HFNO use

in acute respiratory failure

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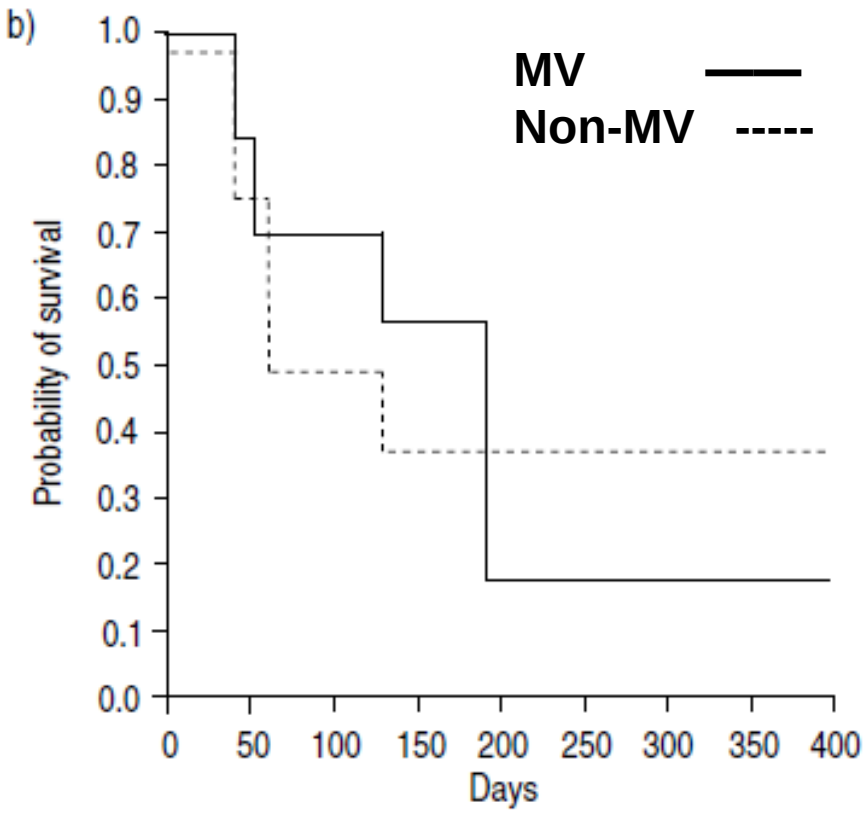
Old dreams to make a detour to invasive MV

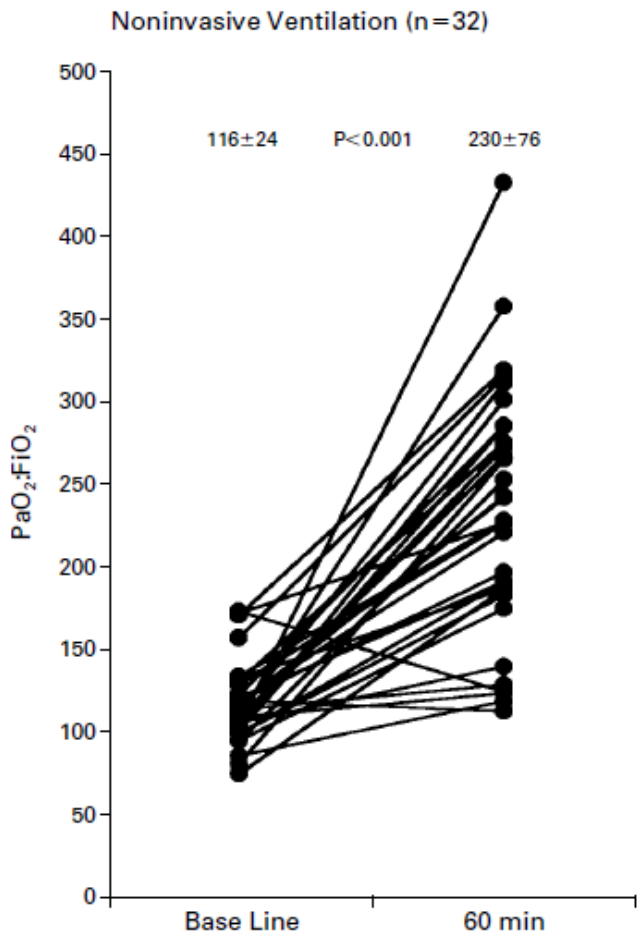
Why NIV ?

- **Mechanical ventilation(MV) is prognostic factor in acute hypoxemic respiratory failure in HIV pts.**



Eur Respir J 1995: 8;1922–28

Non-invasive ventilation VS invasive MV - acute hypoxemic respiratory failure



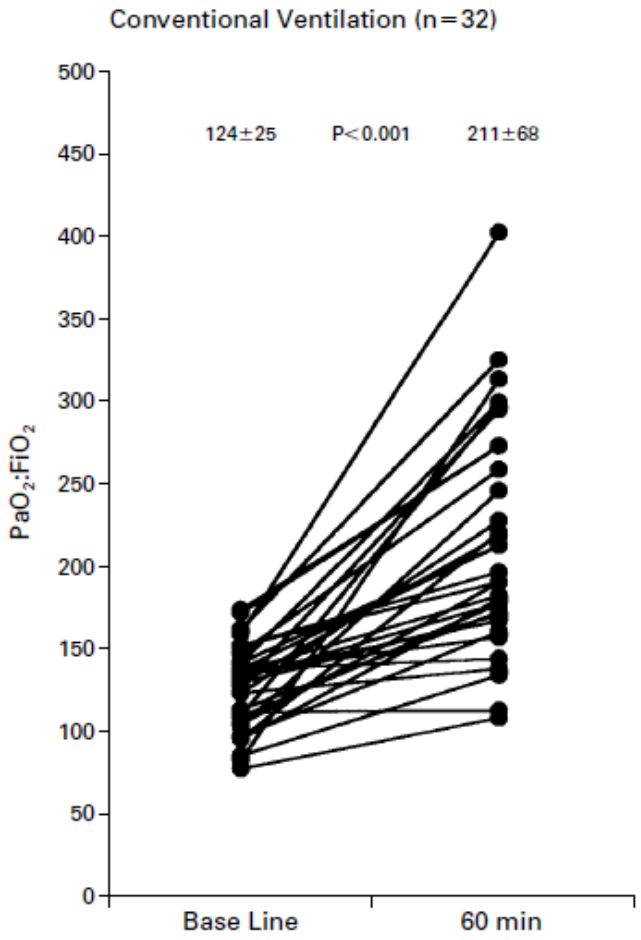
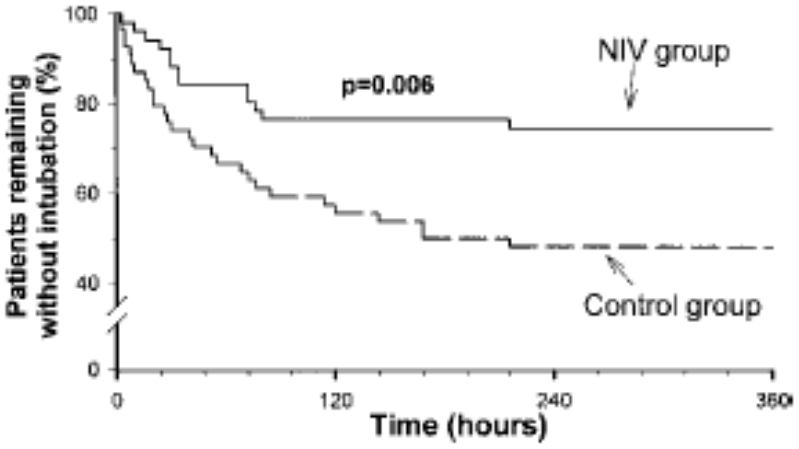


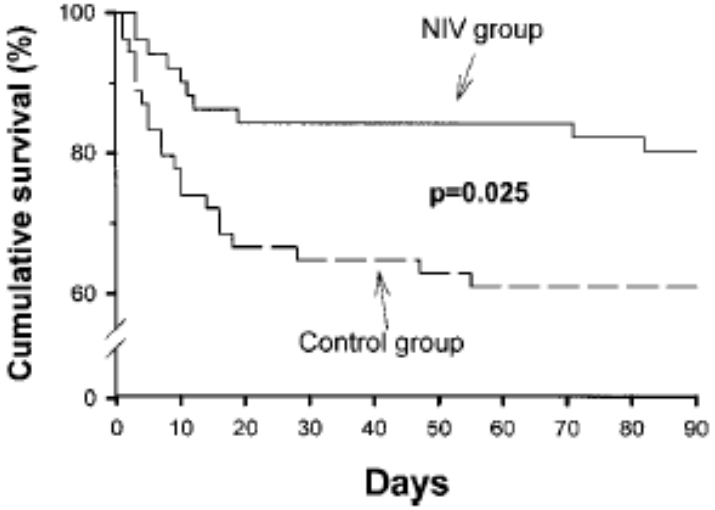
Table 2. Serious Complications and Complications Resulting in Death.

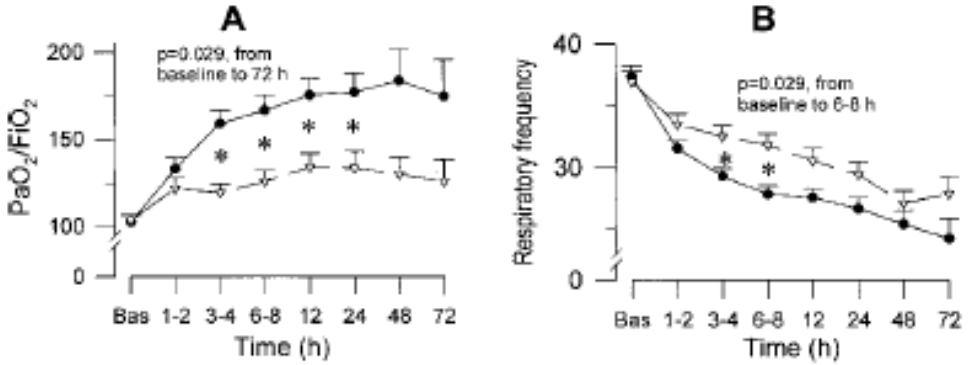
Variable*	Noninvasive-Ventilation Group (N=32)	Conventional-Ventilation Group (N=32)
Patients with complications — no. (%)†	12 (38)	21 (66)
Patients with complications causing death in ICU — no.	9	15
No. of complications per patient‡	1.3	1.7
Death after discharge from ICU — no.	1	1
Complications — total no./no. causing death in ICU (% of group)§		
Myocardial infarction or cardiogenic shock	2/2 (6)	4/4 (12)
Sepsis¶	6/5 (19)	11/6 (34)
Renal failure	3/0 (9)	5/0 (16)
Pancreatitis	1/0 (3)	1/1 (3)
Polyneuropathy of the critically ill	0/0	1/0 (3)
Pneumonia‖	1/0 (3)	8/2 (25)§
Sinusitis‖	0/0	2/0 (6)
Pulmonary embolism	0/0	1/1 (3)
Massive blood loss	0/0	1/1 (3)
Infection at study entry**	2/2 (6)	0/0

N Engl J Med 1998;339:429-35

NIV vs Conventional oxygen therapy -acute hypoxemic respiratory failure



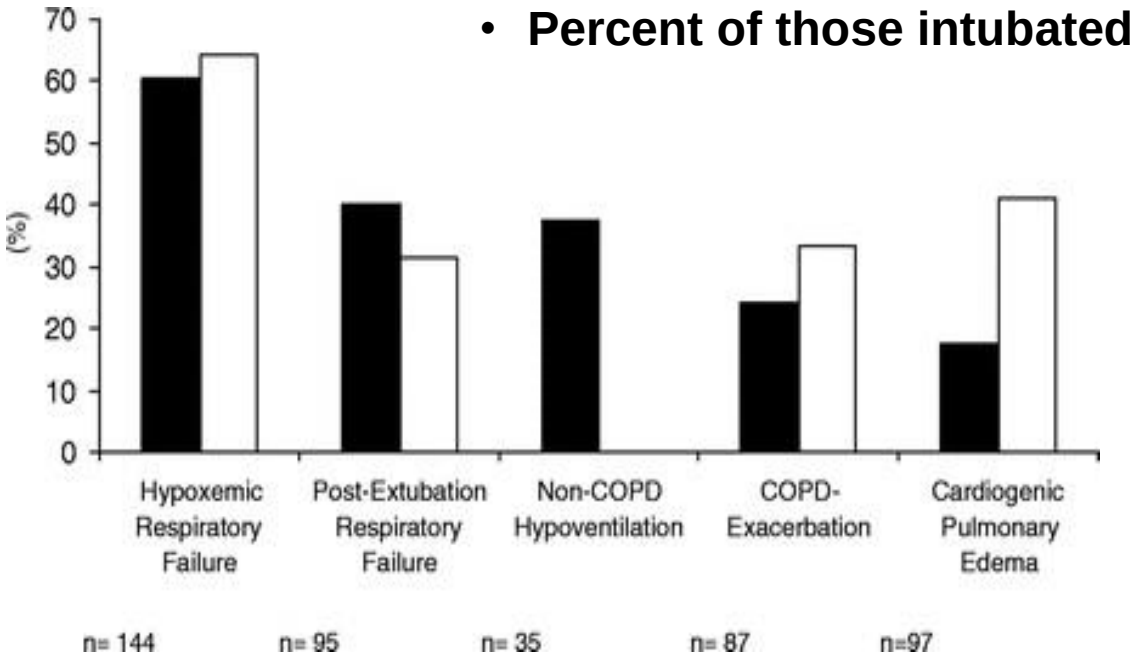




Noninvasive Ventilation in Severe Hypoxemic Respiratory Failure: RCT
Am J Respir Crit Care Med 2003:168;1438–1444

