High Frequency Oscillation [without/with Tracheal Gas] Insufflation in ARDS

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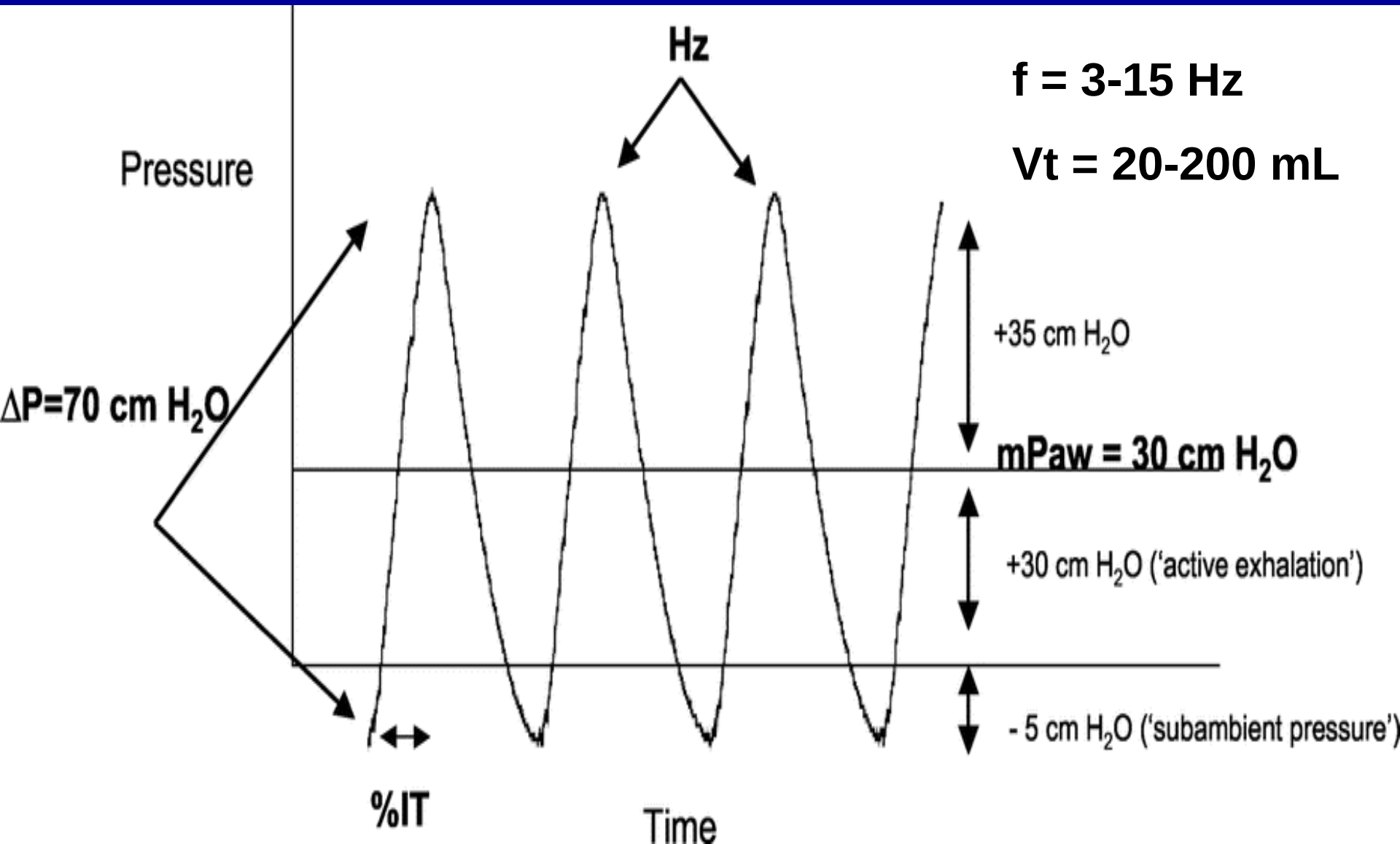
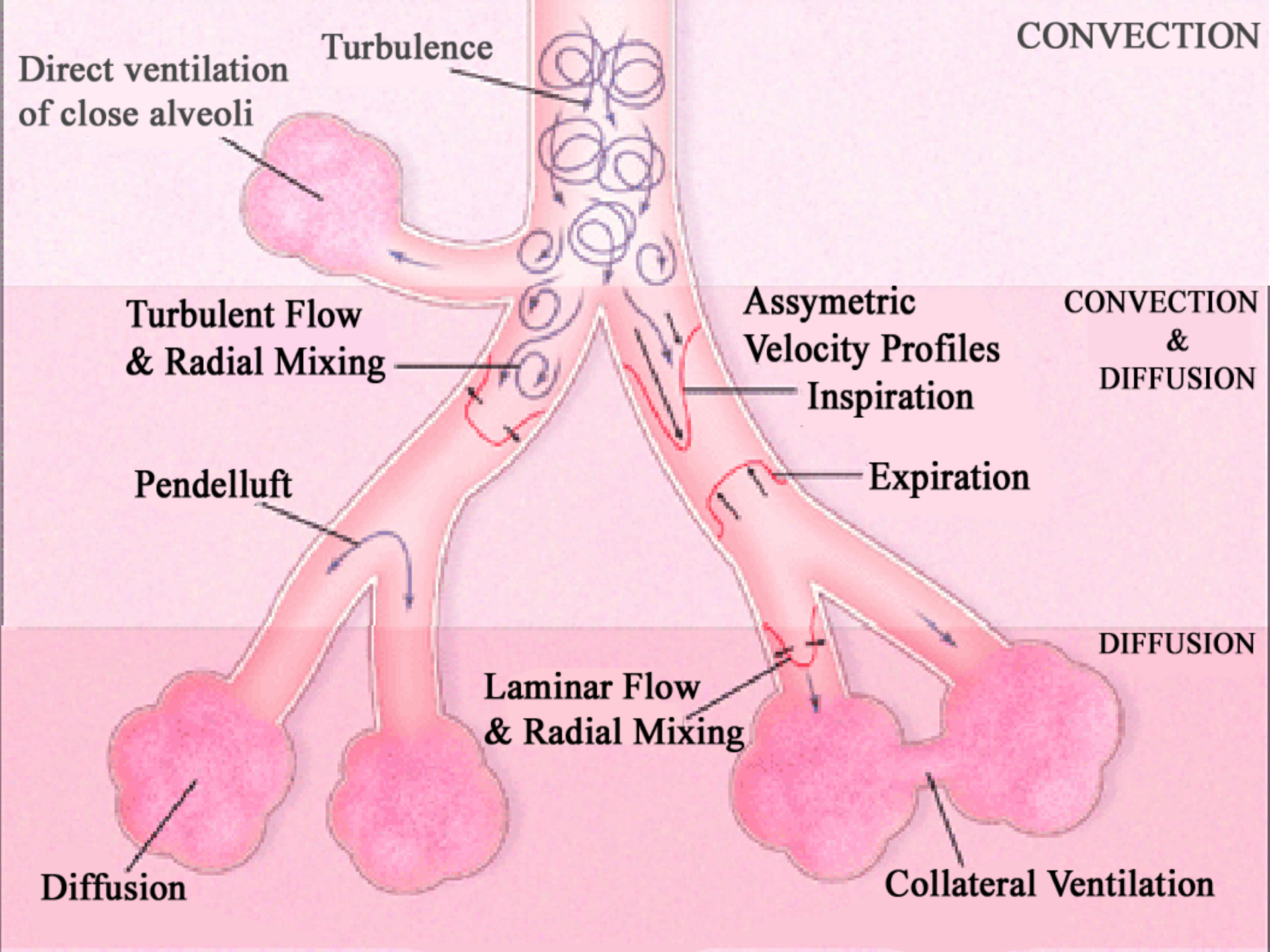
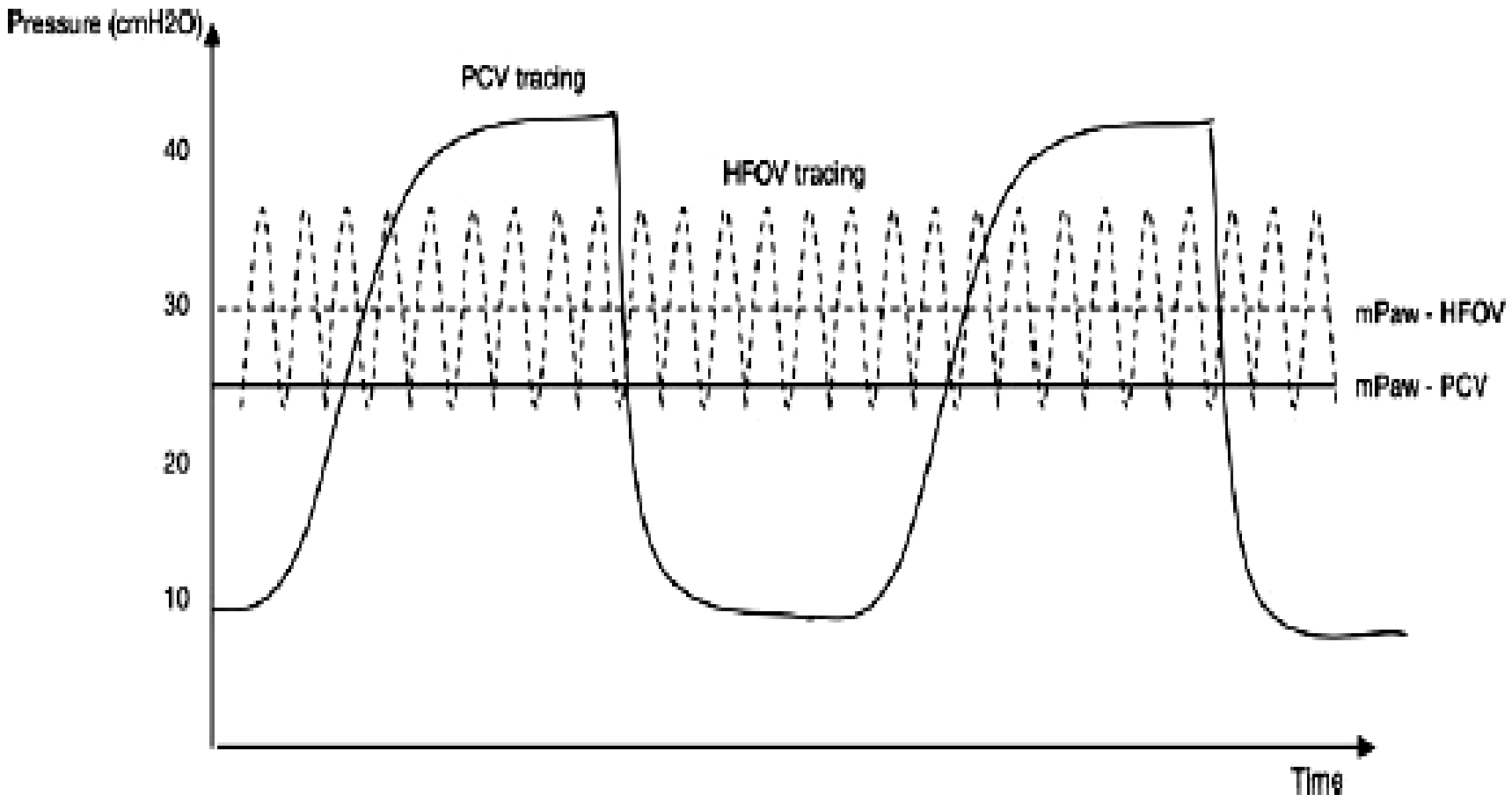
What is HFO?

