0.94), p=0.00057

O_2 is an „*Antibiotic*“

Mauermann WJ:
The Anesthesiologist`s Role in the Prevention of Surgical Site Infections
Anesthesiology 2006;105:413-21

- **Antibiotics**
- **Normothermia**
- **Adequate fluid resuscitation**
- **Adequate hematocrite**
- **Normoglycemia**
- **Hyperoxia**



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Berrios-Torres et al:

Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017

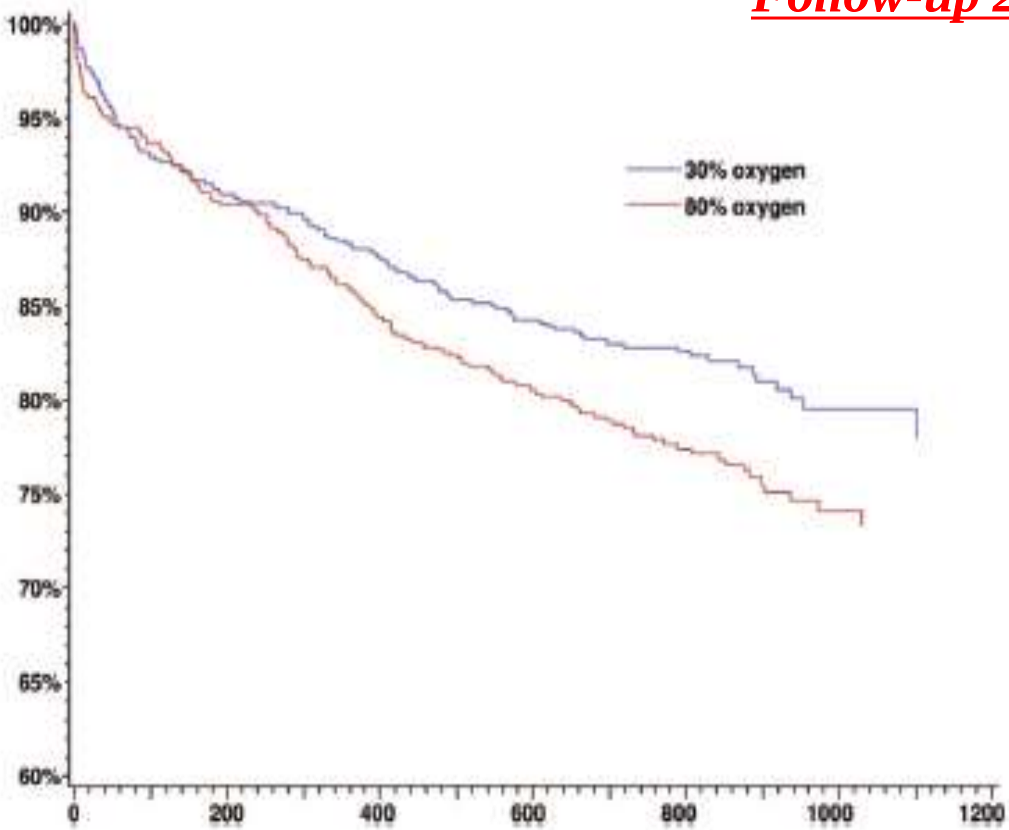
JAMA Surgery 2017;152:784

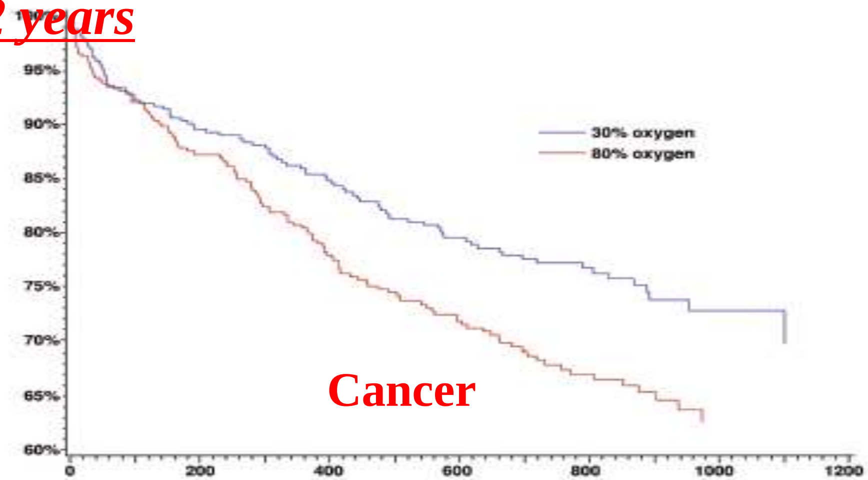
"….Increased FiO_2 should be administered during surgery and after extubation in the immediate postoperative period for patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation…"

Meyhoff et al: Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clincial trial. *Anesth Analg 2012;115:849*

1400 Patients, Urgent- and Elective-Laparotomy, 30% / 80 % O_2 to 2 h post OP;

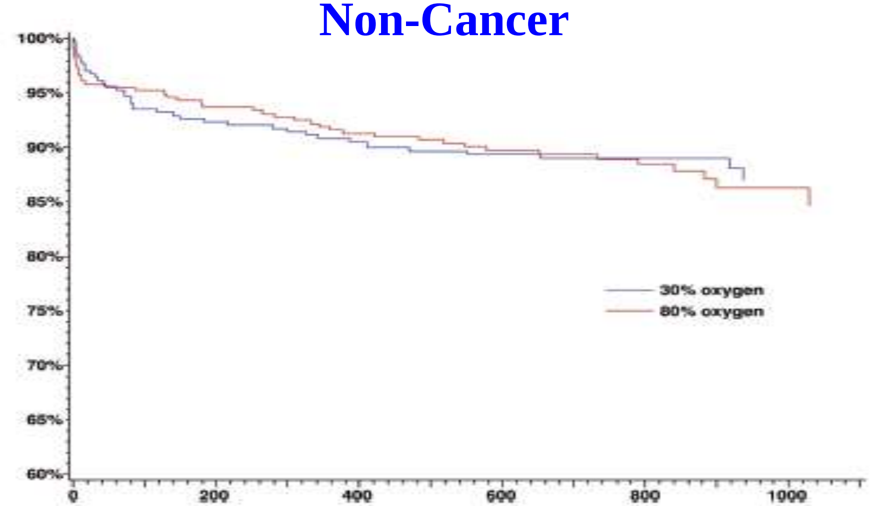
Follow-up 2 years





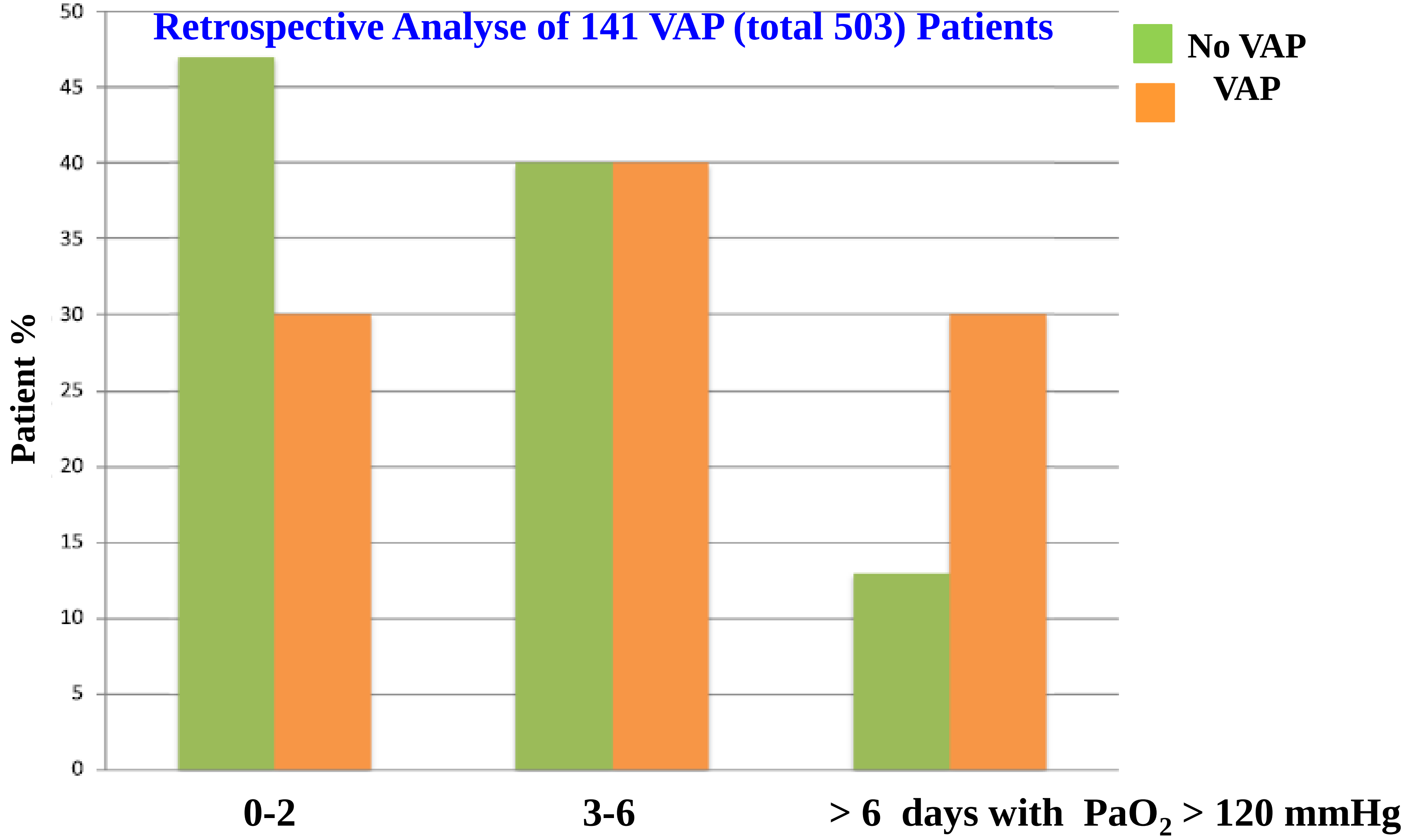
Cancer

Non-Cancer



Hyperoxia and Sepsis

Six et al: Hyperoxemia as a risk factor for ventilator-associated pneumonia. *Crit Care 2016;20:195*