Debate on NIV

- Percent needing intubation (black bars)
- Percent of those intubated who died (white bars)



NIPPV in acute respiratory failure outside clinical trials :Experience at the Massachusetts General Hospital
Critical Care Medicine 2008;36:441-447

Limitation of NIV

- NIV is more beneficial to hypercapnic respiratory failure than to hypoxemic respiratory failure
- Many patients do not tolerate NIV
- Narrow indication
- Broad contra-indication

High flow nasal oxygen therapy (HFNO)
: Flow and FiO_2

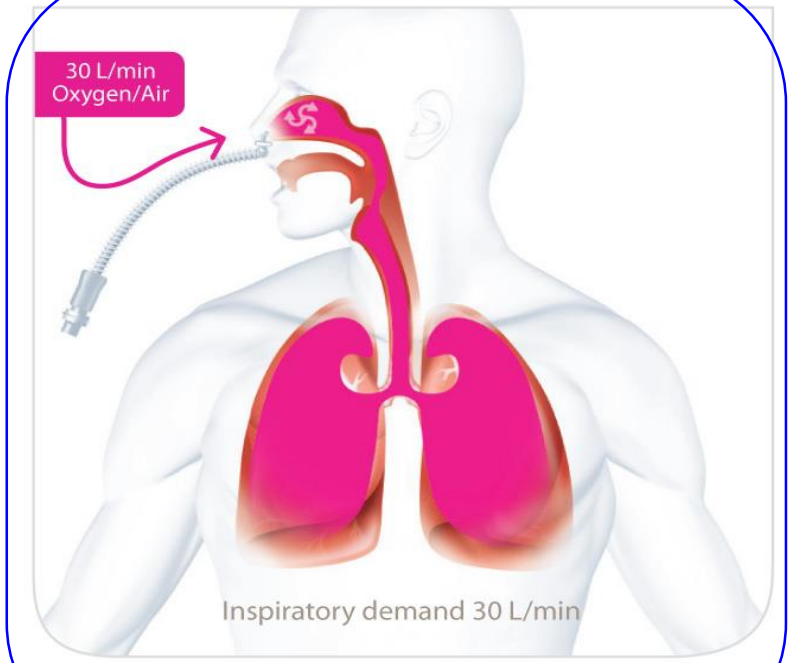


Image 1 – Nasal High Flow

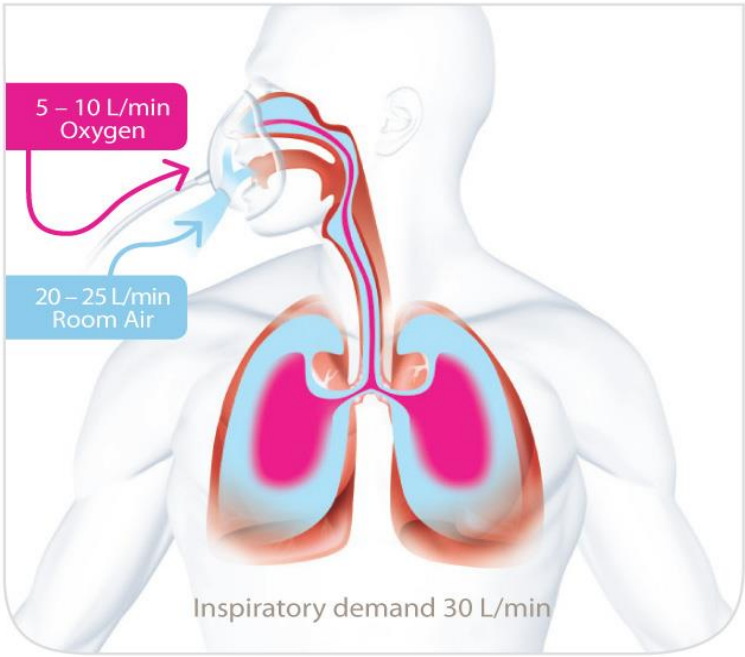


Image 2 – Face Mask Oxygen Therapy

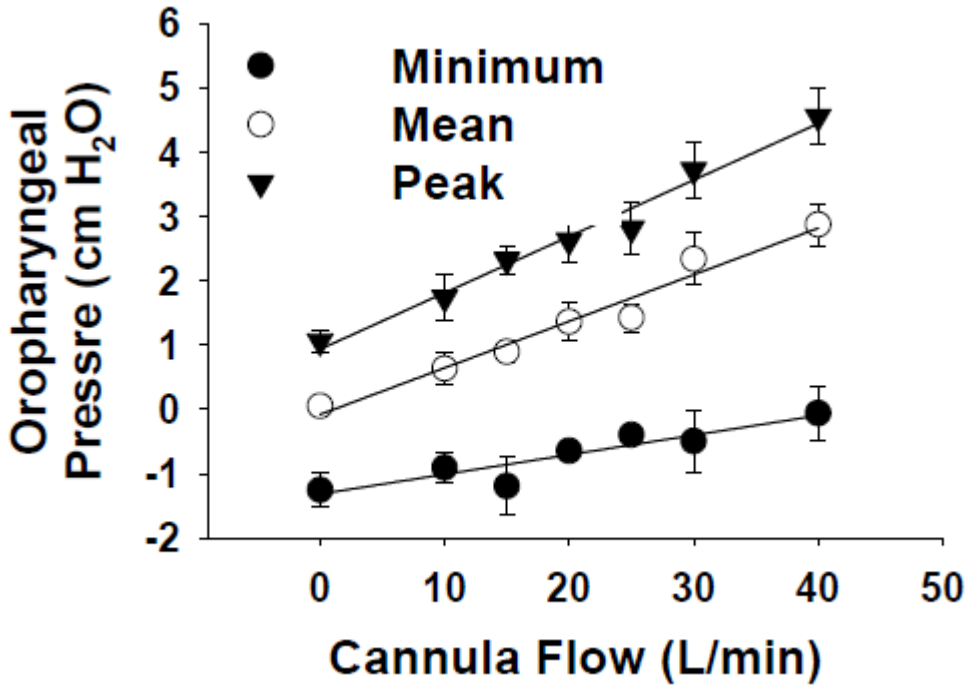
Peak inspiratory flow rate of a resting individual is typically below 30 L/min.

Thorax. 1959; 14: 225–232

Physiologic benefits

- Washout of nasopharyngeal dead space
- Reduction of inspiratory resistance(WOB)
- Improved mechanics by supplying adequately warmed and humidified gas
- Reduction in the metabolic cost of gas conditioning
- Provision of distending pressure

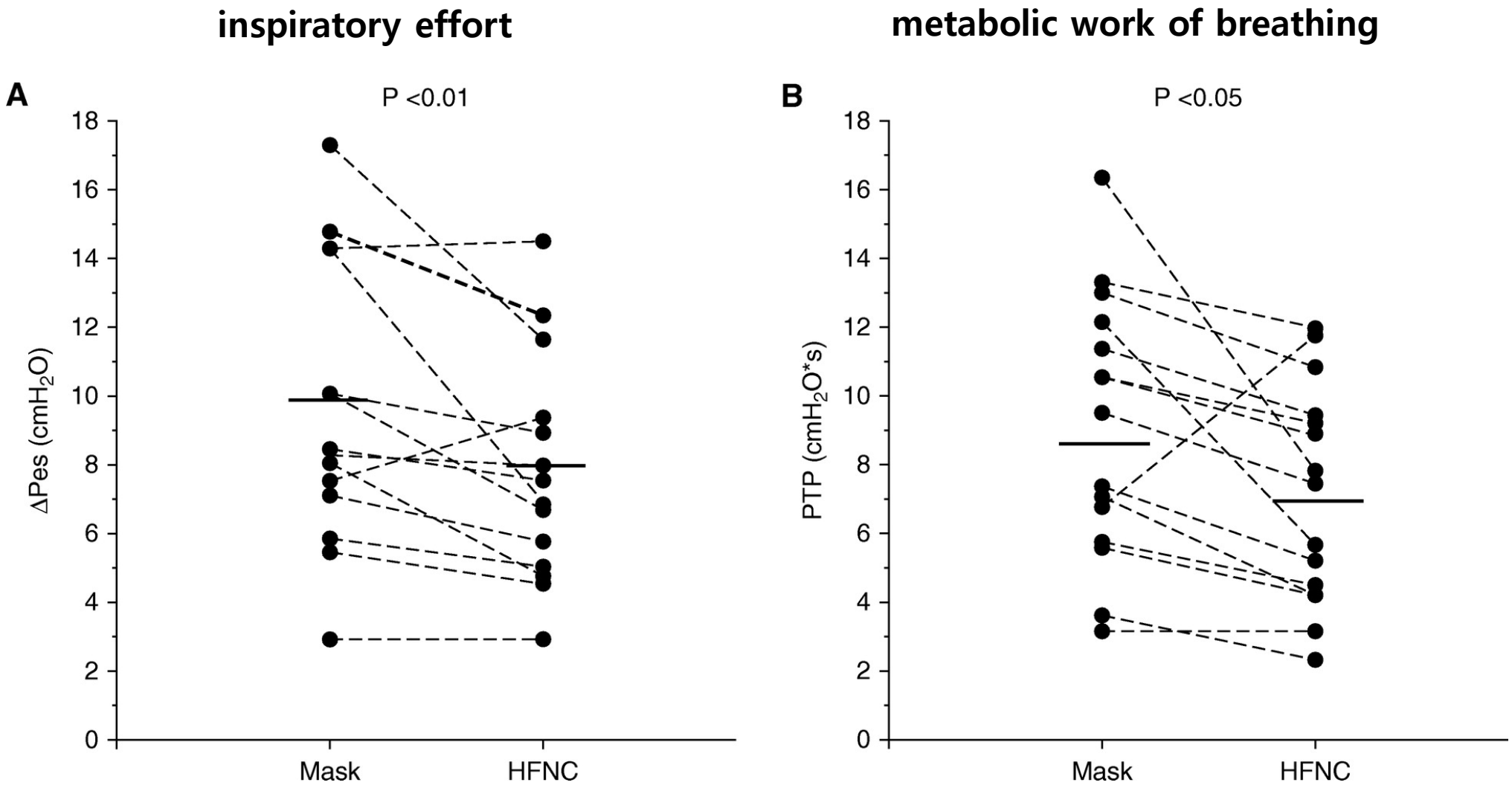
Nasopharyngeal Pressure in the adult



Bamford et al 2004

- Contributing factors
  - Flow rate
  - Patient's size
  - Relationship between cannula size & internal diameter of the nares

WOB: HFNO vs facial mask oxygen



Mauri T et al. Am J Respir Crit Care Med. 2017

Current evidences : up to date

- Acute hypoxemic respiratory failure in various fields
  - **De novo ARF**
  - **Cardiogenic pulmonary edema**
  - **Immune-compromised host**
  - Post-operative
  - Post-extubation