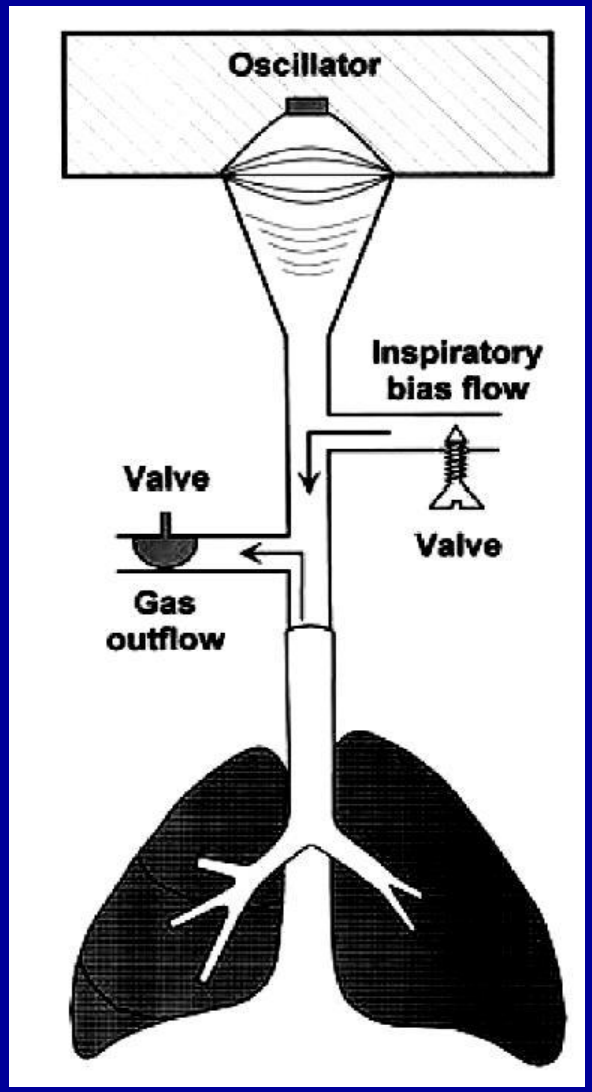

Hz
f = 3-15 Hz
Vt = 20-200 mL
Pressure
+35 cm H_2O
ΔP=70 cm H_2O
mPaw = 30 cm H_2O
+30 cm H_2O ('active exhalation')
- 5 cm H_2O ('subambient pressure')
%IT
Time