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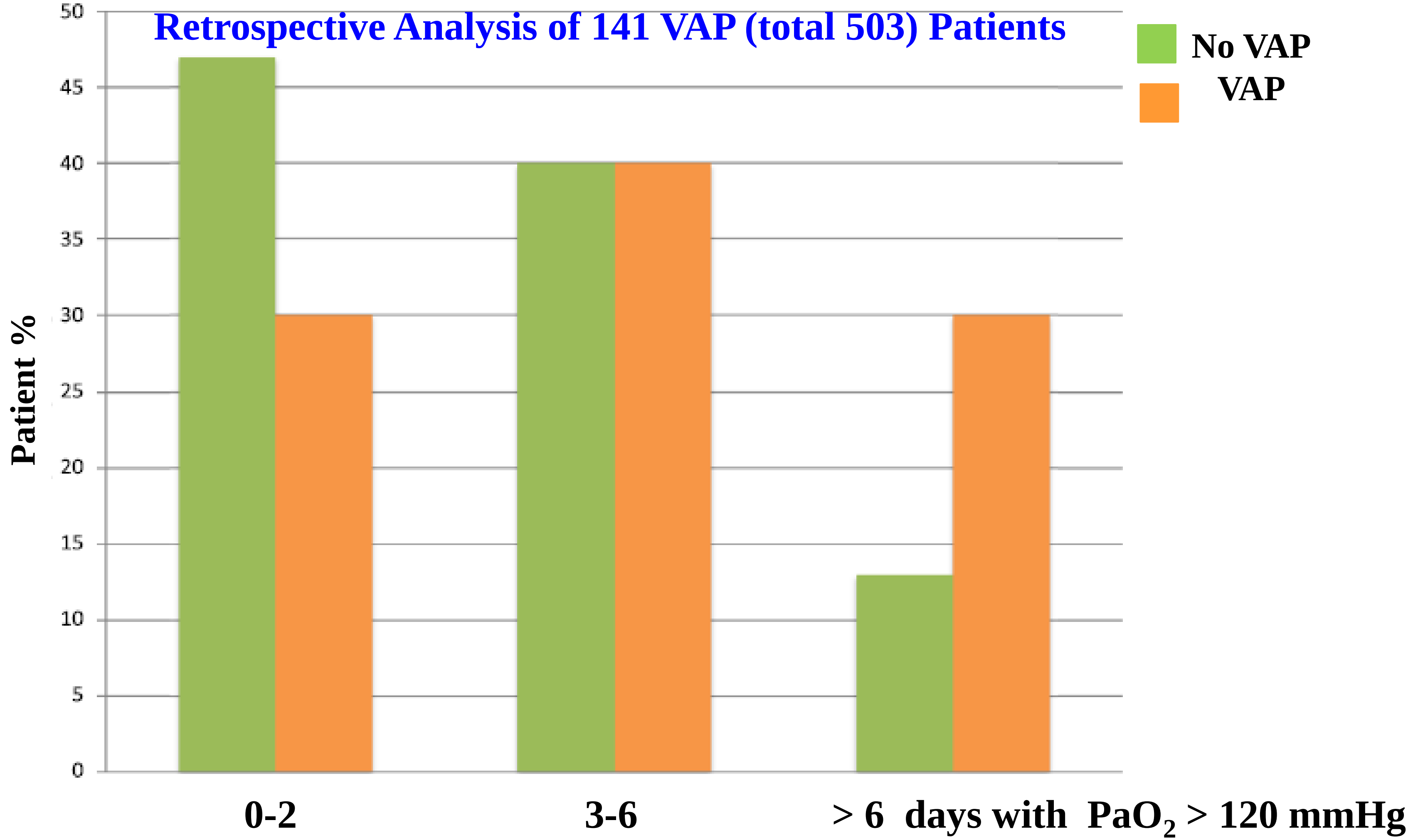
Six et al: Hyperoxemia as a risk factor for ventilator-associated pneumonia.

Crit Care 2016;20:195



But

More PPI, sedation, shocked and RBC-transfused patients!

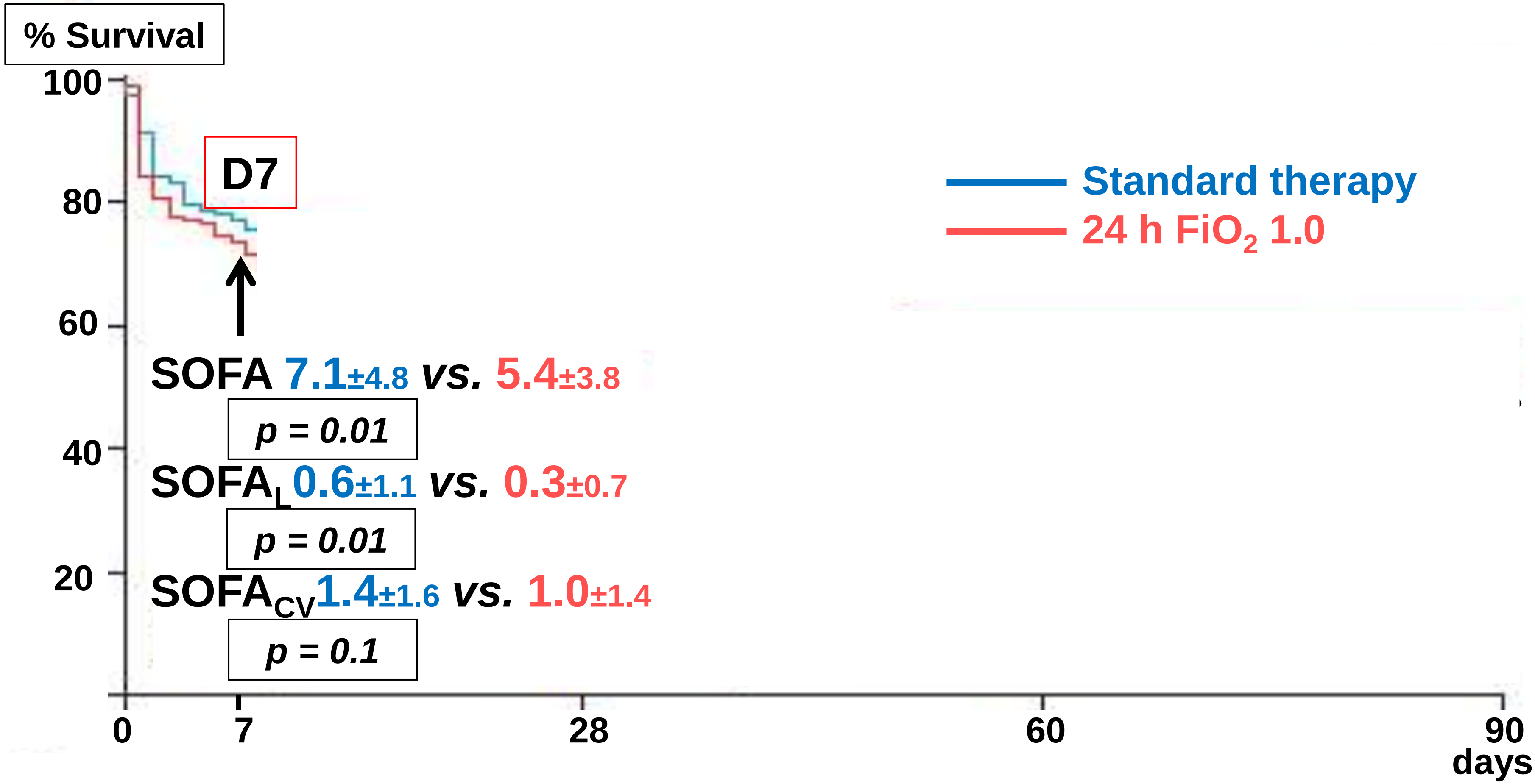
Hyperoxia and Sepsis

Asfar, Schortgen….Radermacher:

Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial.

Lancet Respir Med 2017;180-90

442 patients with septic shock; 24 h FiO_2 1.0 *vs.* standard therapy (SO_2=88-95%)



Hyperoxia and Sepsis

Asfar, Schortgen….Radermacher:

Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial.

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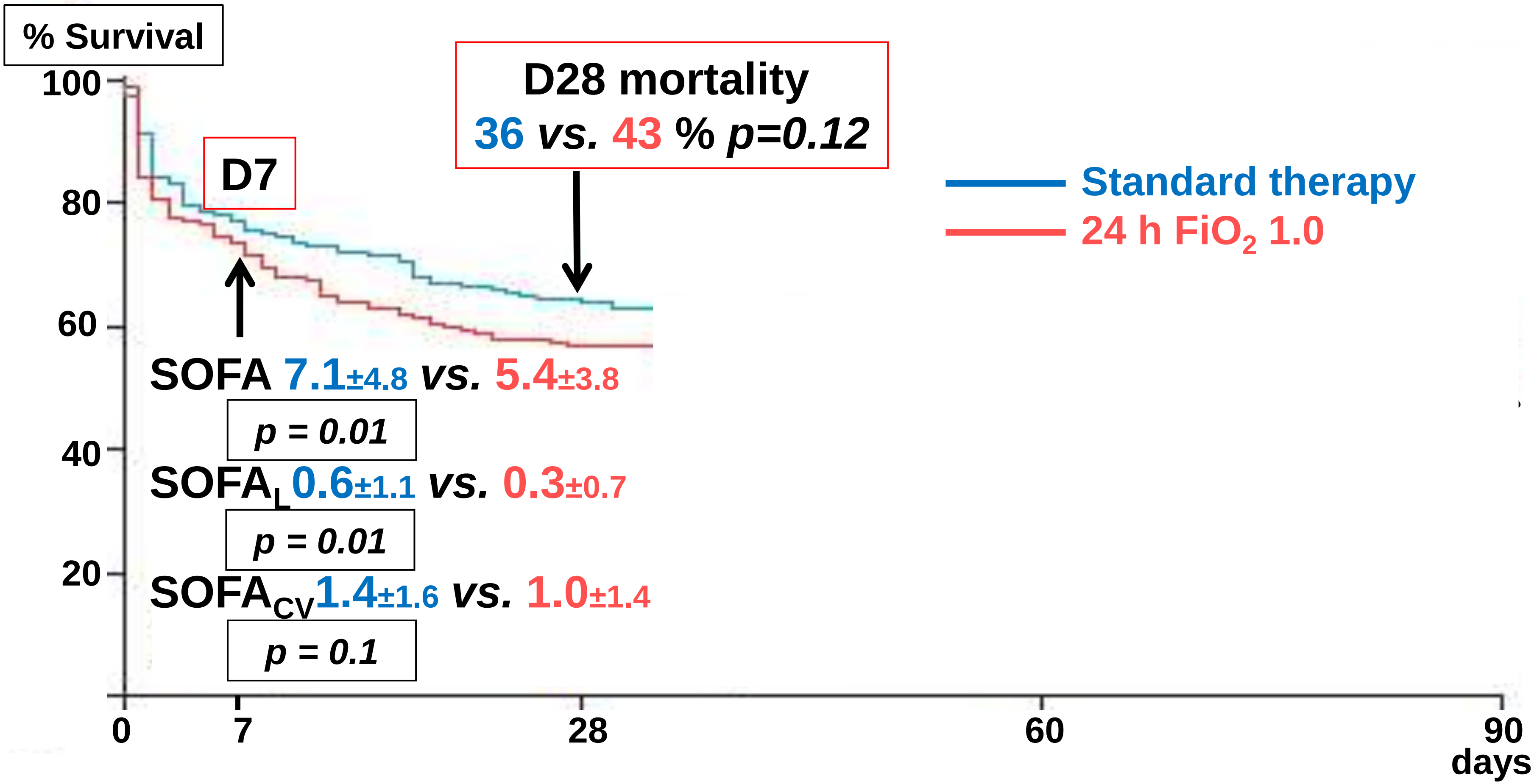