- Acute hypercapnic respiratory failure

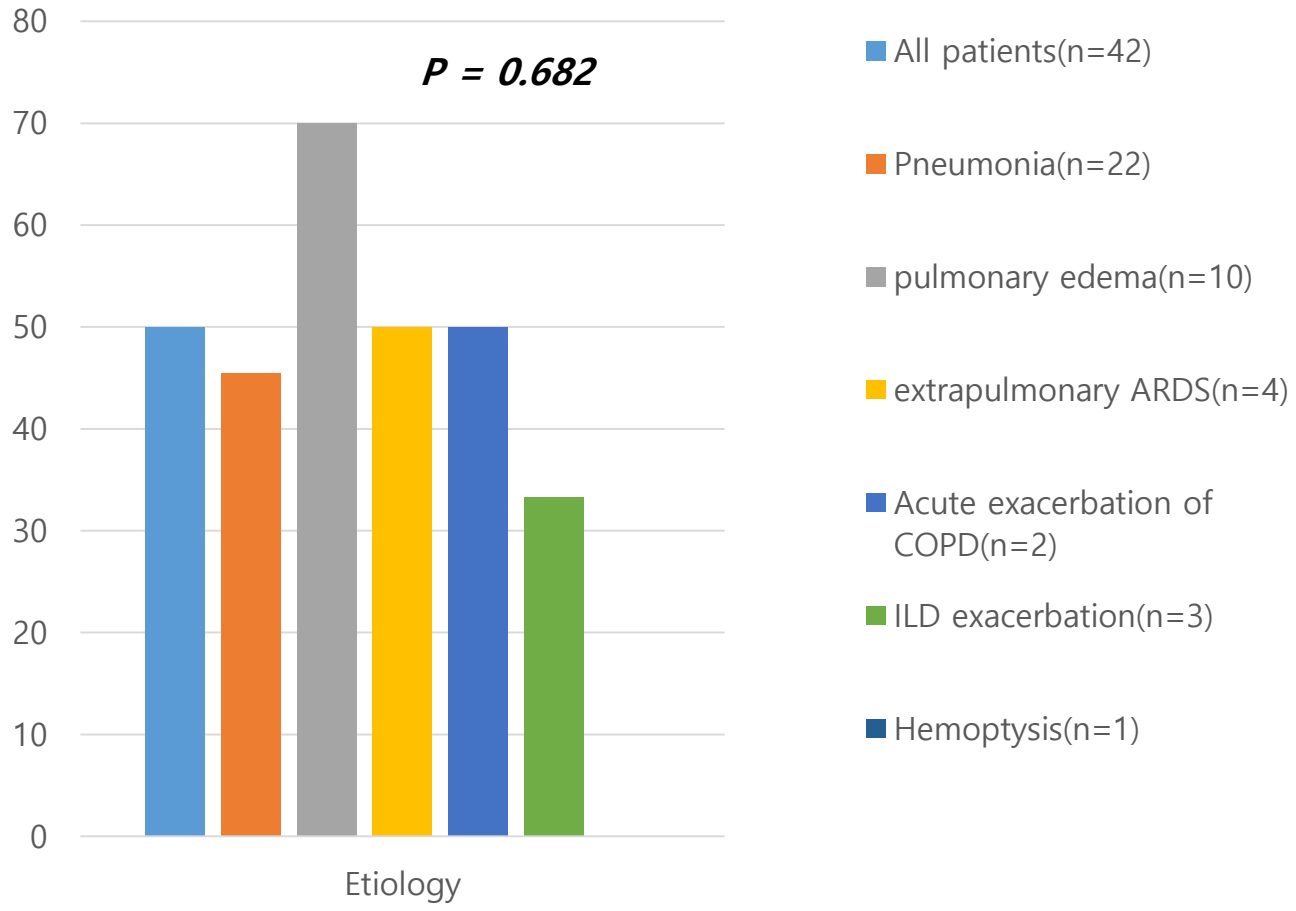
- Why discrepancy ? Physiologic benefit vs Survival benefit

Acute hypoxemic respiratory failure (AHRF)

- De novo AHRF
- Cardiogenic pulmonary edema
- Immunocompromised host
- Postoperative respiratory failure
- Post-extubation

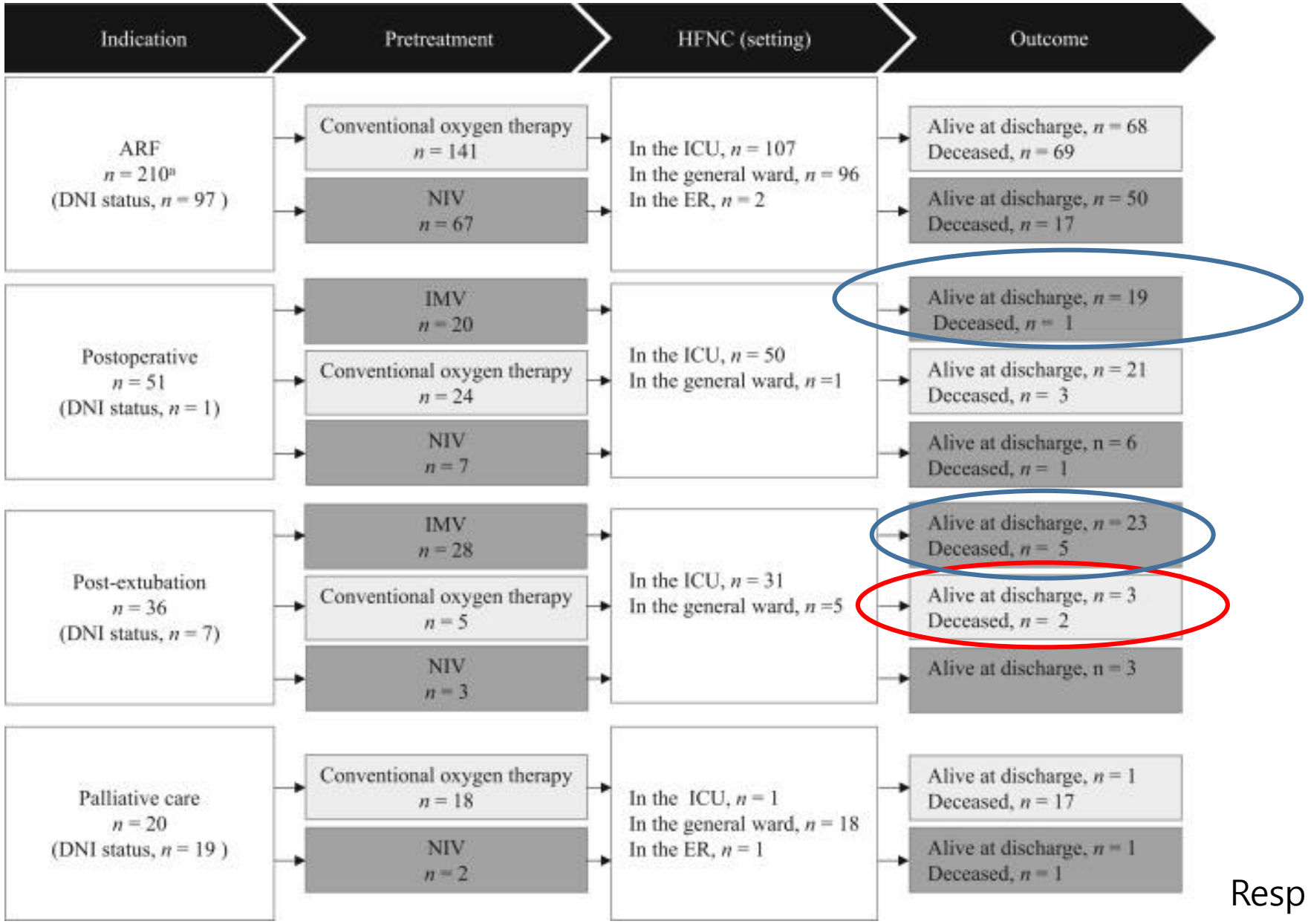
Success rate according to etiology in AHRF

Variables	Patients (n=62)
Respiratory parameter (mean ± SD)	
PaO_2/FiO_2 ratio(PF ratio)	154.8 ± 90.9
pH	7.4 ± 0.1
$PaCO_2$ (mmHg)	30.4 ± 9.3
HCO_3^- (mEq/L)	20.2 ± 4.8
Respiratory frequency(min^{-1})	27.8 ± 5.3
HFNC parameter	
Initial flow rate (L/min)	38.5 ± 7.6
Intial FiO_2 (%)	71.2 ± 19.8
Hemodynamic parameter	
Mean arterial pressure (mmHg)	85.1 ± 14.8
Heart rate (min^{-1})	106.8 ± 20.3