CONVECTION
Turbulence
Direct ventilation
of close alveoli
Turbulent Flow
& Radial Mixing
Assymetric
Velocity Profiles
Inspiration
CONVECTION
&
DIFFUSION
Expiration
Pendelluft
DIFFUSION
Laminar Flow
& Radial Mixing
Diffusion
Collateral Ventilation

Comparative Ventilation Pressure Variations During CMV and HFO

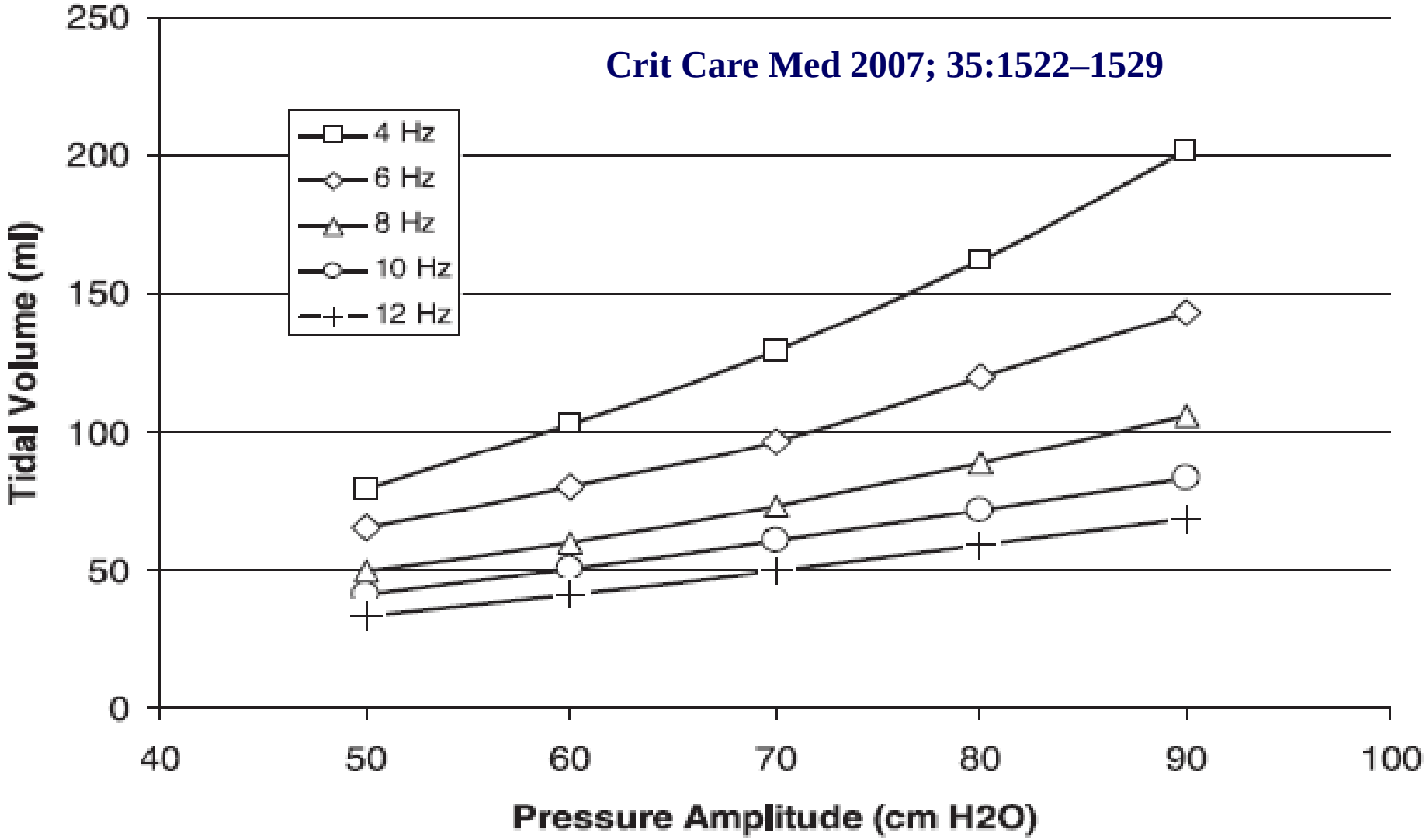


HFO Characteristics

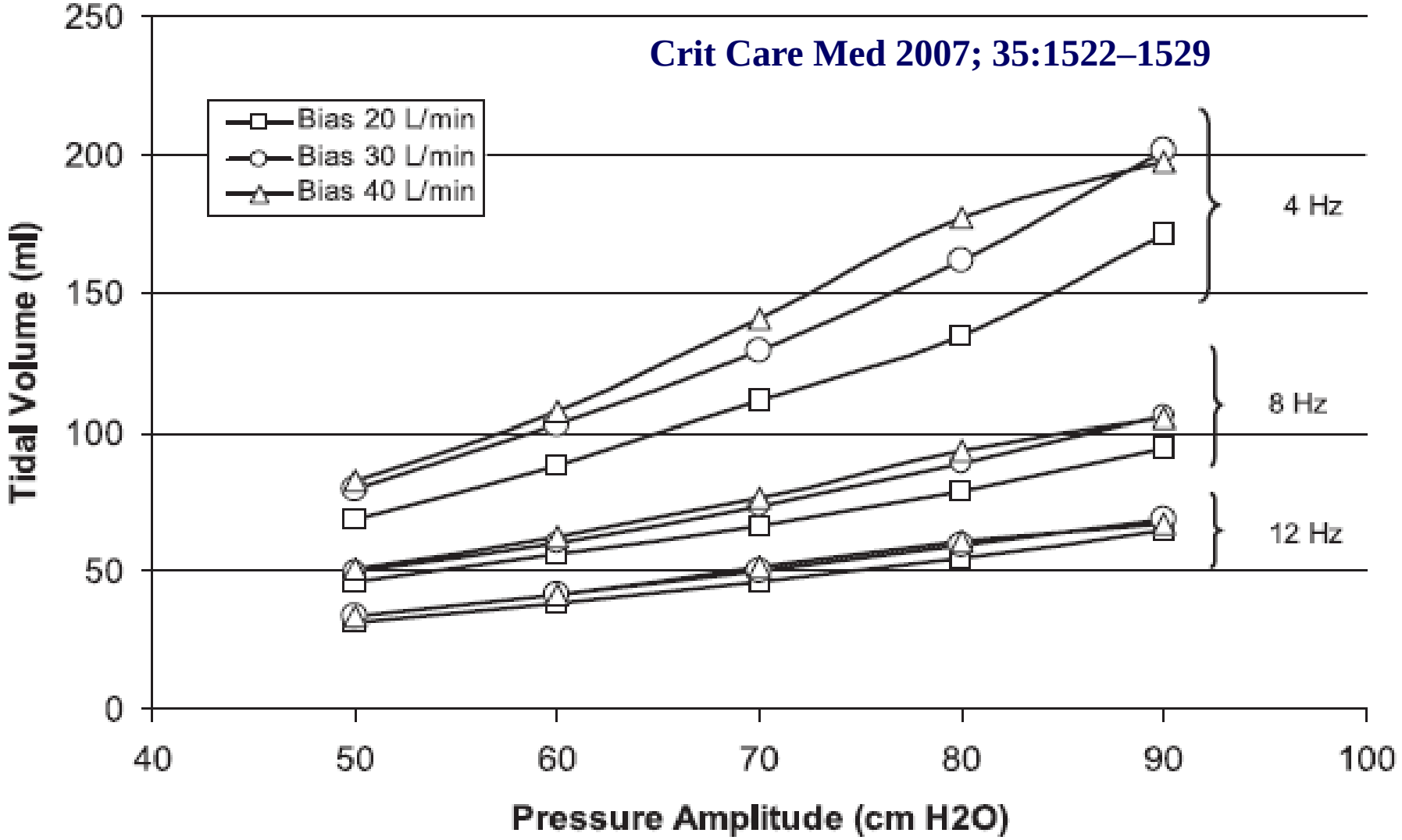


- **Oscillating Piston coupled to Diaphragm**
- **Bias flow of** (20-60 L/min) + PEEP valve for mPaw control
- **Active Exhalation**
- Oxygenation dependent mainly on mPaw and FiO_2
- Ventilation dependent on f, ΔP, and Bias Flow
- **↑Vt with** ↓ f, ↑ ΔP, ↑ I/E ratio

↓ f → ↑ Vt


Crit Care Med 2007; 35:1522–1529
4 Hz
6 Hz
8 Hz
10 Hz
12 Hz
Tidal Volume (ml)
250
200
150
100
50
0
40
50
60
70
80
90
100
Pressure Amplitude (cm H2O)