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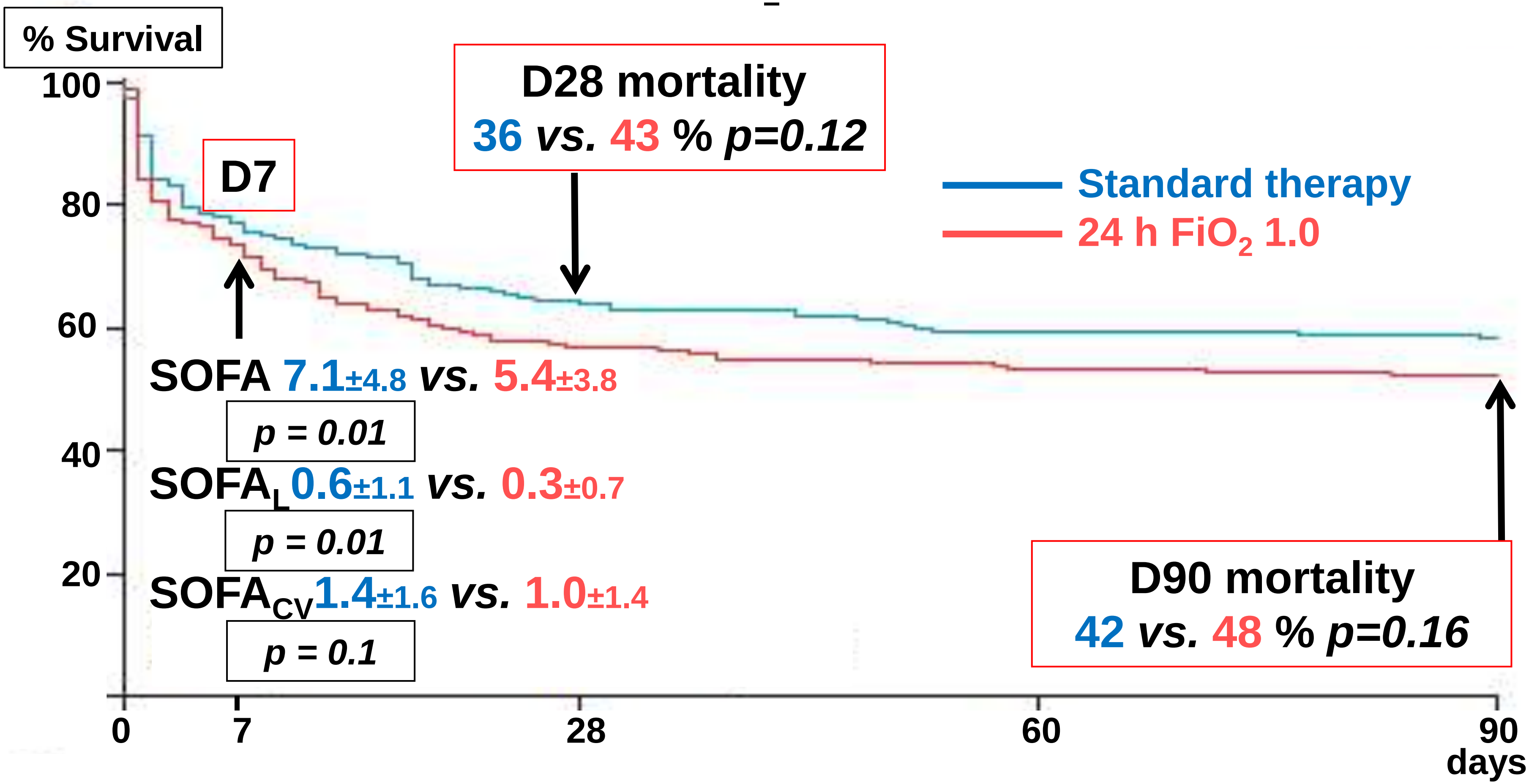

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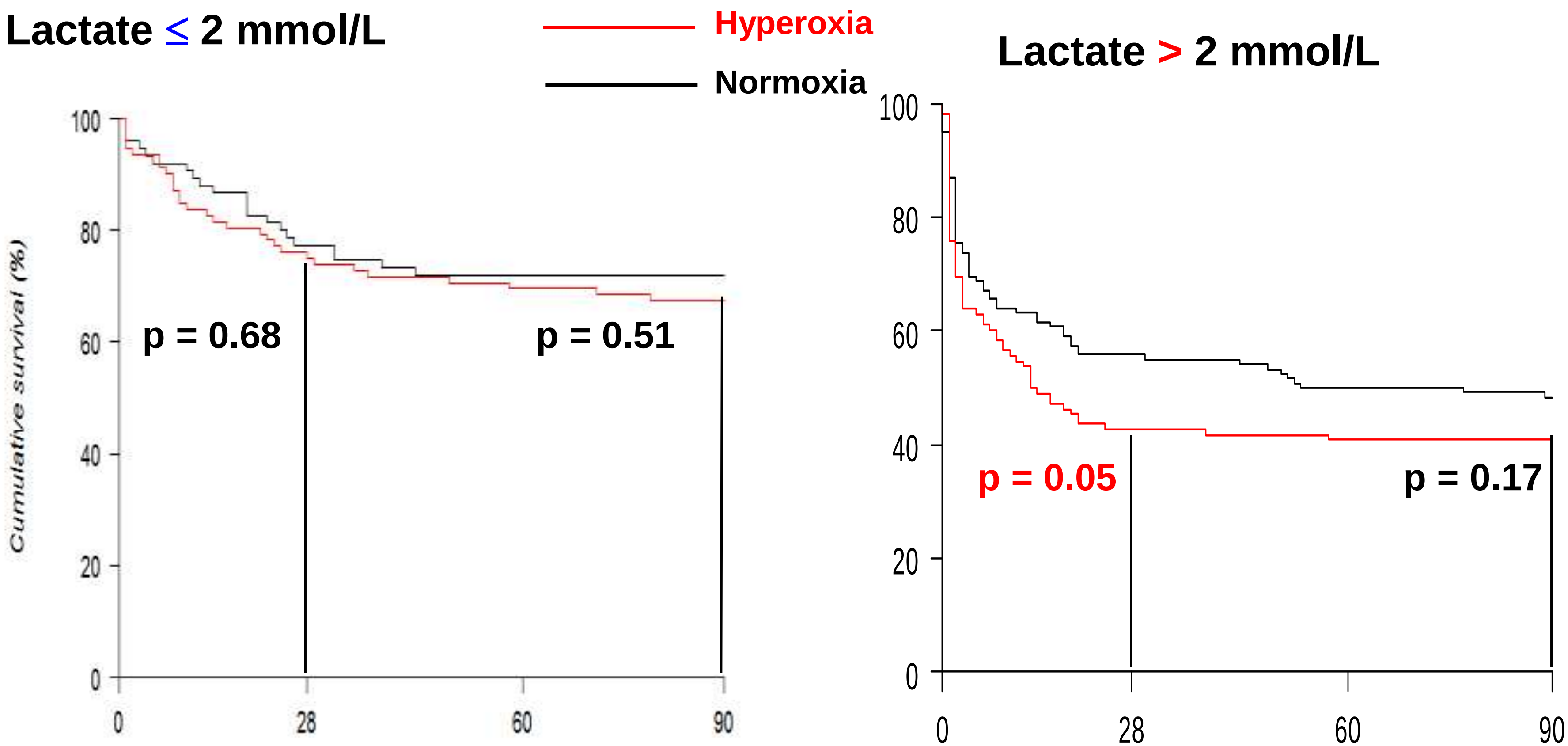
No. (%) patients	Standard therapy	24 h FiO_2 1.0	p value
≥ 1 nosocomial infection	45 (21)	45 (21)	1.0
≥ 1 nosocomial pneumonia	32 (15)	30 (14)	0.78
≥ 1 serious adverse event	165 (76)	185 (85)	0.02
Atelectasis	13 (6)	26 (12)	0.04
ICU-acquired weakness	13 (6)	24 (11)	0.06

Hyperoxia and Sepsis

Demiselle, Wepler, Hartmann et al:
***A post hoc* analysis of the HYPER2S trial using the Sepsis-3 criteria.**
submitted