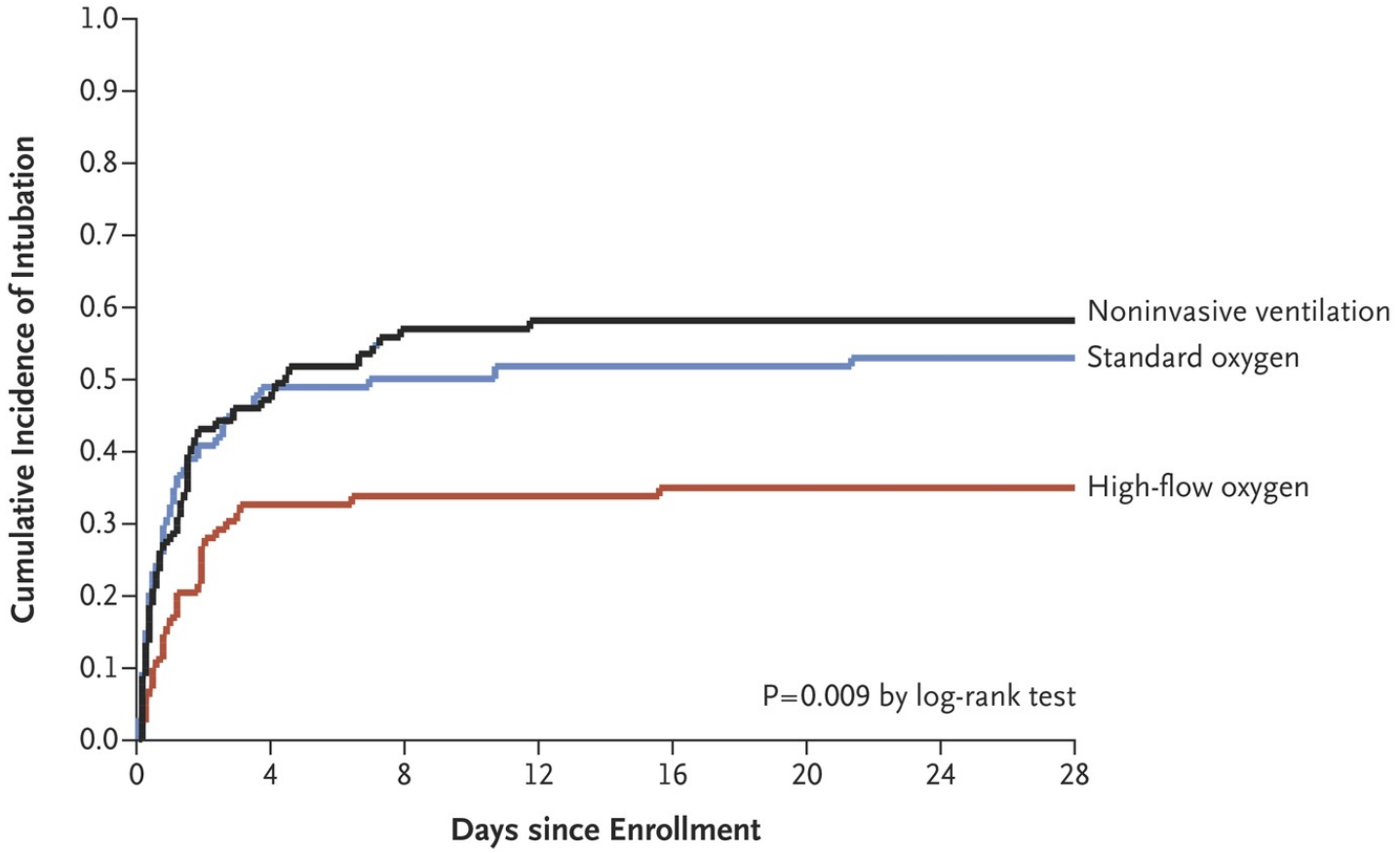
Cho wh et al, ATS abstract 2013

HFNO in the real world
: A Japanese cross-sectional multicenter survey



Respiratory Investigation, 2018

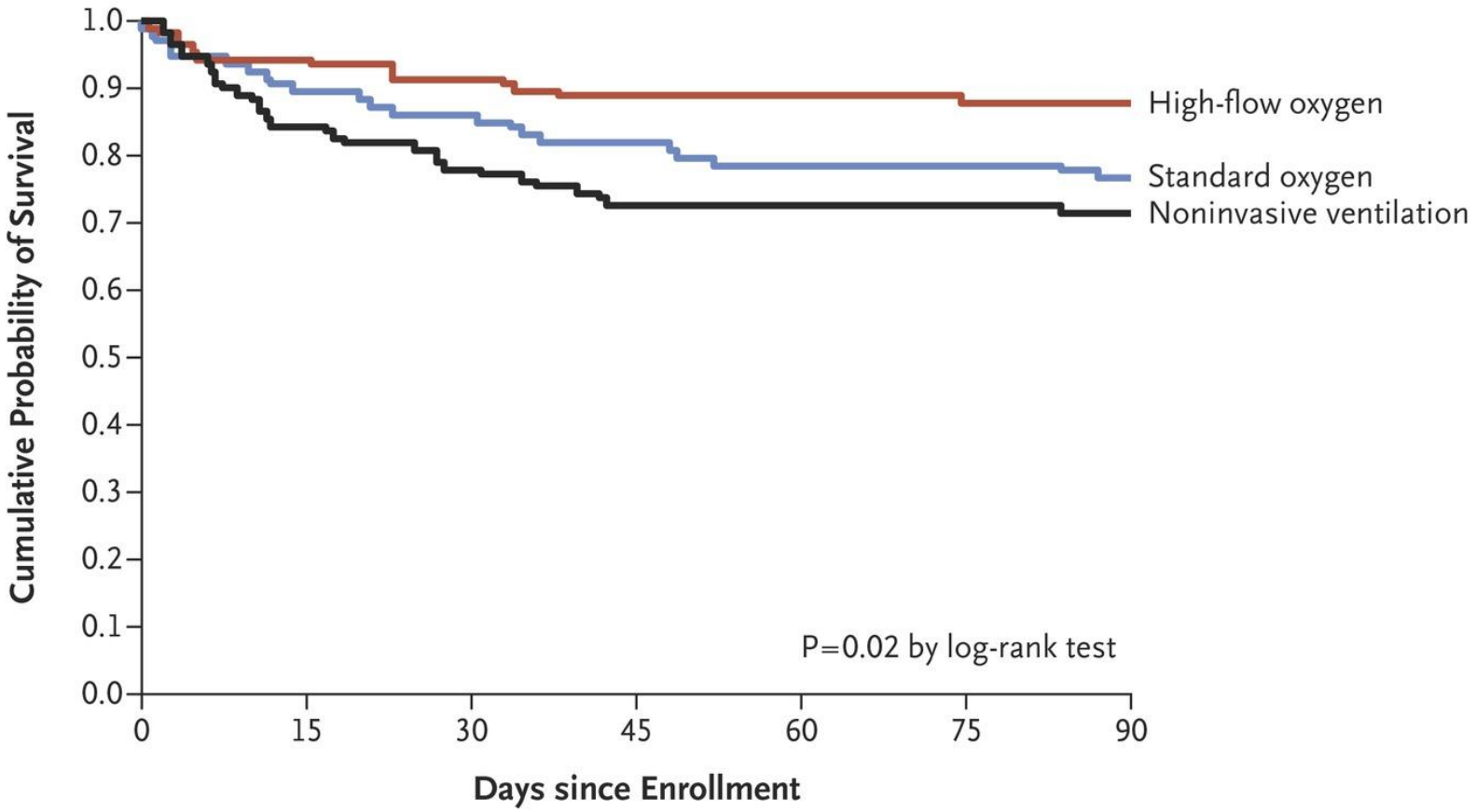
De nova AHRF



No. at Risk								
High-flow oxygen	83	55	54	54	53	53	53	53
Standard oxygen	74	37	35	34	34	34	33	33
Noninvasive ventilation	81	41	34	32	32	32	32	32

Frat JP et al. N Engl J Med. 2015

De nova AHRF



No. at Risk							
High-flow oxygen	106	100	97	94	94	93	93
Standard oxygen	94	84	81	77	74	73	72
Noninvasive ventilation	110	93	86	80	79	78	77

Frat JP et al. N Engl J Med. 2015

Cardiogenic pulmonary edema

	Univariate analysis		Multivariate analysis	
Variables	OR (95% C.I.)	P	OR (95% C.I.)	P
APACHE II score	0.84 (0.74-0.94)	0.003	0.82 (0.69-0.97)	0.019
SOFA score	0.77 (0.65-0.97)	0.002	0.70 (0.54-0.91)	0.007
Cardiogenic pulmonary edema	3.19 (0.82-12.38)	0.094	13.3 (1.75-101.82)	0.013
PaO_2 improvement at 1h	3.64 (1.36-9.73)	0.010	5.59 (1.07-29.25)	0.042
PaO_2 improvement at 24h	4.41 (1.60-12.15)	0.004	5.36 (1.12-25.61)	0.035

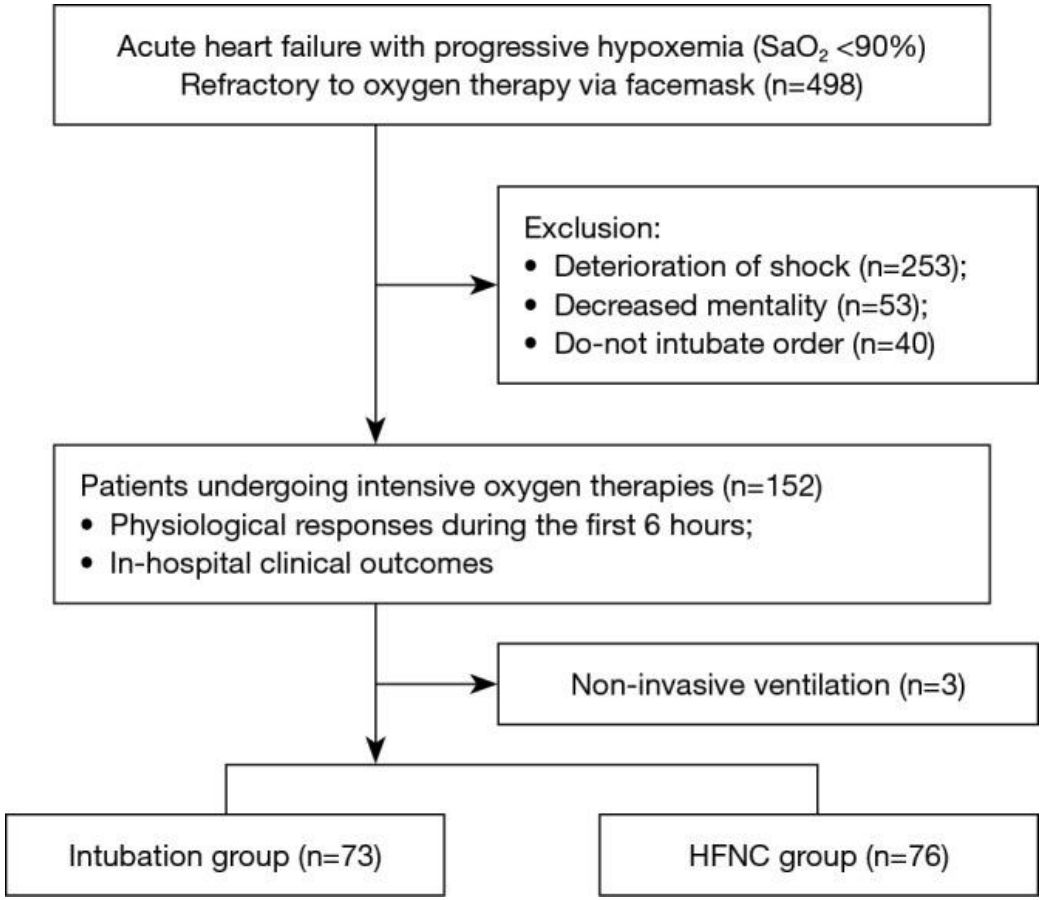
Hosmer-Lemeshow test (Chi-square = 6.372, df = 8, P=0.606)

OR, odds ratio; CI, confidence interval

Cho wh et al, Internal Medicine 2015

Cardiogenic pulmonary edema

HFNO is an acceptable for bridging therapy in cardiogenic pulmonary edema.



Variables	Total (n=149)	Intubation group (n=73)	HFNC group (n=76)	P
Hospital stay (days)	9 [6–14]	9 [7–16]	9 [6–14]	0.353
Vasopressor use	88 (59.1)	30 (41.1)	20 (26.3)	0.051
Hospital acquired pneumonia	17 (11.4)	10 (13.7)	7 (9.2)	0.389
All-cause death	11 (7.4)	7 (9.6)	4 (5.3)	0.313
Cardiac death	9 (6.0)	6 (8.2)	3 (3.9)	0.274
Requiring intubation*	–	–	10 (13.2)	–

Kang MG et al. J Thorac Dis. 2019

Immunocompromised host

; 2h HFNO vs Venturi

; Primary endpoint – need for IMV or NIV

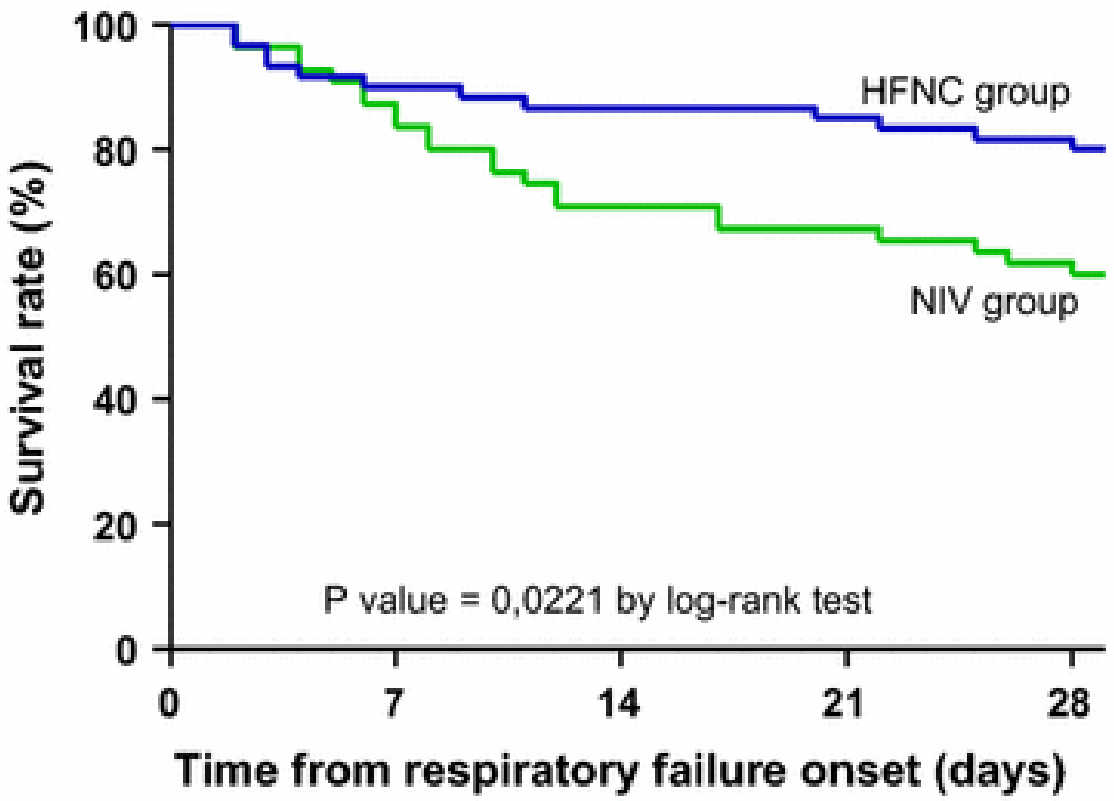
Clinical status at randomization		
Respiratory rate, breaths/min	26 [21.7–31.2]	27 [22–32.2]
SpO_2, %	96 [94–98]	96 [95–98.2]
Estimated PF ratio at adm	**128** [48–178]	**100** [40–156]
Mean arterial pressure, mmHg	86.8 [82.2–95.3]	80 [74–89.3]
Normal GCS score, n (%)	49 (94.2)	48 (100)
Confusion, n (%)	4 (7.7)	1 (2.1)

Values are given as median [25th-75th percentile]

	HFNO group (n = 52)	Venturi group (n = 48)	*P*
Primary endpoint			
Number (%) requiring MV	8 (15 %)	4 (8 %)	0.36
NIV	6[a]	3[a]	
IMV	4	2	
Secondary endpoints, median [25th–75th percentile] at 2h			
Discomfort VAS score[b]	3 [1–5]	3 [0–5]	0.88
Dyspnea VAS score[b]	3 [2 – 6]	3 [1–6]	0.87
Thirst VAS score[b]	6 [3–8]	6 [5 – 9]	0.40
RR, breaths/min	25 [22–29]	25 [21–31]	
Heart rate, beats/min	98 [90–110]	99 [83–112]	0.43