Bias Flow or ΔP → ↑ Vt



HFO and Lung Protection

- ↑ Oxygenation, ↑ Compliance
- ↑ Surfactant Activity
- ↓ Parenchymal Stress
- ↓ Inflammation

J Appl Physiol 2001;91:1836-1844

Intensive Care Med 2007;33:1423-1433

Crit Care Med 2001;29:2176-2184

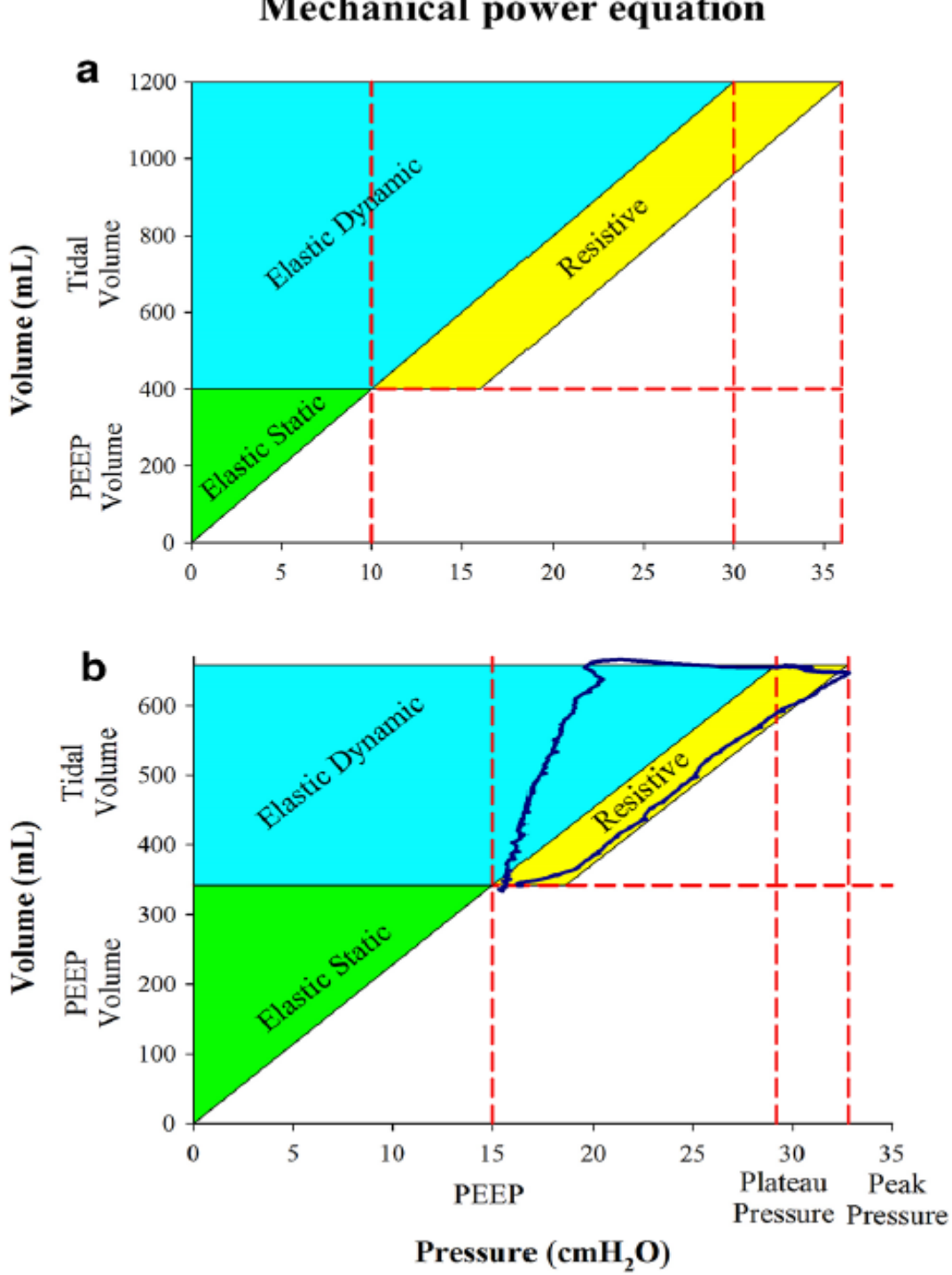
Anesthesiology 2004;99:1102-1011

Pediatr Res 2004;55:339-346

Ventilatc … g injury:
the mecl … (2016) 42:1567–1575

$\text{Power}_{rs} = \text{RR} \ldots + \Delta V \cdot \text{PEEP} \}$

Take-home m … be associated
with lung injury … power
delivered to the … se accurately
reflects the mea … xponentially
with TV, ΔP_{aw}, fl … and linearly
with PEEP.