Hyperoxia and traumatic brain injury

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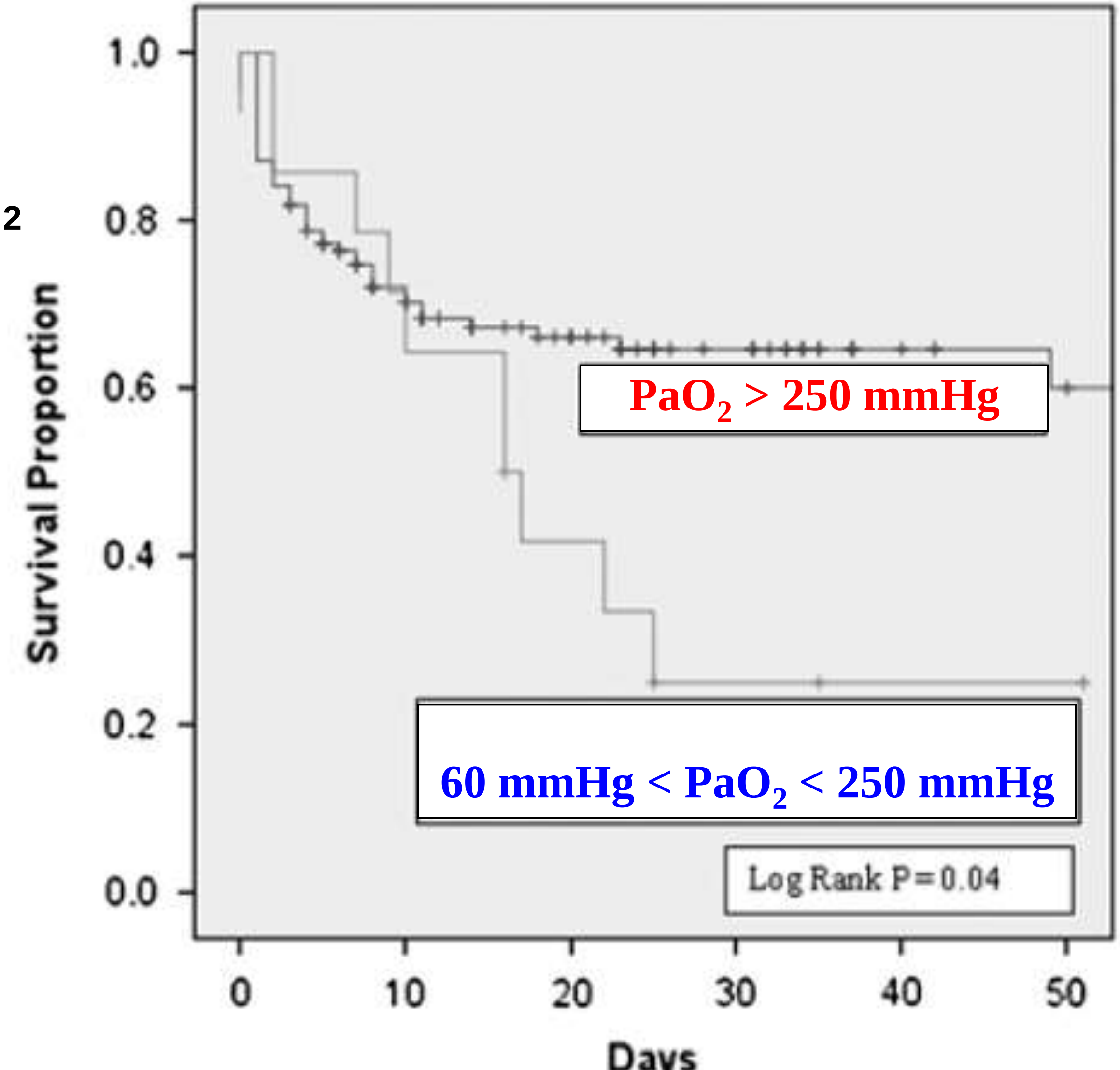
Hyperoxia and TBI

Asher et al:
Survival advantage and PaO_2 threshold in severe traumatic brain injury.
J Neurosurg Anesthesiol 2013:25:168

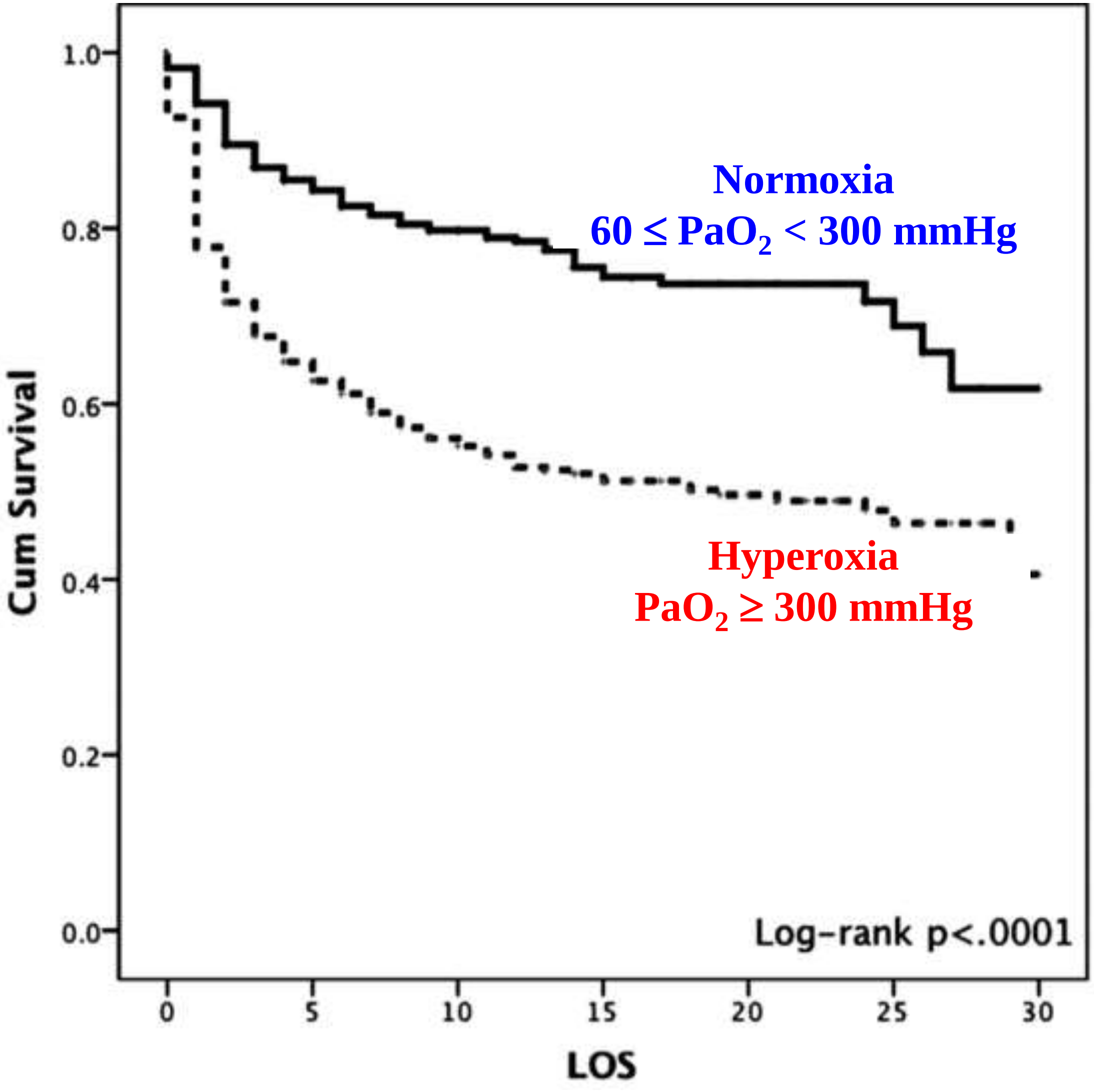
n=193; GCS < 8



Hyperoxia and TBI

Rincon et al:
Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicenter cohort study.
J Neurol Neurosurg Psychiatry 2014:85:799

n=1212 during 5 years
mechanically ventilated



Hyperoxia and TBI

"…The emerging clinical experience demonstrates that hyperoxia is safe and beneficial to the brain…"

" "

Narotam:

Eubaric hyperoxia: controversies in the management of acute traumatic brain injury.

Crit Care 2013;17:197

" …Hyperoxia may be associated with increased mortality in patients with (...) traumatic brain injury…"

Damiani et al.

Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis.

Crit Care 2014;18:711

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Hyperoxie und SHT

Taher et al: **Effects of normobaric hyperoxia in traumatic brain injury: a randomized controlled clinical trial.** ***Trauma Mon 2016;21:e26772*** ***prospective!***

"… oxygen therapy…in the first 6 hours after injury in patients with severe TBI can improve the final GOS, barthel index, and mRS scores… " (n=68)

Fujita et al: **Early-stage hyperoxia is associated with favorable neurlogical outcomes and survival after severe traumatic brain injury: a post-hoc analysis of the Brain Hypothermia study.** ***J Neurotrauma Mon 2017;34:1565-70*** ***retrospective!***

"… PaO_2 was independently associated with survival… hyperoxia might be associated with favorable neurological outcomes…following severe TBI" (n=129)

Russel et al: **Early exposure to hyperoxia and mortality in critically ill patients with severe traumatic injuries.** ***BMC Pulm Med 2017;17:29*** ***retrospective!***

"… In the subgroup with head trauma (n=266)…maximum PaO_2 was not associated with increased mortality"

Lång et al: **A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress.** ***Acta Anaesthesiol Scand 2018; doi: 10.1111/aas.13093***

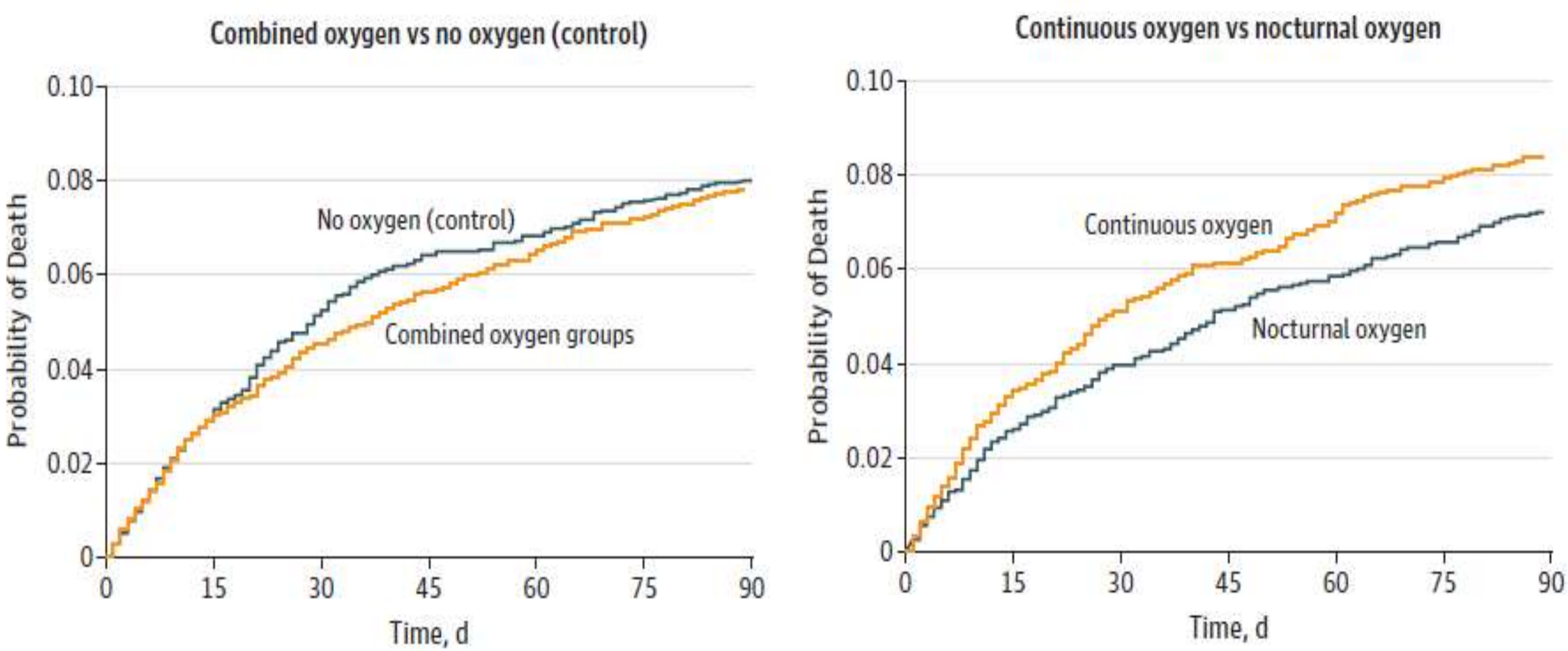
"… Higher fraction of inspired oxygen (n=27) did not increase…oxidative stress, inflammation or neurological injury… in severe TBI…