Virginie Lemiale et al. Critical Care 2015

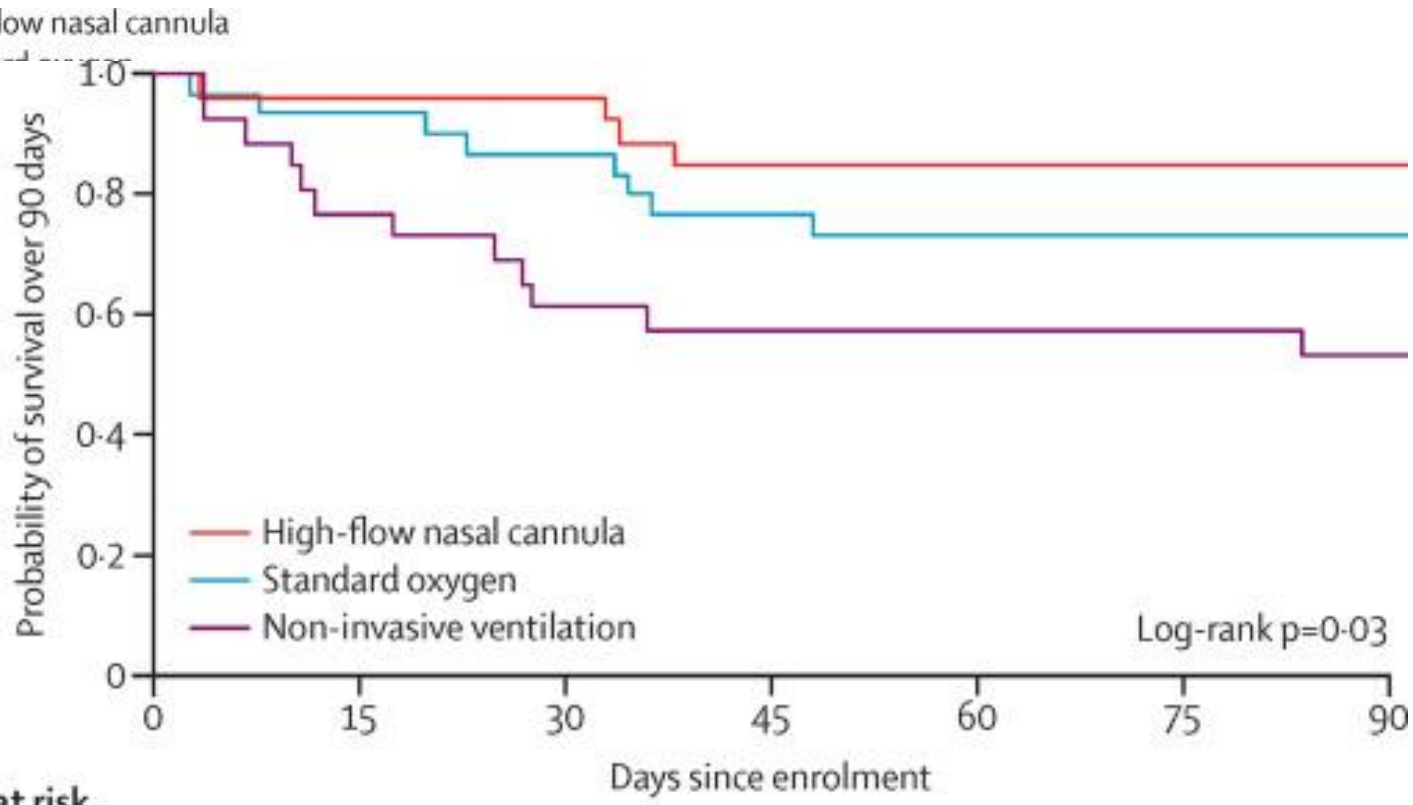
Immunocompromised host



- In conclusion, HFNO is better than NIV, not sure for conventional oxygen therapy.

Coudroy R et al. Ann Intensive Care. 2016

Immunocompromised host, Posthoc analysis of RCT



Number at risk							
High-flow nasal cannula group	26	25	25	22	22	22	22
Standard oxygen group	30	28	26	23	22	22	22
Non-invasive ventilation group	26	20	16	15	14	14	13

Frat JP et al. Lancet Respir Med. 2016

Ongoing trial (HIGH study; NCT02739451)

- Immunocompromised patients (oxygen > 6L/min of NP)
- A prospective, multicenter, open-label RCT
- **HFNO vs low/medium-flow oxygen**
- Primary end point
  - day-28 mortality
- Secondary endpoints
  - intubation rate on day 28
  - patient comfort VAS
  - dyspnea (VAS and Borg scale)
  - respiratory rate & oxygenation
  - incidence of ICU-acquired infections.

Postoperative respiratory failure

;Early HFNO vs NIV, RCT (Cardiothoracic surgery)

;Primary endpoin –incidence of postop. hypoxia(PF<300mmHg)

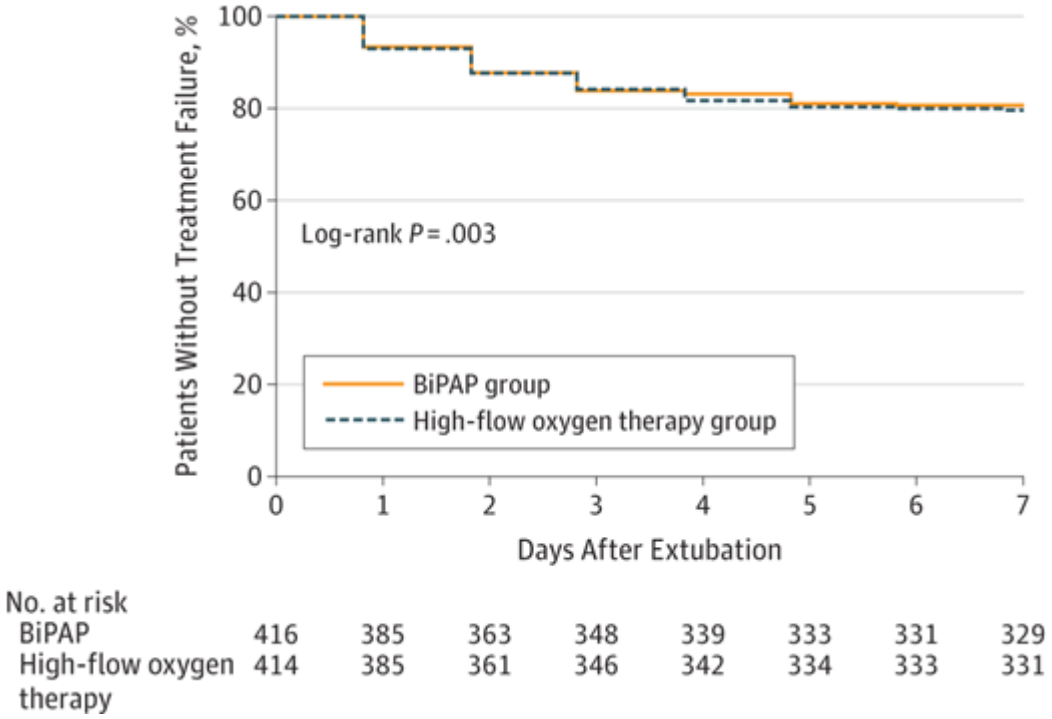


Table 4. Clinical Outcomes and Adverse Events During the Intensive Care Unit Stay

Events	Group: BiPAP (n = 416)	Group: HFNO (n = 414)	P Value
Nosocomial pneumonia, No. (%) [95% CI]	90 (21.6) [17.8-25.9]	83 (20.0) [16.4-24.3]	.57
Pneumothorax, No. (%) [95% CI]	7 (1.7) [0.7-3.6]	8 (1.9) [0.9-3.9]	.86
Acute colonic pseudo-obstruction, No. (%) [95% CI]	8 (1.9) [0.9-3.9]	9 (2.2) [1.0-4.2]	.86
No. of days with respiratory support, median (IQR)	2 (1-3)	2 (1-3)	.59
Stay length, median (IQR), d			
ICU	6 (4-10)	6 (4-10)	.77
Hospital	14 (9-20)	13 (9-22)	.59

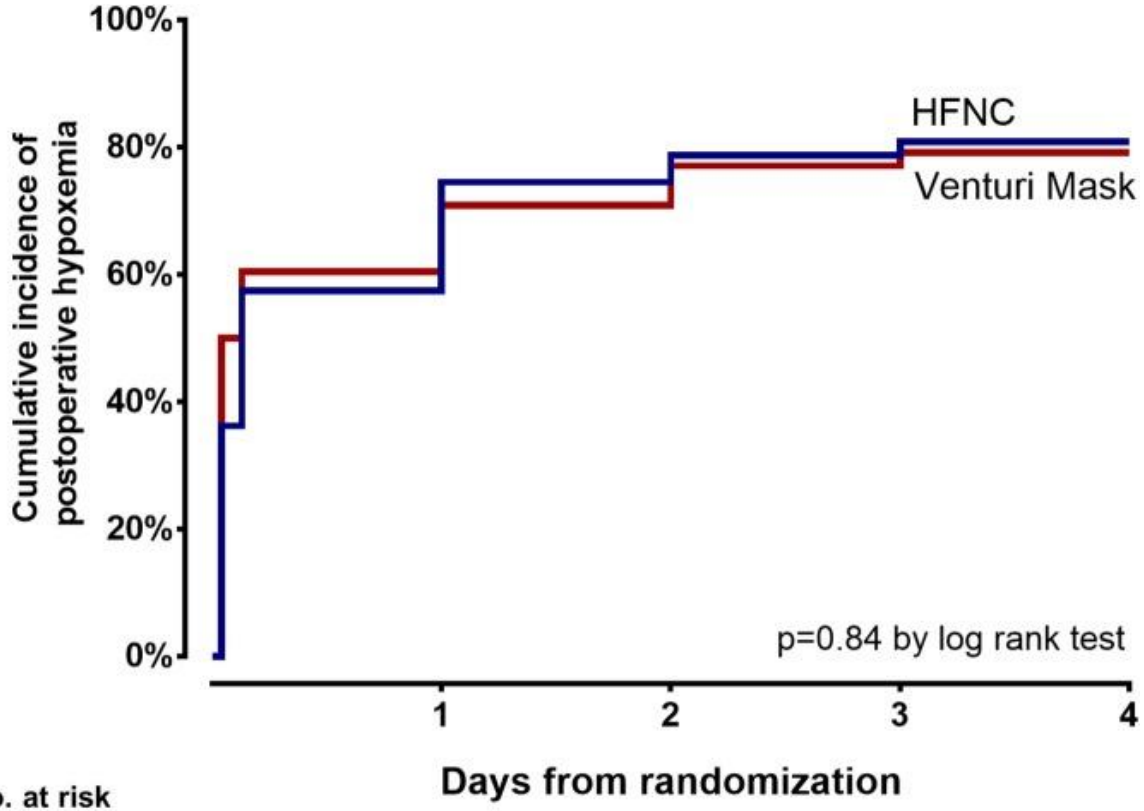
Among cardiothoracic surgery patients with or at risk for respiratory failure, the use of HFNO therapy compared with intermittent BiPAP did not result in a worse rate of treatment failure.