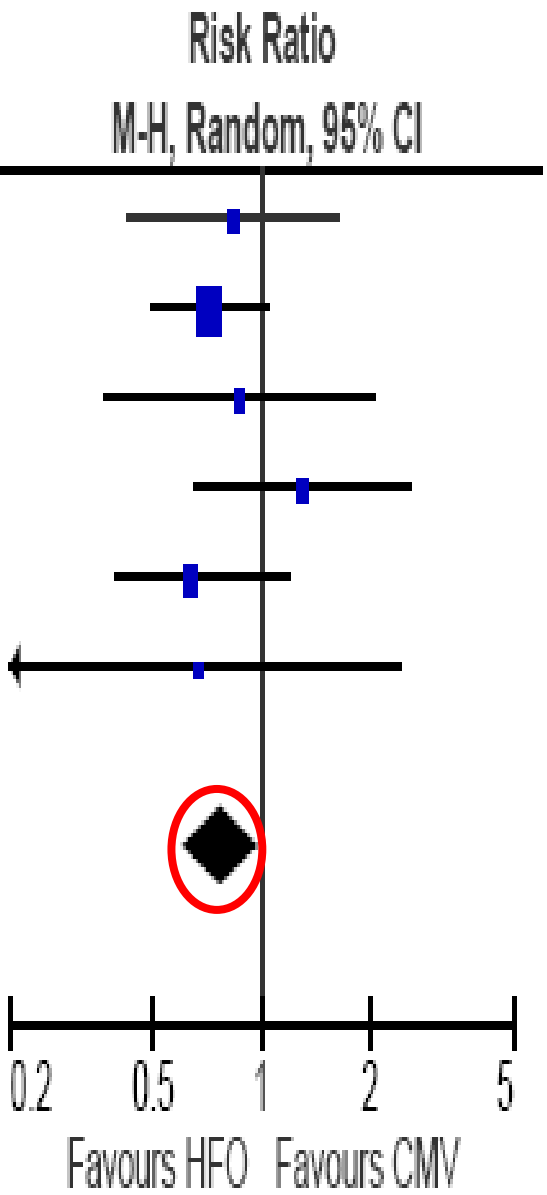
High Frequency Oscillation (HFO)