Hyperoxia and Stroke

Roffe et al: **Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke. *JAMA 2017;318:1125***

8003 Patients; 2-3 L/min O_2 72 h after stroke onset , night/oxygen if/$S_{tc}O_2$ < 93%;

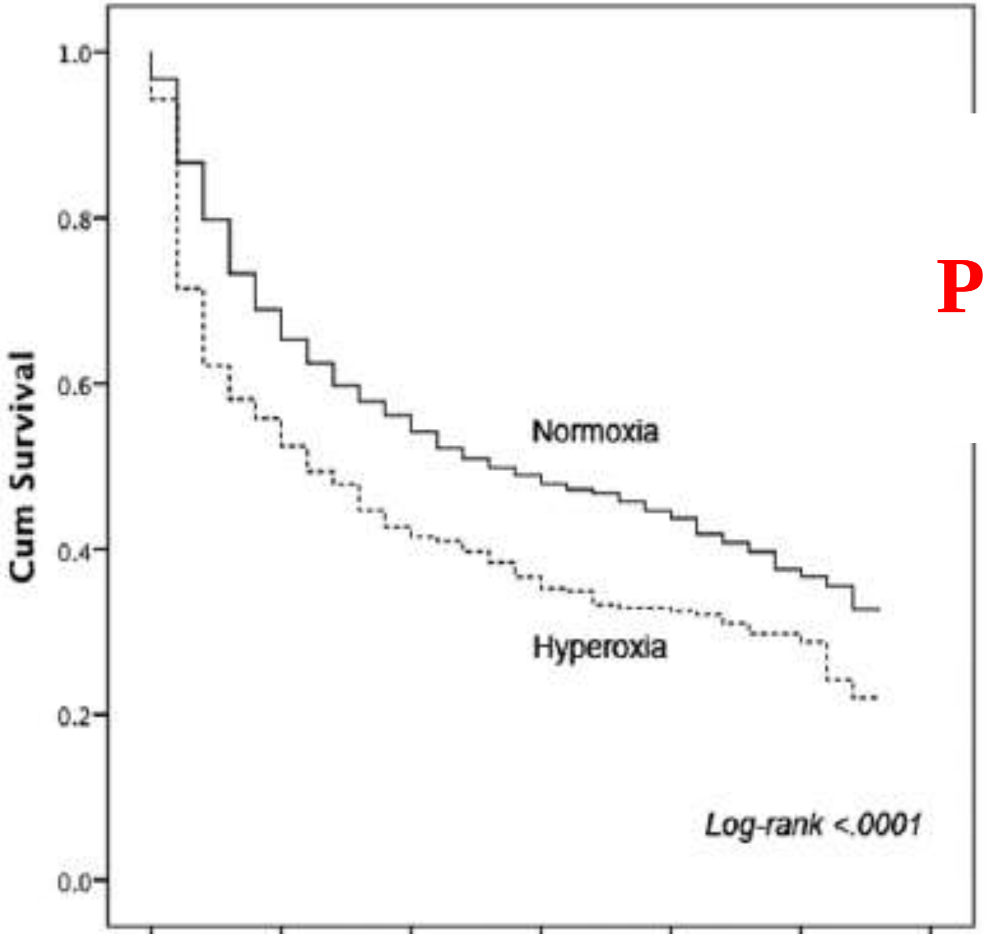
⇒ ∅ Effect!



Hyperoxia and Stroke

Rincon et al: **Hyperoxemia and long-term outcome after traumatic brain injury.** ***Crit Care Med 2014;42:387***

n=2894 (AIS 19%; SAH 32%; ICH 49%)



Hyperoxia (n = 1084)

PaO_2 > 300 mmHg → 16% (n = 450)

Hyperoxia and Stroke

Jeon et al: **Hyperoxemia may be related to *delayed cerebral ischemia (DCI)* and poor outcome after subarachnoidal haemorrhage.**

J Neurol Neurosurg Psychiatry 2014;85:1301

n=252 prospective observational

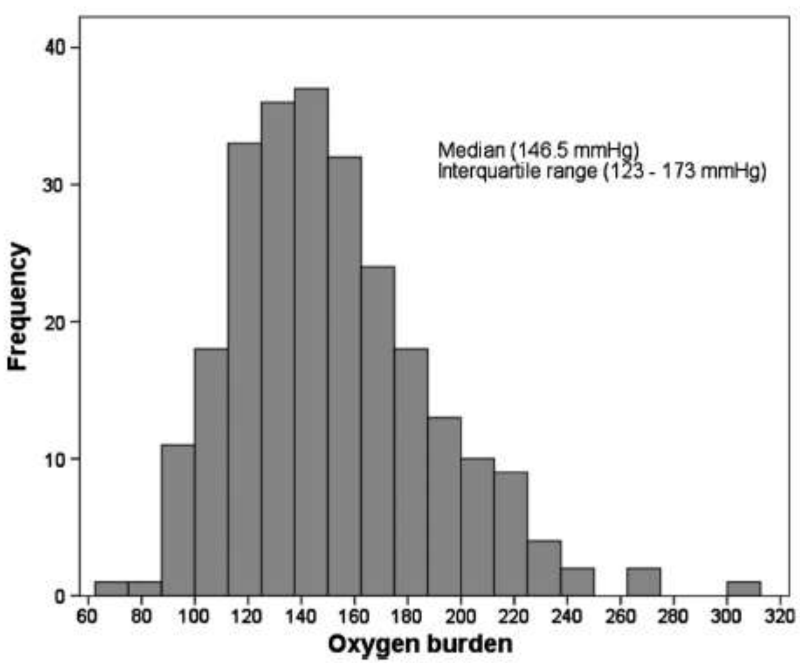
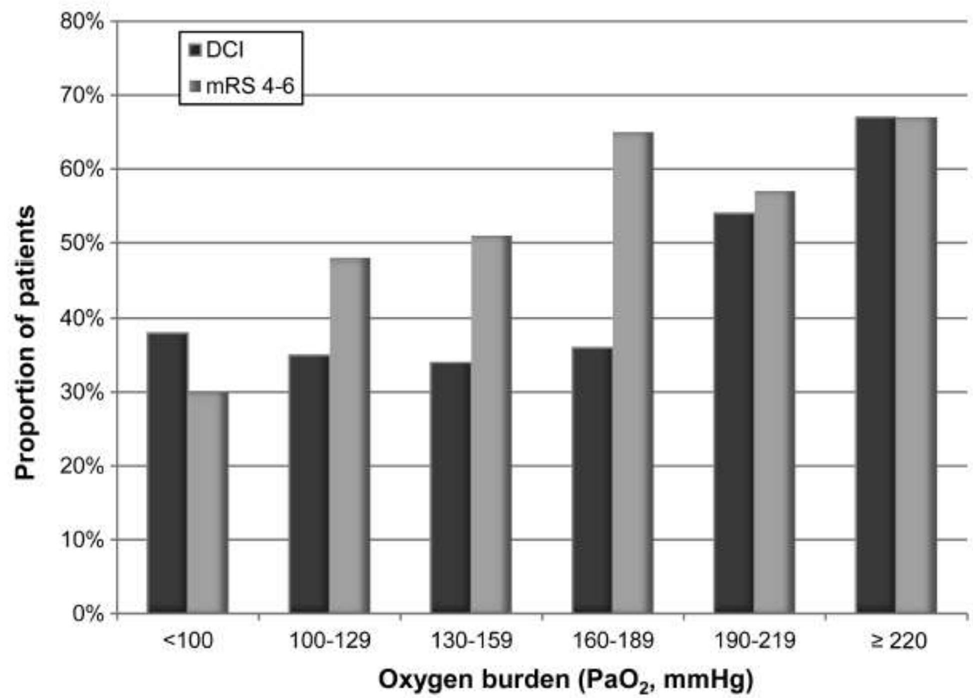


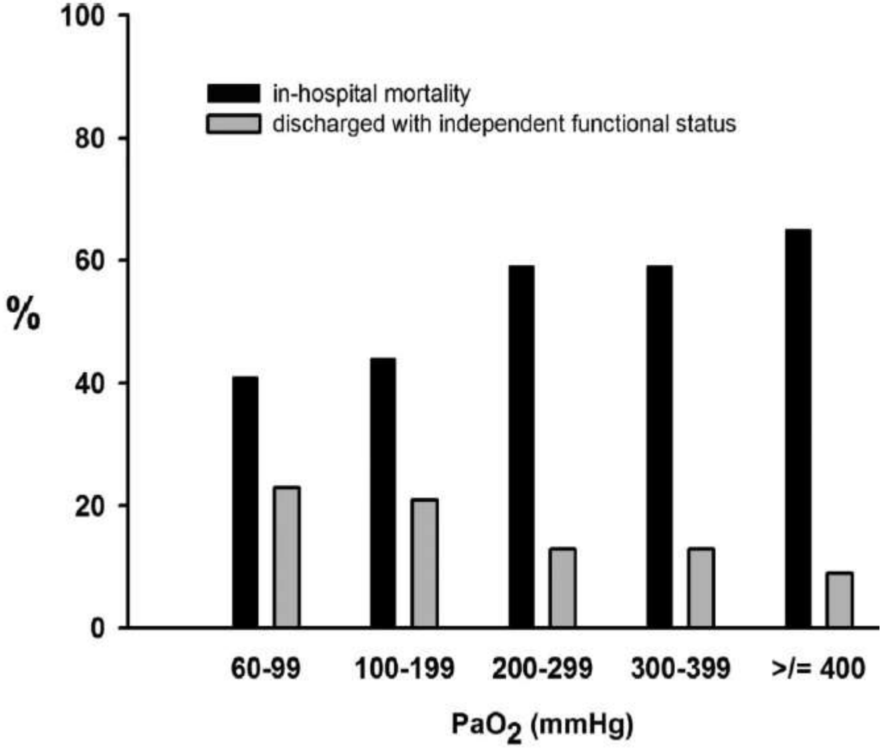
Figure 1 Distributions of oxygen burden.