Stéphan F et al, JAMA. 2015

Postoperative respiratory failure

;Early HFNO vs Venturi, RCT (Lobectomy)

;Primary endpoin –incidence of postop. hypoxia(PF<300mmHg)



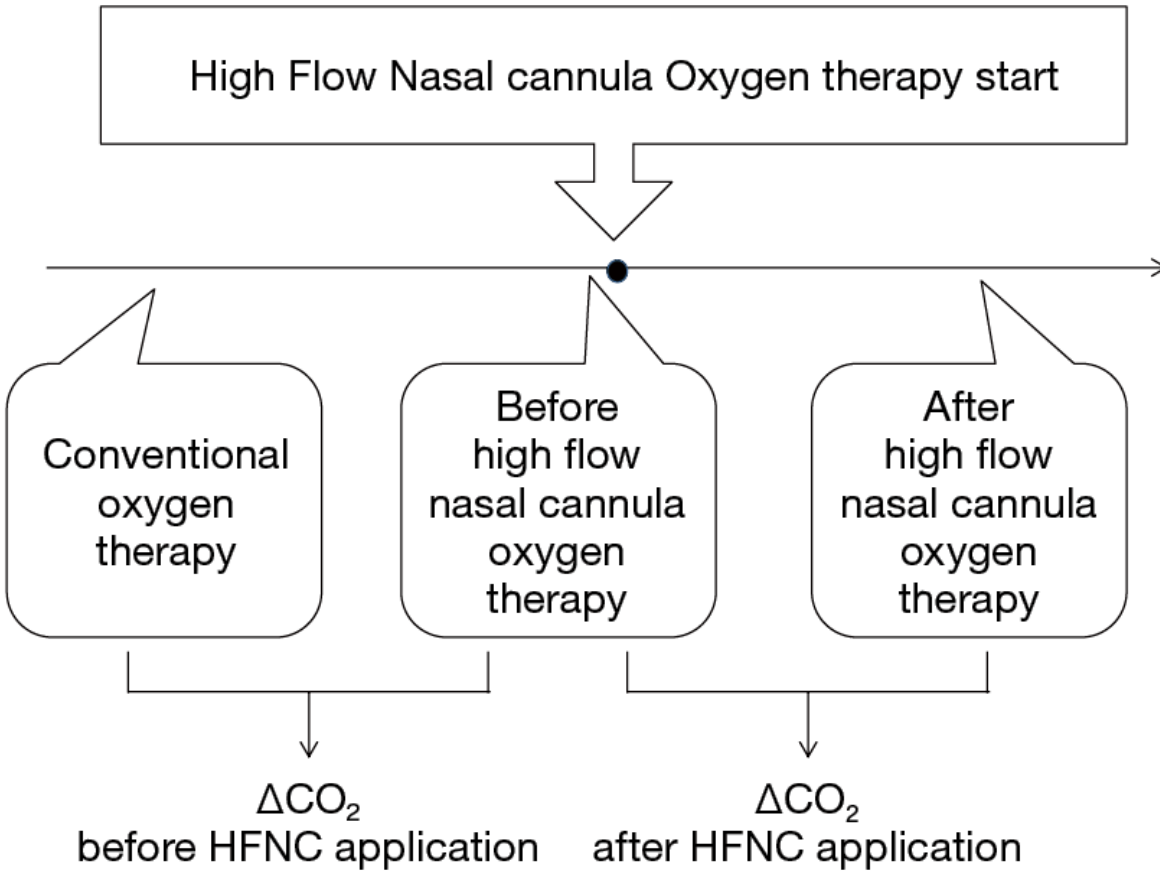
No. at risk					
HFNC	47	20	12	10	9
Venturi Mask	48	19	14	11	10

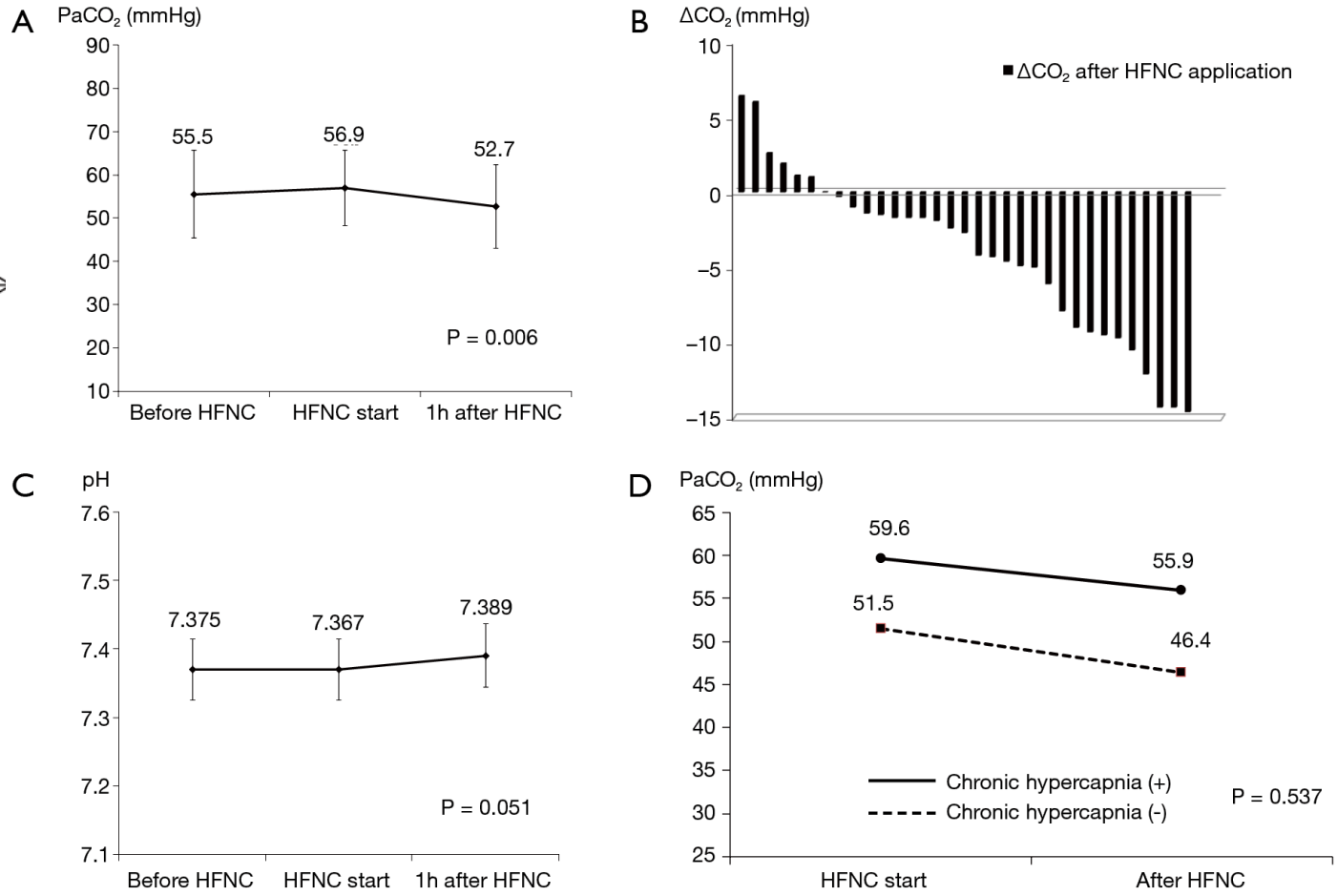
No difference in

- Need for supplemental oxygen after treatment discontinuation
- postoperative respiratory failure requiring ventilatory support
- postoperative pulmonary complications

Pennisi et al. Crit Care. 2019

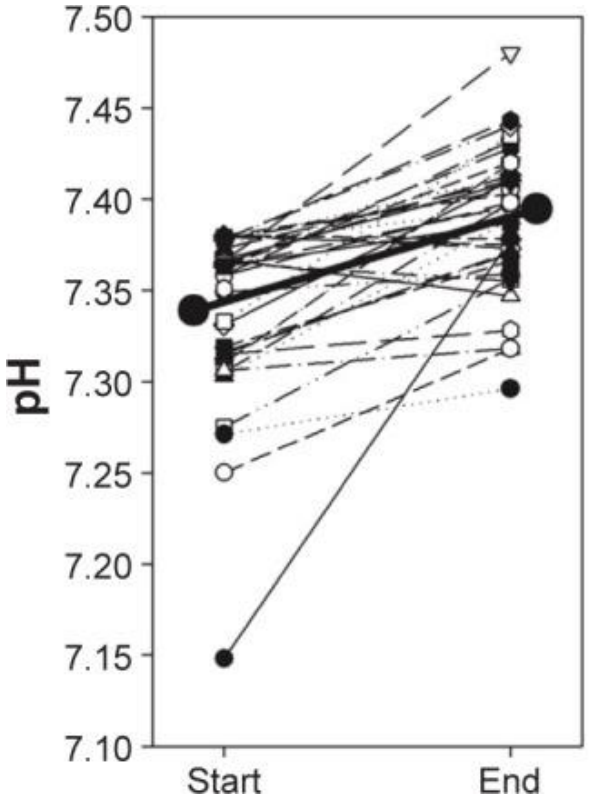
ARF with hypercapnia; physiologic effect

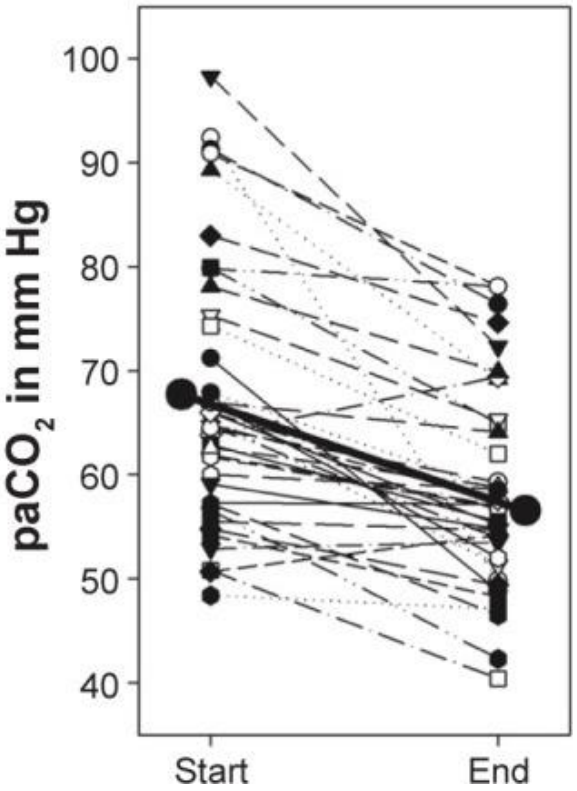




Kim ES et al. J Thorac Dis. 2018

Acute hypercapnic exacerbation of COPD





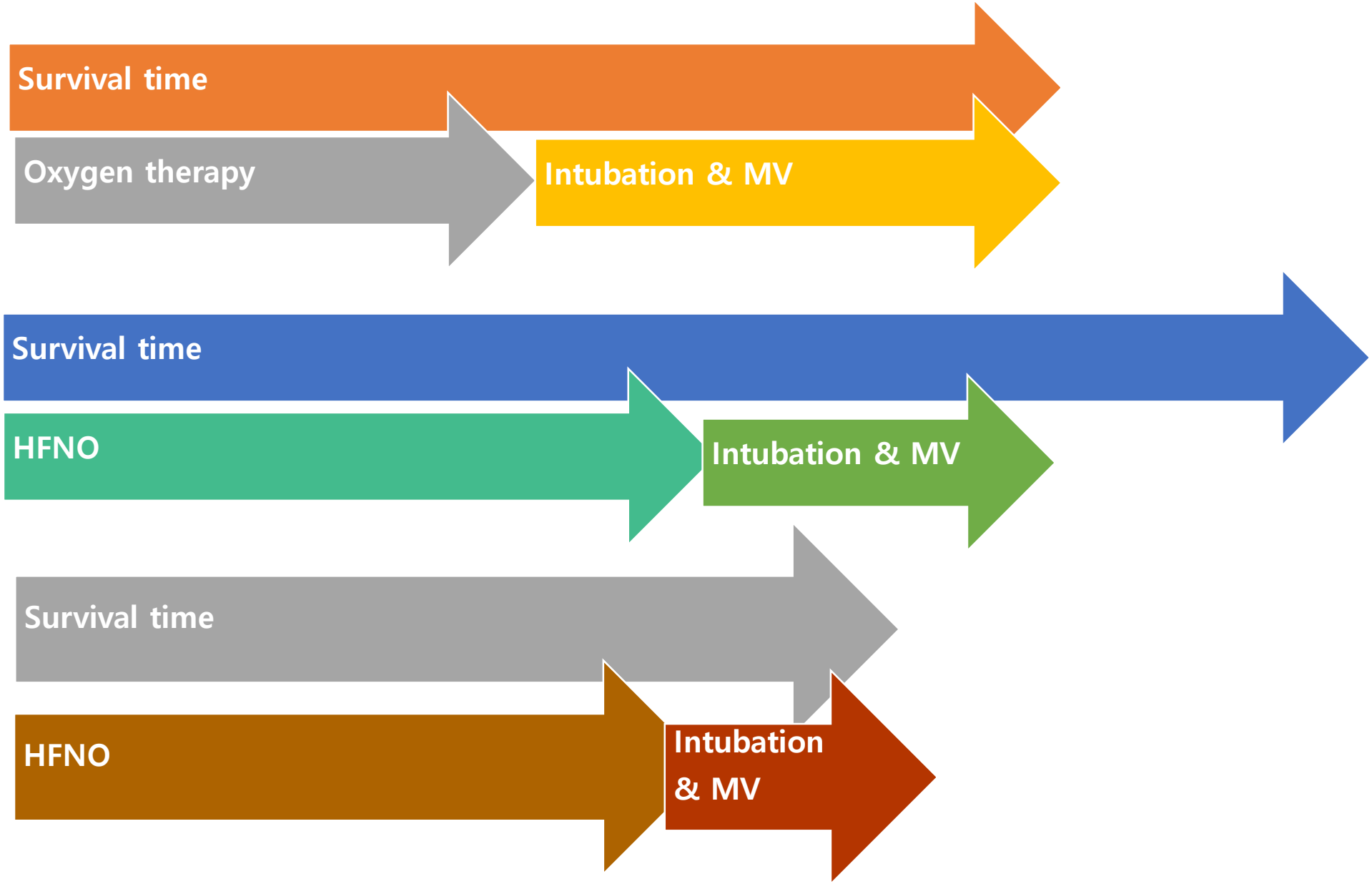
Parameters	All patients (pH ≤7.38; n=38)			
	Baseline (mean±SD)	End (mean±SD)	Change (mean±SD)	*P*-value
pH	**7.339±0.041**	**7.392±0.048**	**0.052±0.048**	**0.000**
pCO_2 mmHg	**67.6±12.9**	**58.5±9.7**	**−9.1±8.8**	**0.001**
pO_2 mmHg	58.3±15.2	58.3±17.6	–	0.983
HCO_3 mmol/L	30.8±5.1	31.6±5.3	–	0.636
NHF flow L/min	–	25.8±8.2	–	–
Treatment time min	–	195±231	–	–
	Patients with pH <7.35 (n=17)			
pH	**7.298±0.046**	**7.379±0.051**	**0.082±0.060**	**0.000**
pCO_2 mmHg	**73.7±13.7**	**59.6±11.2**	**−14.2±10.6**	**0.002**
pO_2 mmHg	56.9±14.8	55.6±20.7	–	0.845
HCO_3 mmol/L	31.6±5.5	32.5±5.6	–	0.661
NHF flow L/min	–	26.3±7.9	–	–
Treatment time min	–	252±251	–	–

Jens Bräunlich et al. Int J Chron Obstruct Pulmon Dis. 2018

Why discrepant results in clinical trials…

- Primary endpoint : avoidance of intubation vs **mortality**
- Underlying disease : various cause of RF & different settings
- Tolerability : person to person
- Target of comparison : vs NIV or conventional oxygen therapy

Intubation rate vs mortality



Analysis of hospital outcomes for the early(<48h) HFNC failure group compared with the late(≥48h) HFNC failure group

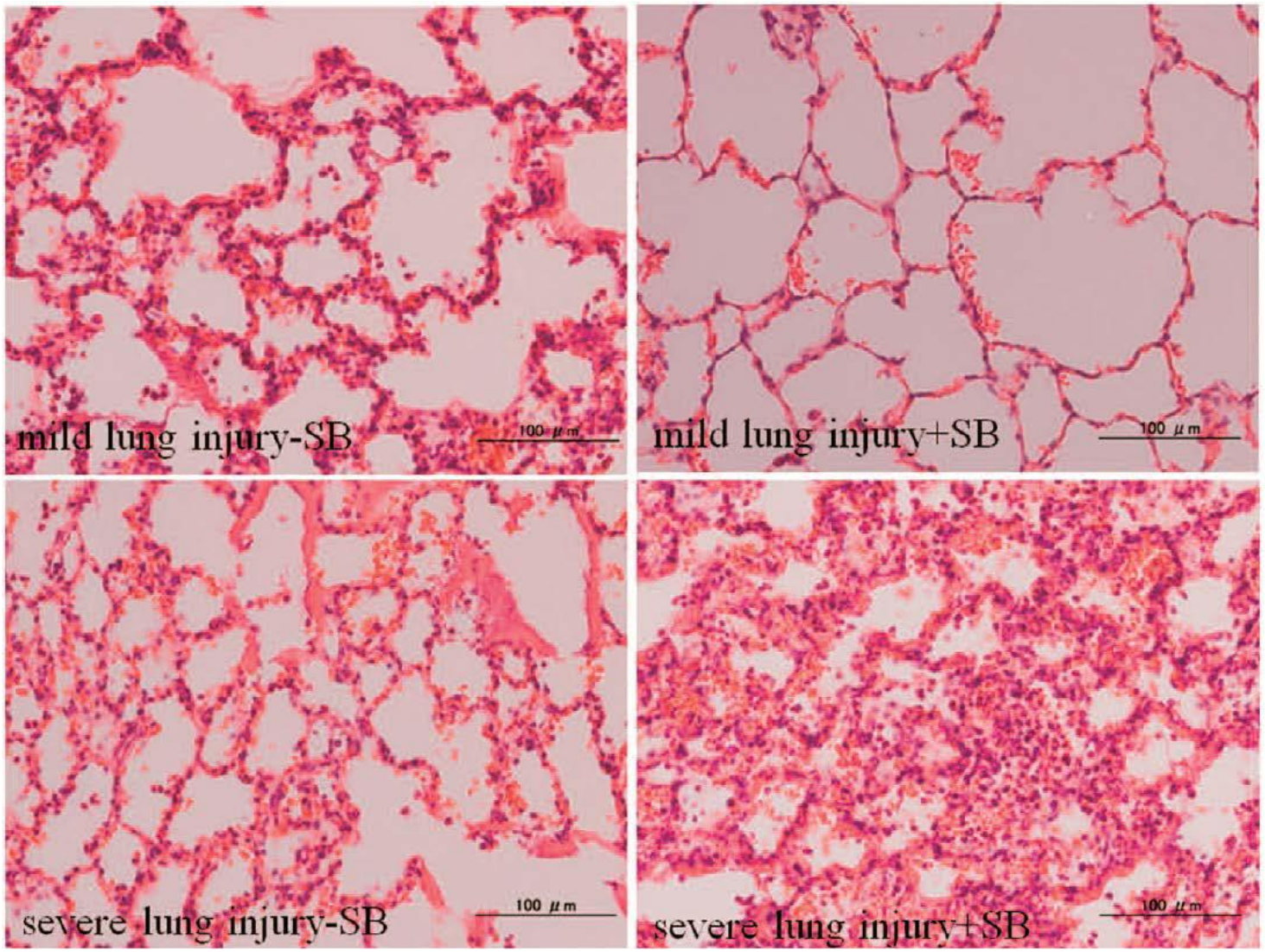
Variables	Crude		Propensity-adjusted[a]		Propensity-matched[b]	
	Odds ratio (95 % CI)	*P*[c]	Odds ratio (95 % CI)	*P*[c]	Odds ratio (95 % CI)	*P*[c]
Primary outcome						
Overall ICU mortality	0.323 (0.158–0.658)	0.002	0.317 (0.143–0.700)	0.005	0.369 (0.139–0.984)	**0.046**
Secondary outcomes						
Extubation success	3.284 (1.361–7.923)	0.008	3.091 (1.193–8.013)	0.020	2.057 (0.746–5.672)	0.163
Ventilator-weaning	3.056 (1.470–6.351)	0.003	3.380 (1.492–7.656)	0.004	2.495 (1.039–5.991)	0.041
Ventilator-free days to 28d	0.542 (0.383–0.768)[d]	0.001[e]	0.516 (0.349–0.763)[d]	0.001[e]	0.639 (0.431–0.946)[d]	0.026[e]

[a]The individual propensity score was integrated into each outcome model as a covariable (all study patients were included)

[b]Of the 175 patients, 37 pairs were matched

Kang BJ et al. ICM 2015

Thoracic swing & lung injury

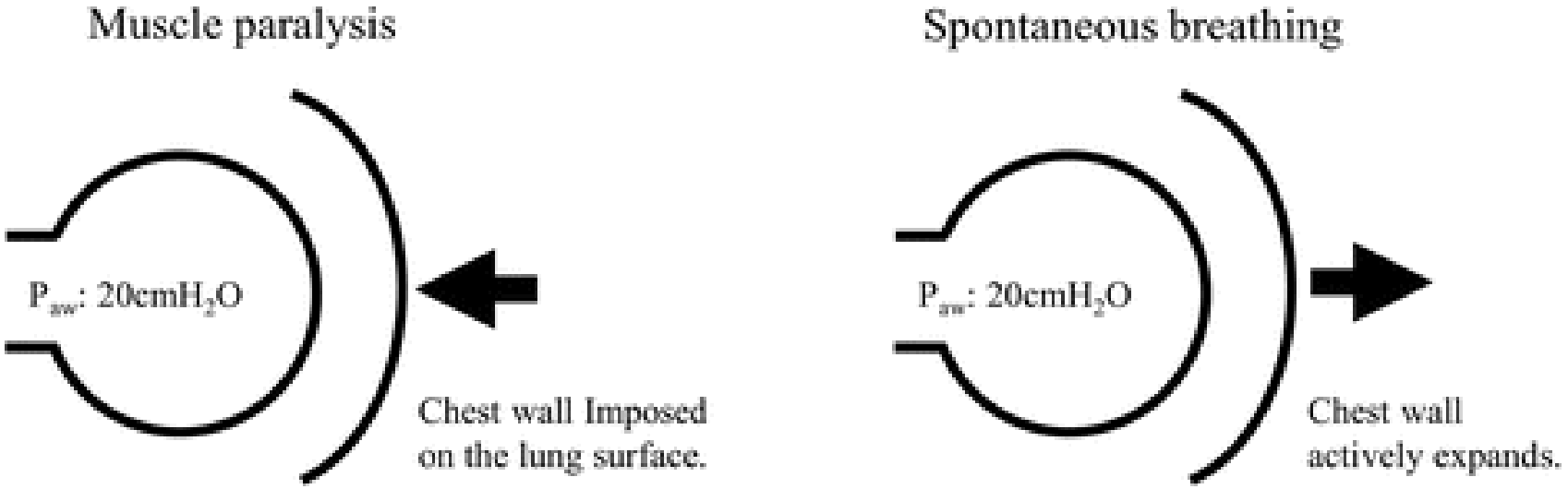


Spontaneous breathing exaggerate the acute lung injury in animal model.

Crit Care Med. 2012;40:1578–85

Spontaneuous breathing in ARDS

Harm or good ?



P_L (15cmH$_2$O)=P_{aw} (20cmH$_2$O) – P_{pl} (+5cmH$_2$O)

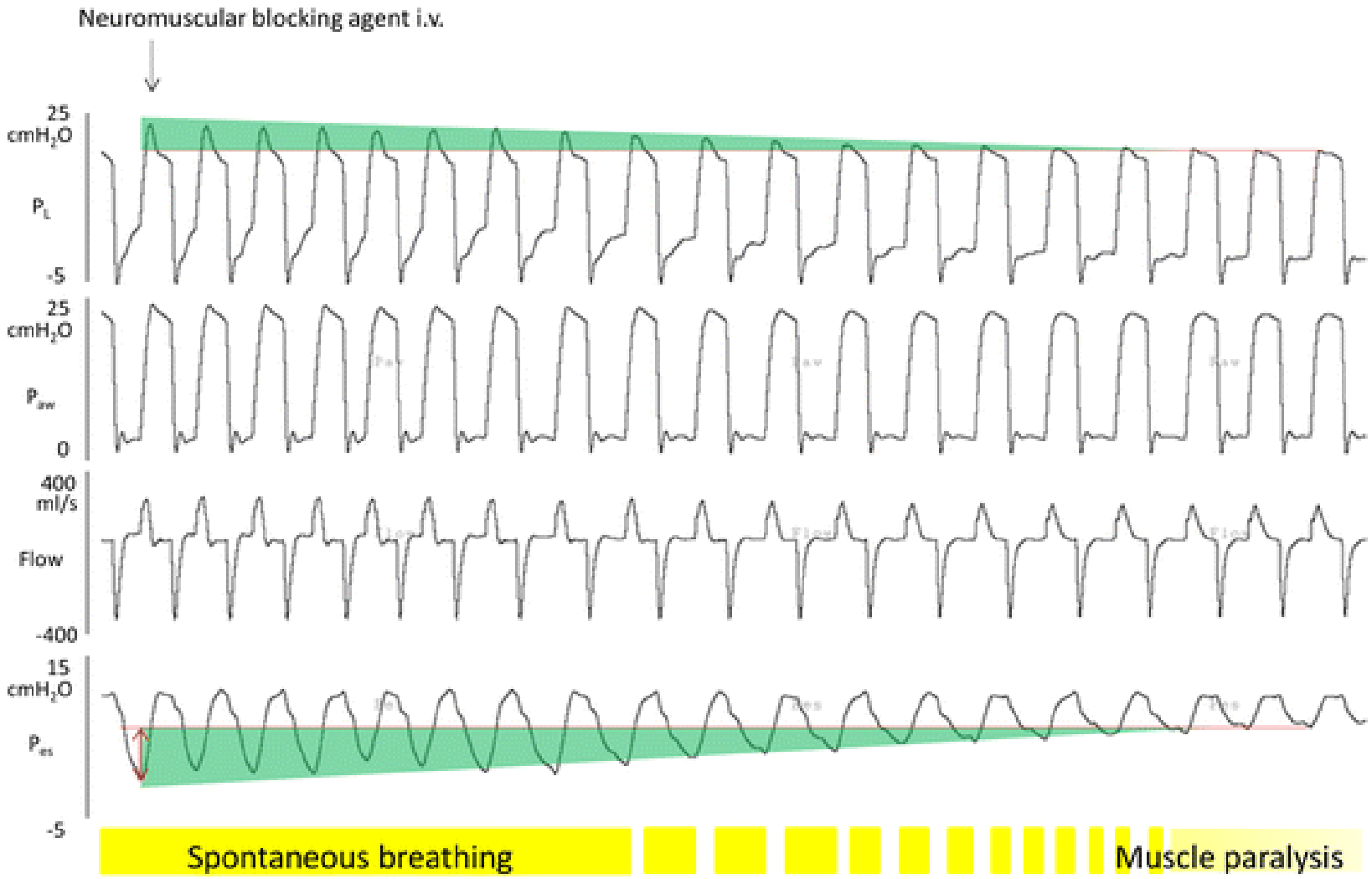
P_L (25cmH$_2$O)=P_{aw} (20cmH$_2$O) – P_{pl} (–5cmH$_2$O)