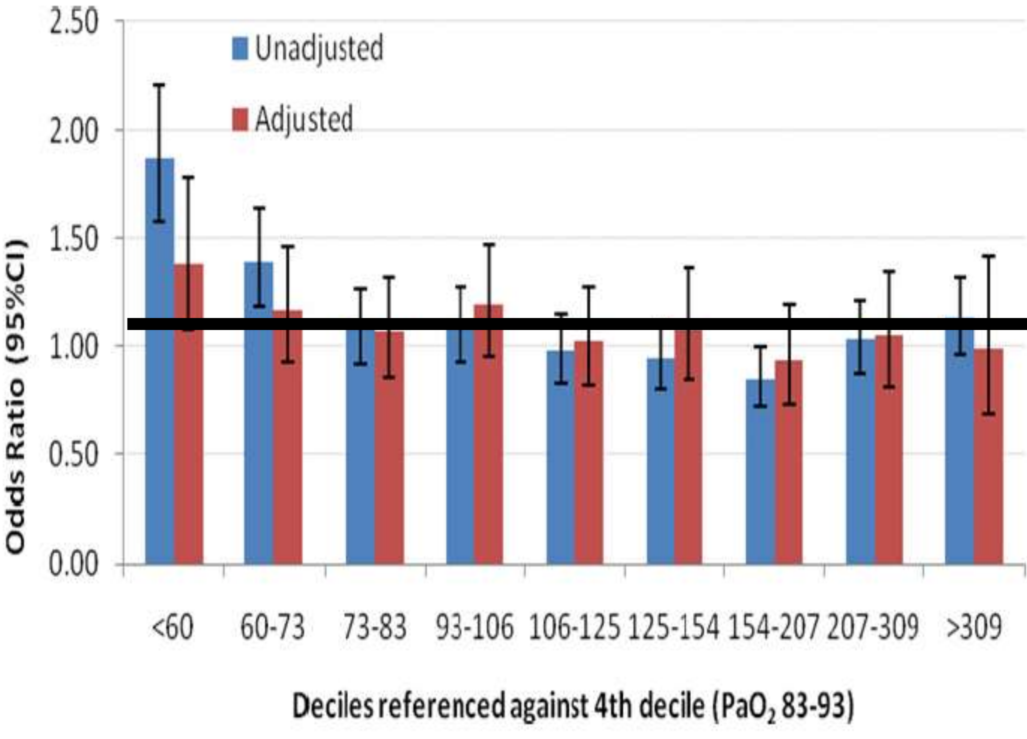
mRS: modified Ranson Scale



Hyperoxia and CPR

Hyperoxia and CPR





Kilgannon *JAMA 2010* 6326 patients

Bellomo *Crit Care 2011* 12108 patients

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Roberts et al:

Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: a prospective multi-center protocol-derived cohort study.

Circulation 2018;137:2114

105/280 (38%) Patients, PaO_2 > 300 mmHg during the 6 first h after ROSC; Poor outcome = Rankin Scale > 3 (70% of patients)

- **77% _vs._ 65% PaO_2 > 300 mmHg ⇒ poor neurological function [relative risk 1.23 (95% CI 1.11-1.35)])**
- **1-h longer duration ⇒ 3% increase in risk of poor neurological outcome [relative risk 1.03 (95% CI 1.02-1.05)]**
- **association with poor neurological outcome PaO_2 > 300 mmHg**

Hyperoxia and CPR

Helmerhorst et al: **Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meataanalysis, and meta-regression of cohort studies.**

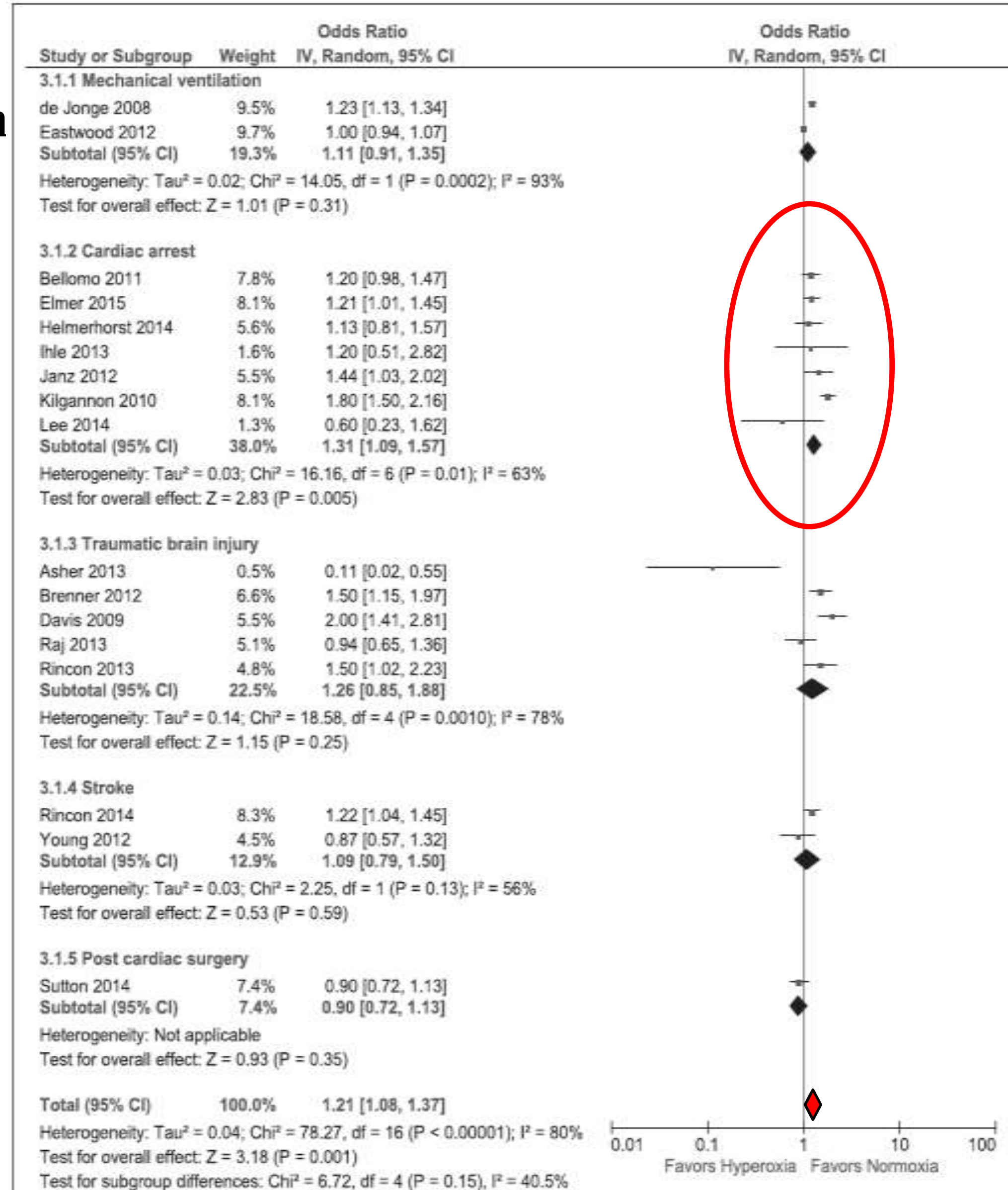
Crit Care Med 2015;43:1508-19

"..Considering the substantial heterogeneity..more evidence is needed.."

Damiani et al: **Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis.**

Crit Care 2014;18:711

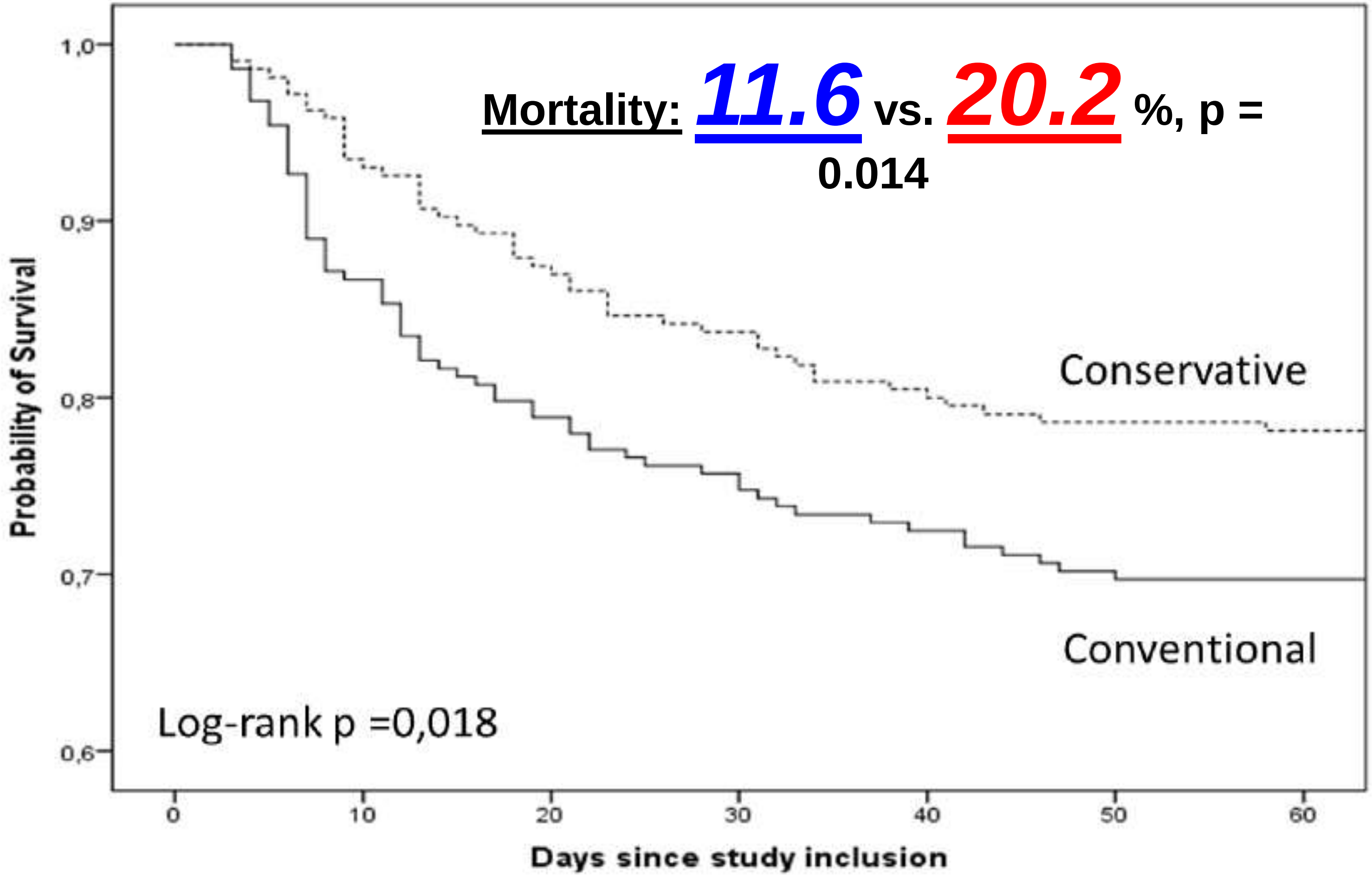
"..However,..results are limited by the high heterogeneity.."