P_L : Transpulmonary pressure

P_{aw} : Airway pressure

P_{pl} : Pleural pressure

Spontaneuous breathing in ARDS



Insp transpulmonary pr. decreases

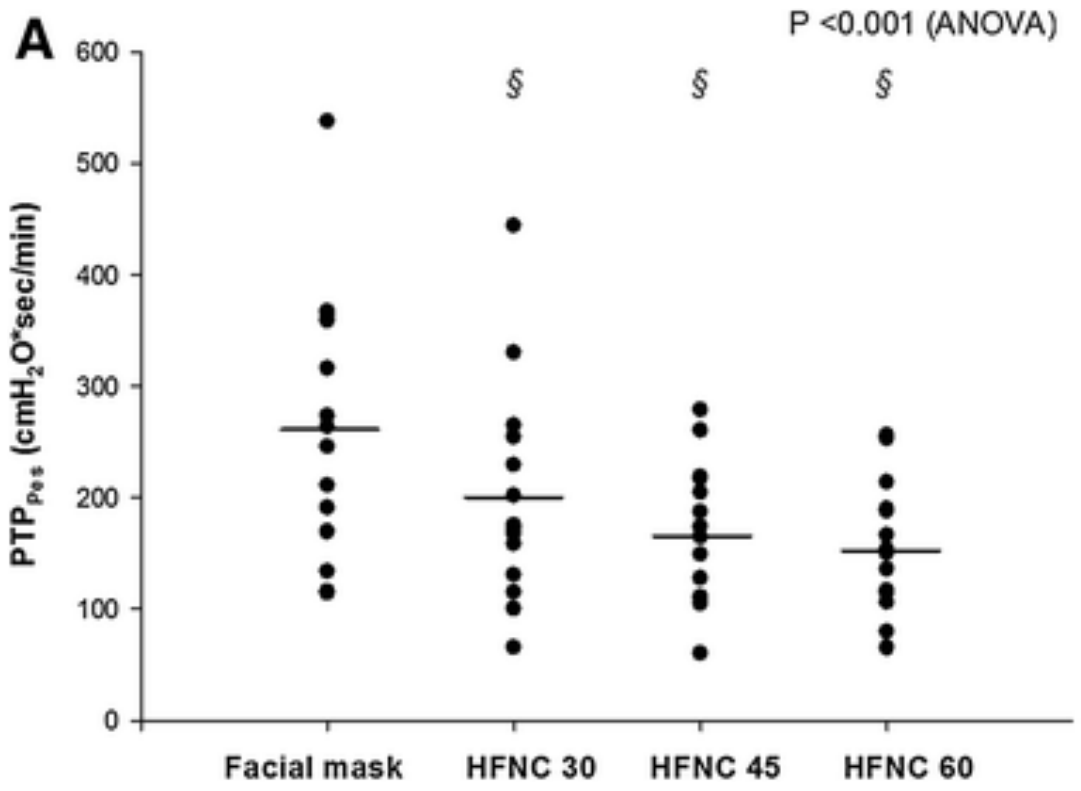
negative swing in esophageal pr. is decreasing.

Table 4. Factors associated with **intensive care unit mortality in the treatment failure group**

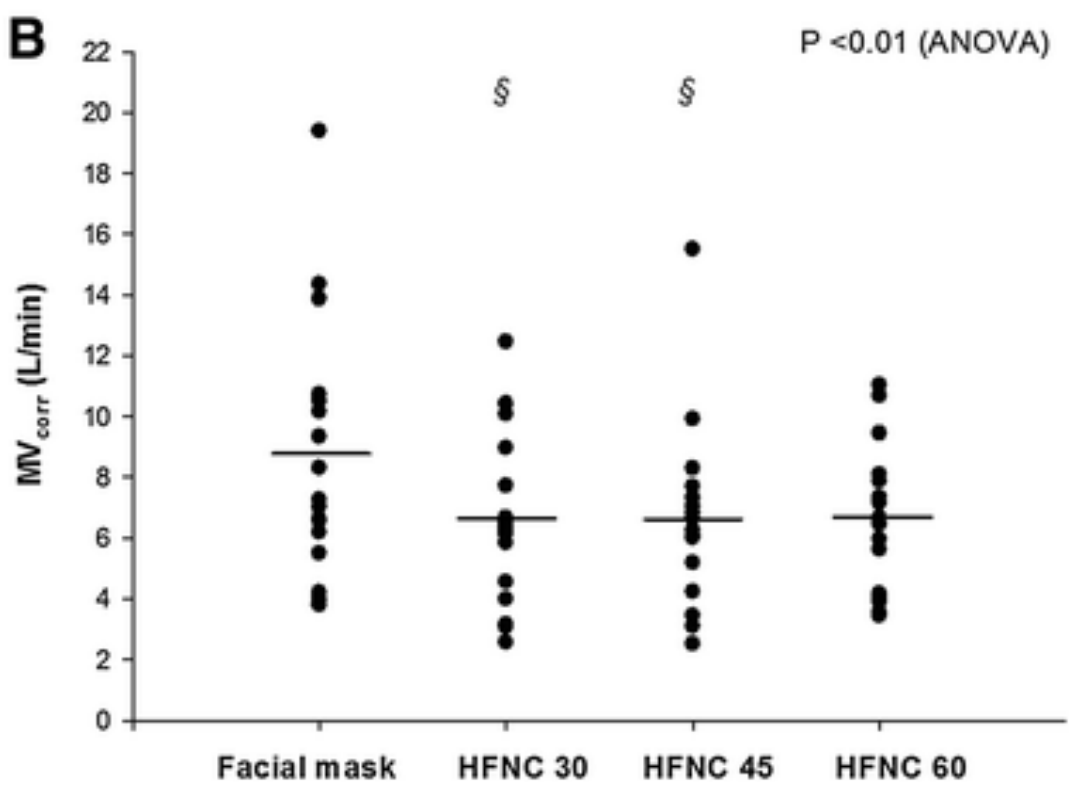
	No.	Unadjusted HR		Adjusted HR	
	Death/Total (%)	HR (95% CI)	p	HR (95% CI)	p
APACHE II score		1.12 (1.01–1.25)	0.030	1.07 (0.96–1.17)	0.235
Cause of respiratory failure					
Other causes	9/17 (52.9)	1			
Pneumonia	10/11 (90.9)	3.85 (1.43–10.38)	0.008	1.78 (0.61–5.21)	0.296
Vasopressor					
Not used	13/21 (61.9)	1			
Used	6/7 (85.7)	5.55 (1.81–17.02)	0.003	**4.22** (1.24–14.37)	0.021
PaO_2 improvement at 1 h					
No	14/17 (82.4)	3.90 (1.27–11.98)	0.017	**3.379** (1.04–11.02)	0.043
Yes	5/11 (45.5)	1			

Cho wh et al, Internal Medicine 2015

Non-linear physiologic effects of high-flow nasal cannula (*HFNC*) delivered at increasing flow rates.



a measure of patient effort



MV needed to maintain a physiologic arterial carbon dioxide tension

Tommaso Mauri et al, ICM 2017

Take Home message

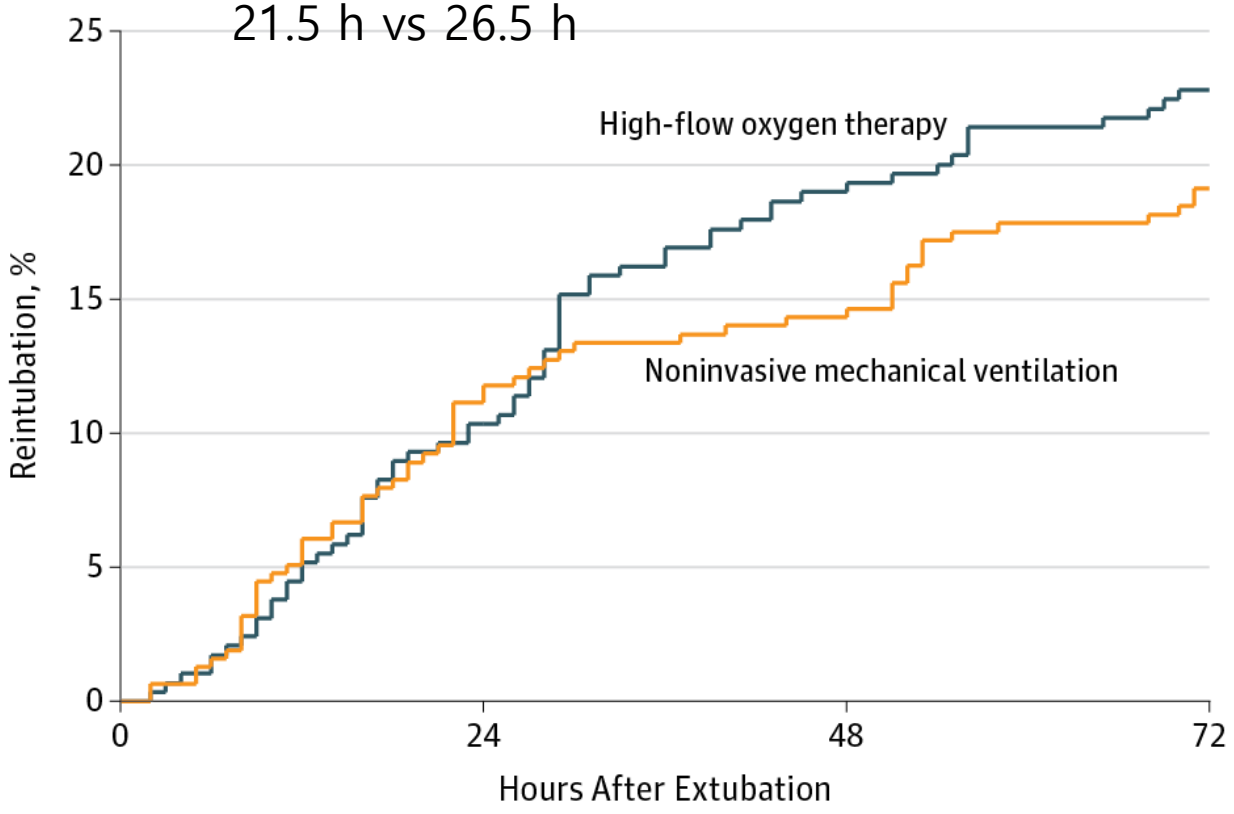
- HFNO is a effective oxygenation modality with variable level of reduced WOB.
  - Potentially effective in de novo, post-extubation ARF and cardiogenic pulmonary edema.
  - Cautiously should be applied in immune-compromised host
- HFNO decreases $PaCO_2$.
- Late intubation can be a disaster!

Post-extubation

High risk,
NIV vs HFNC; Non-inferiority

19.1 % vs 22.8 %

21.5 h vs 26.5 h



Low risk,
Oxygen mask vs HFNC; Non-inferiotry

12.9% vs 4.9 %

15 h vs 19 h