Hyperoxia and ICU Outcome

Girardis et al: **Effect of *conservative* vs. *conventional* oxygen therapy on mortality among patients in an ICU. *JAMA* 2016;316:1583-9**

434 Patients, PaO_2/SaO_2 70-100 mmHg/94-98 % vs. PaO_2/SaO_2 -150 mmHg/97-100%



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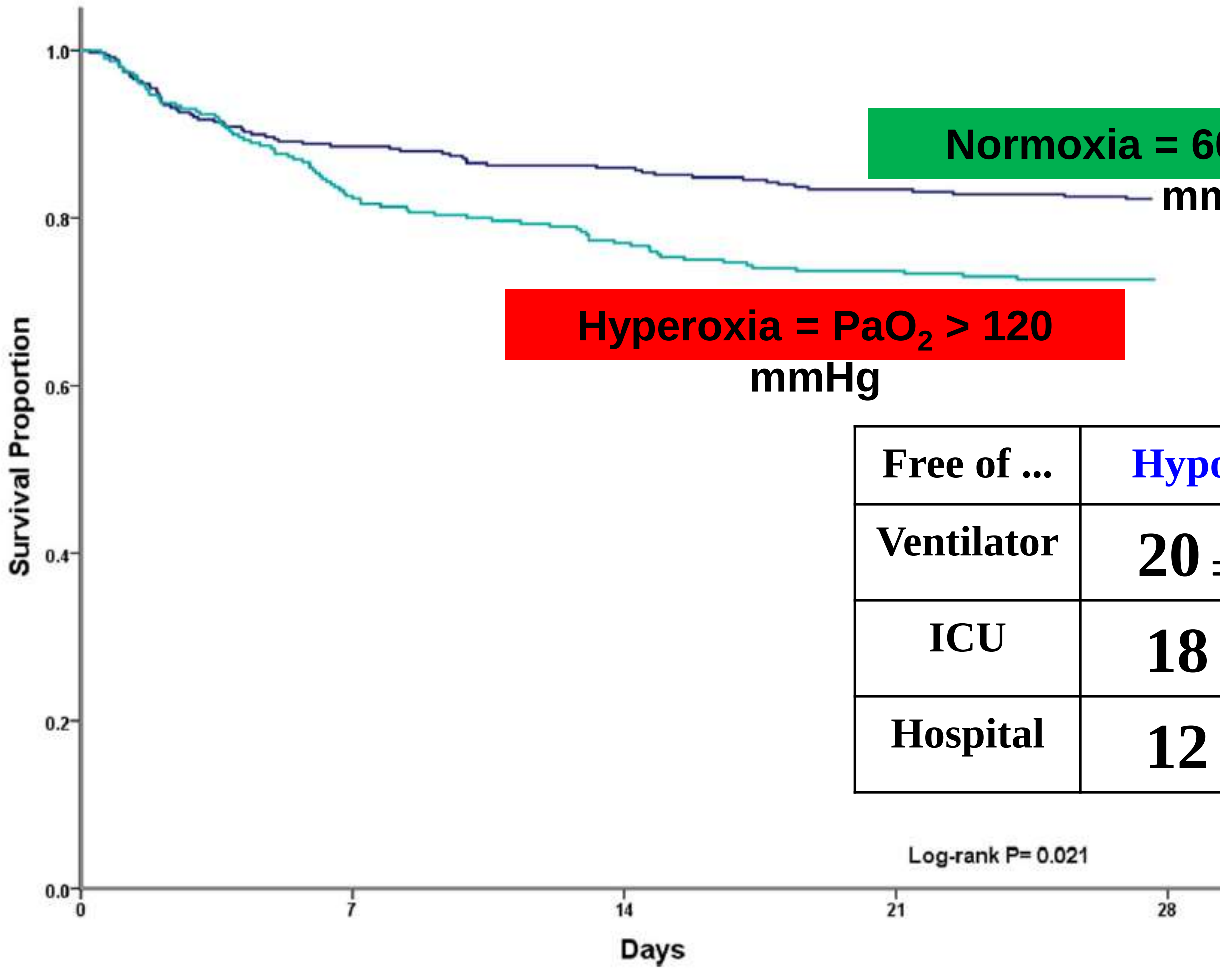
	Conservative	Conventional	p-value
Shock	8 (3.7 %)	23 (10.6 %)	0.006
Liver failure	4 (1.9 %)	14 (6.4 %)	0.02
Bacteremia	11 (5.1 %)	22 (10.1 %)	0.049

Hyperoxia and ED Outcome

Page et al: **Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study.** ***Crit Care 2018;22:9***

Retrospective, 688/3525 ventilated ER patients

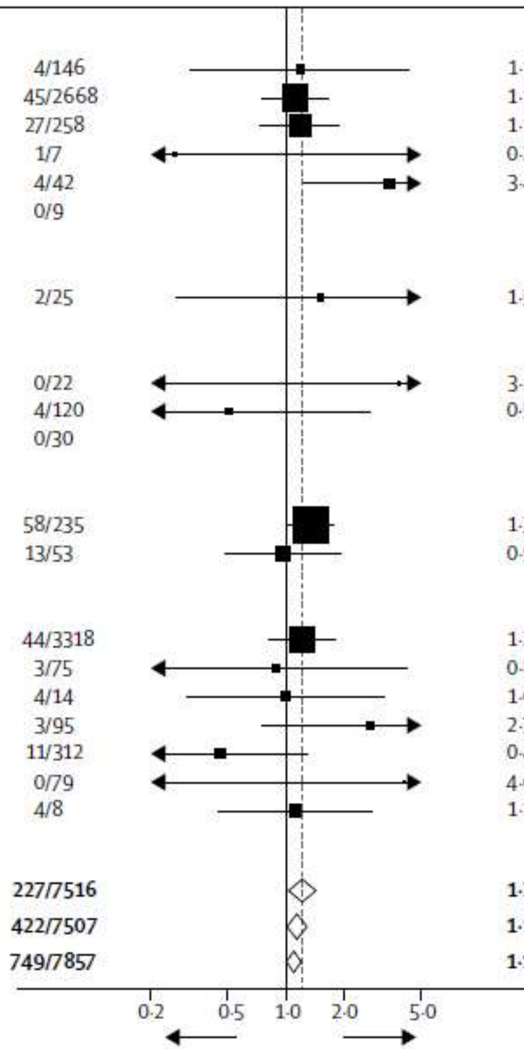


Free of ...	Hypoxia	Normoxia	Hyperoxia
Ventilator	20 ± 10	18 ± 10	14 ± 11
ICU	18 ± 9	17 ± 10	13 ± 11
Hospital	12 ± 9	11 ± 9	9 ± 9

Hyperoxia and ICU Outcome

Chu et al: **Mortality and morbidity in acutely il adults treated with liberal versus conservative oxygen therapy (IOTA): a systemic review and meta-analysis. *Lancet 2018;391:1693***

	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**



Hyperoxia and ICU Outcome

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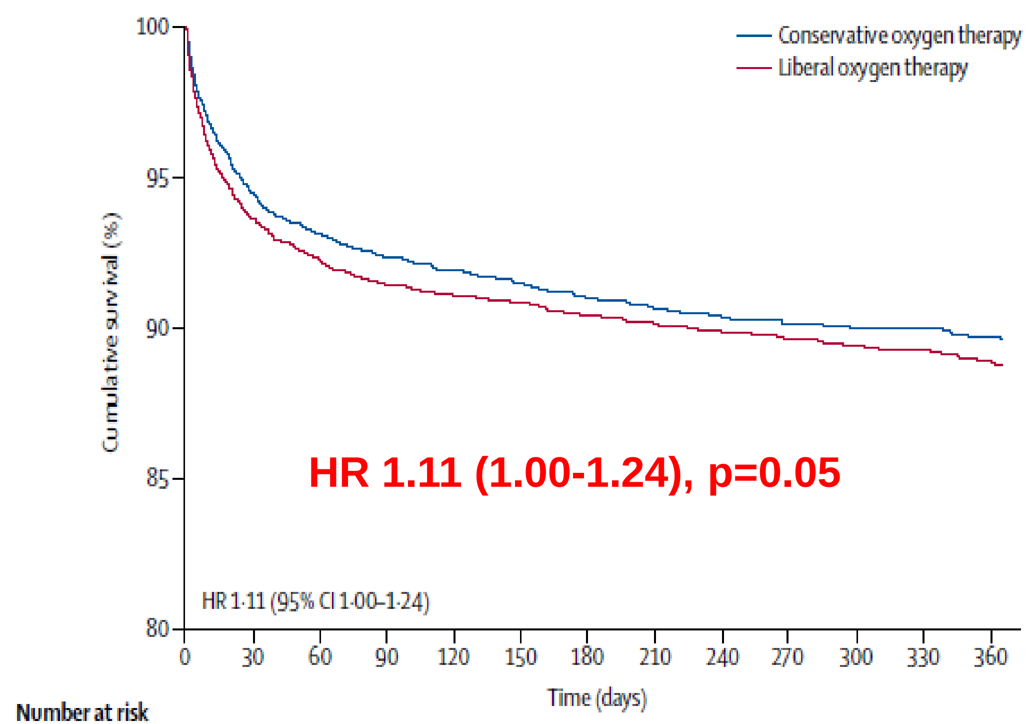
Meta-Analyse from 25 RCT with16.037 Patients!



Number at risk

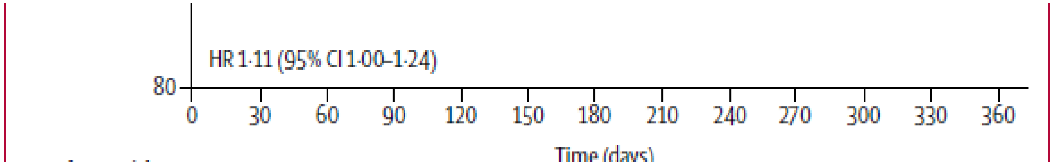
Conservative	6900	6484	6372	6130	3542	3527	3507	3372	3361	3352	3345	3344	3334
Liberal	6943	6450	6345	6119	3564	3554	3539	3402	3390	3381	3370	3365	3351

Hyperoxia and ICU Outcome

Chu et al: **Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systemic review and meta-analysis.** ***Lancet 2018;391:1693***

Meta-Analyse from 25 RCT with16.037 Patients!

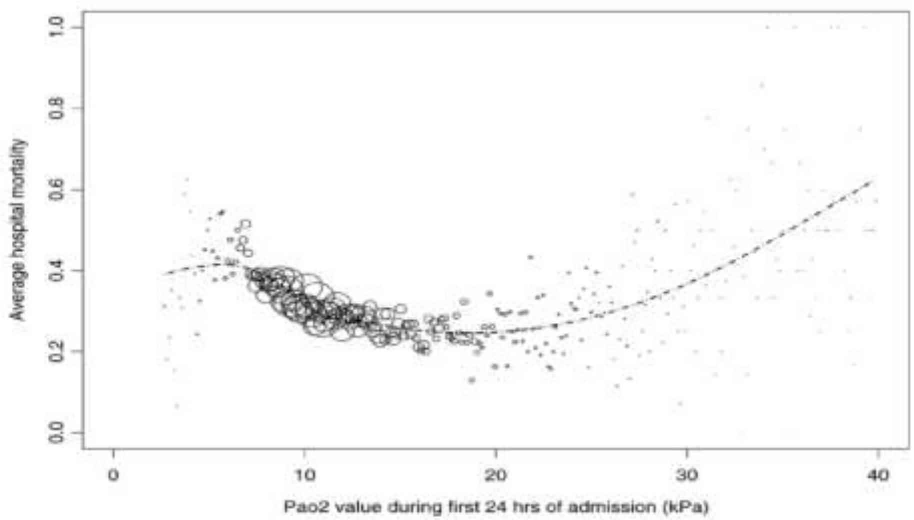
Interpretation In acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO_2 range of 94–96%. These results support the conservative administration of oxygen therapy.

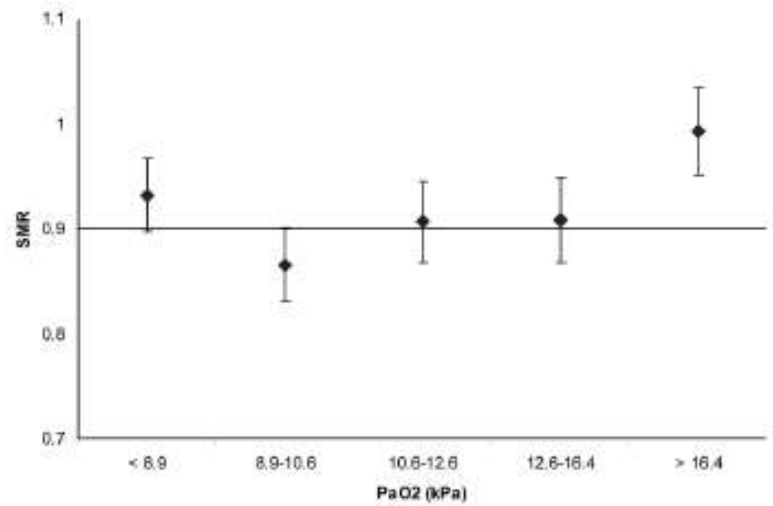


Number at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
Conservative	6900	6484	6372	6130	3542	3527	3507	3372	3361	3352	3345	3344	3334
Liberal	6943	6450	6345	6119	3564	3554	3539	3402	3390	3381	3370	3365	3351

Optimal PO_2?

de Jonge et al:* Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care patients. *Crit Care 2008;12:R156

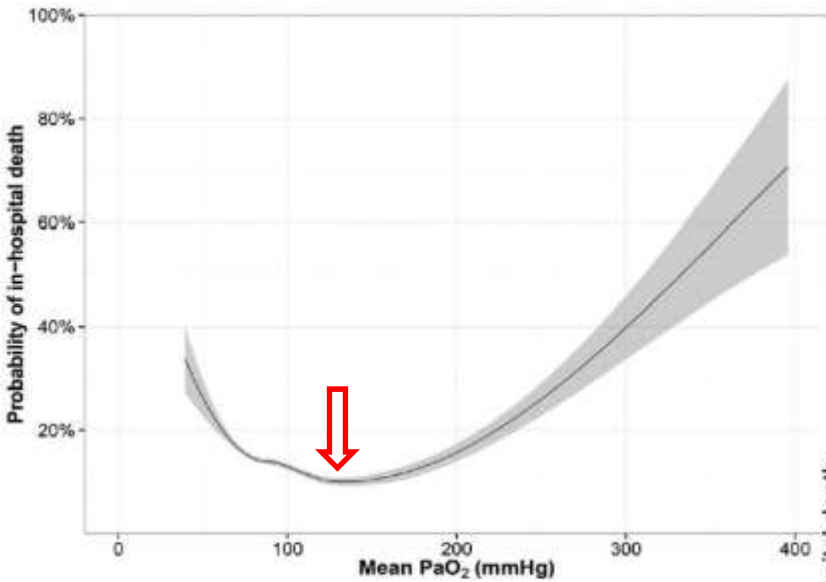




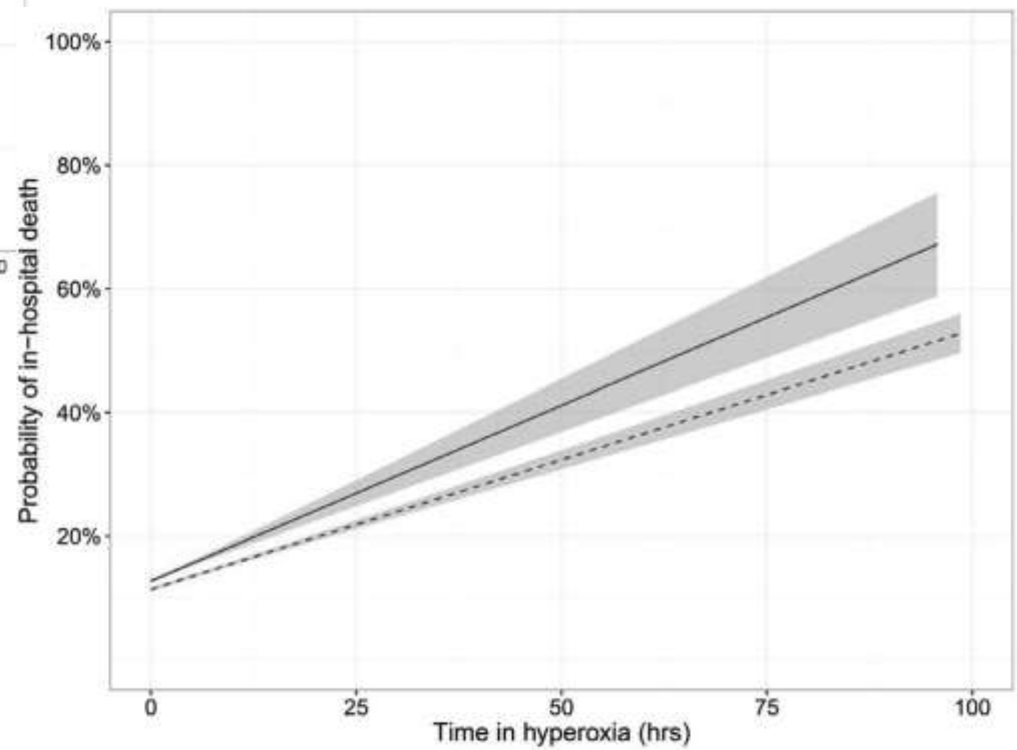
36 000 pts, 50 centers

Optimal PO_2?

Helmerhorst et al:* Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med 2017;45:187-95



14 000 pts 3 centers



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

Pierre Asfar, Frédérique Schortgen, Julie Boisramé-Helms, Julien Charpentier, Emmanuel Guérot, Bruno Megarbane, David Grimaldi, Fabien Grelon, Nadia Anguel, Sigismond Lasocki, Matthieu Henry-Lagarrigue, Frédéric Gonzalez, François Legay, Christophe Guitton, Maleka Schenck, Jean Marc Doise, Jérôme Devaquet, Thierry Van Der Linden, Delphine Chatellier, Jean Philippe Rigaud, Jean Dellamonica, Fabienne Tamion, Ferhat Meziani, Alain Mercat, Didier Dreyfuss, Valérie Seegers, Peter Radermacher, for the HYPER2S Investigators* and REVA research network

	Normoxia (n=217)	Hyperoxia (n=217)	Isotonic saline (n=220)	Hypertonic saline (n=214)
PaO_2:FiO_2 ratio (mm Hg)				
Mean (SD)	228 (103)	220 (103)	223 (106)	225 (100)
Median (IQR)	200 (140–280)	198 (145–263)	196 (140–266)	200 (145–282)
Patients with PaO_2 >120 mm Hg	121 (56%)	110 (51%)	107 (49%)	124 (58%)
ARDS with PaO_2:FiO_2 ratio <200 mm Hg	107 (49%)	114 (53%)	114 (52%)	107 (50%)

Lancet Respir Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Frat JP et al NEJM 2014

Table S5. Assessment of tolerance to the oxygenation strategy at inclusion and 1 hour after inclusion *

	High-Flow Oxygen group (n=106)	Standard Oxygen group (n=94)	NIV group (n=110)	P Value
PaO_2 – mm Hg				<0.05
H1	106±66	91±32	118±72	<0.05
H6	90±35	93±36	111±59	<0.01
FIO_2 §				
H1	0.82±0.21	0.66±0.16	0.67±0.24	<0.001
H6	0.75±0.22	0.64±0.18	0.63±0.21	<0.001

SpO2 : Quels messages ?

- SpO2 = 100 % → Situation à risque

  - PaO2 possiblement très élevée

  → Risque lié à l'hyperoxie

  → Perte de la pertinence de la SpO2 pour détecter précocement un événement clinique

- Précision SpO2 assez médiocre

  → Prudence avec les SpO2 « limites » (88 % - 90 %)

- SpO2 92 % - 96 % : Objectif raisonnable dans l'attente des résultats des études en cours

CONCLUSIONS

Données convergentes sur les effets toxiques de l'administration libérale d'oxygène.

L'hyperoxie > 120 mm Hg est très fréquente.

Si les effets à court terme de l'oxygène sont plutôt favorables les effets secondaires à moyen et long terme sont inquiétants.

En attendant les résultats des essais en cours une PaO_2 en deçà de 90-100 mm Hg est un objectif raisonnable.