RCT Data

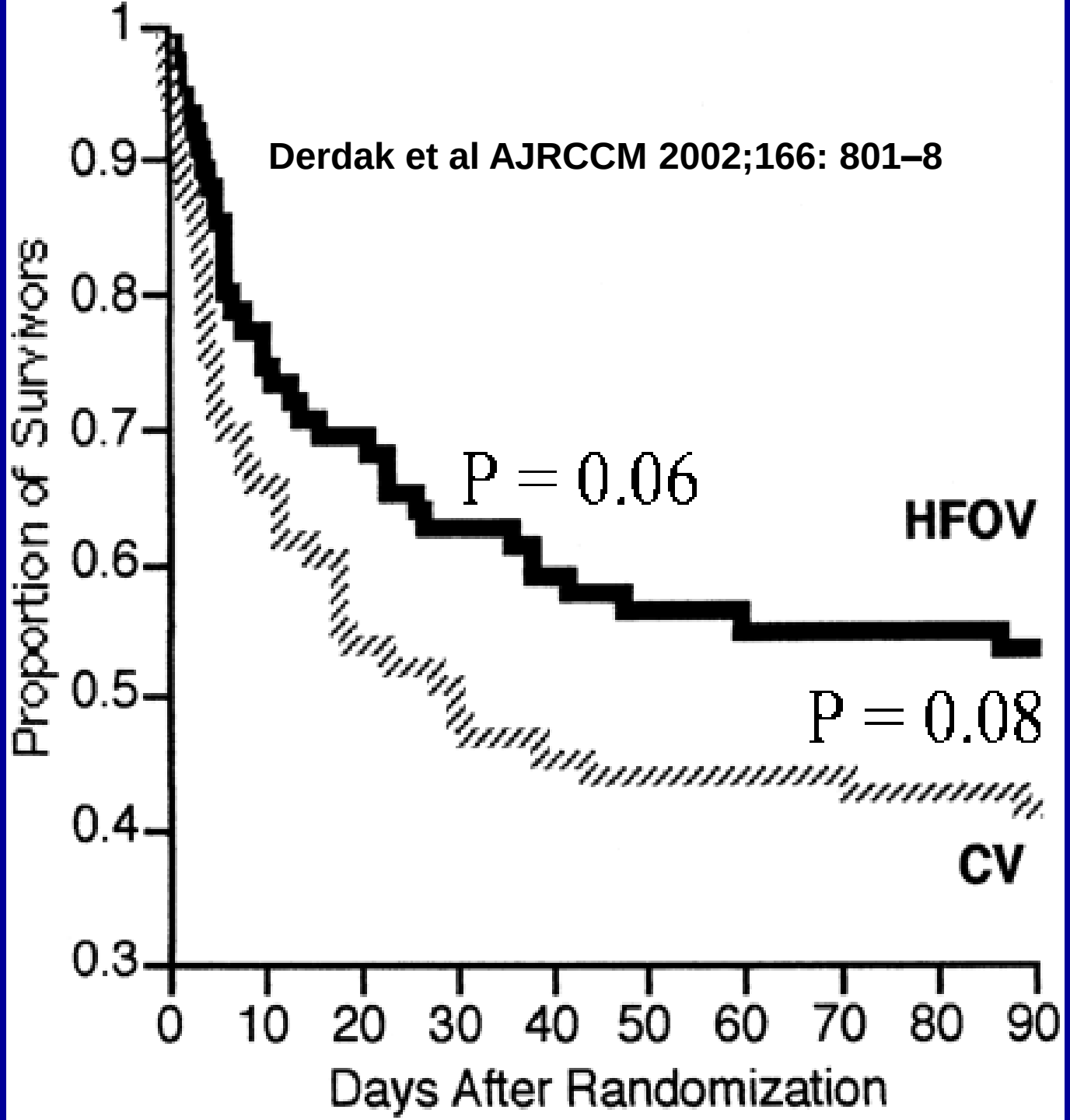
Study or Subgroup	HFO Events	HFO Total	CMV Events	CMV Total	Weight	Risk Ratio M-H, Random, 95% CI
Arnold 1994	10	29	12	29	13.3%	0.83 [0.43, 1.62]
Derdak 2001	28	75	38	73	43.3%	0.72 [0.50, 1.03]
Shah 2004	6	15	6	13	8.0%	0.87 [0.37, 2.04]
Bollen 2005	16	37	8	24	12.8%	1.30 [0.66, 2.55]
Mentzelopoulos 2007	9	27	16	27	19.1%	0.69 [0.40, 1.09]
Samransamruajkit 2007	2	6	5	10	3.5%	0.67 [0.18, 2.42]
Total (95% CI)		**189**		**176**	**100.0%**	**0.79 [0.62, 0.97]**
Total events	73		85			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.73$, df = 5 (P = 0.74); $I^2 = 0\%$

Test for overall effect: Z = 1.96 (P < 0.05)



SURVIVAL TO HOSPITAL DISCHARGE **BMJ 2010; 340: c2327.**


Derdak et al AJRCCM 2002;166: 801–8
Proportion of Survivors
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
P = 0.06
HFOV
P = 0.08
CV
0
10
20
30
40
50
60
70
80
90
Days After Randomization

Major Common Features of earlier RCTs on HFO

- Low f of 4-5 Hz; Low mPaw of ~5 cmH2O above the mPaw of preceding CMV
- ↑ PaO_2/FiO_2 during HFO indicating lung recruitment
- Moderate-to-minimal increases in $PaCO_2$ during HFO
- No report of HFO-induced deterioration in hemodynamics
- Comparison with potentially "less protective CMV“ i.e. higher VT-lower PEEP CMV compared to current protocols (N Engl J Med 2013;368:795-805.)

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

Table 1. Ventilator Protocols.*

Component Variable	HFOV	Control Ventilation
Ventilator mode	High-frequency oscillatory ventilation	Pressure control
Tidal volume target (ml/kg of predicted body weight)	NA	6
Tidal volume range (ml/kg of predicted body weight)	NA	4–8
Plateau airway pressure (cm of water)	NA	≤35
Positive end-expiratory pressure (cm of water)	NA	Adjusted according to oxygenation†
Mean airway pressure (cm of water)	Adjusted according to oxygenation†	Measured but not adjusted
Respiratory frequency	3–12 Hz	≤35 breaths/min
Pressure amplitude target (cm of water)	90	NA
Partial pressure of arterial oxygen (mm Hg)	55–80	55–80
Oxygen saturation by pulse oximetry (%)	88–93	88–93
Arterial blood pH	7.25–7.35	7.30–7.45
Ratio of inspiratory-to-expiratory time	1:2	1:1–1:3
Recruitment maneuvers	Yes	Yes

* The full version of the study protocol is available at NEJM.org. HFOV denotes high-frequency oscillatory ventilation, and NA not applicable.
† For more information on the protocol for adjustment, see Table 2.

Ferguson ND et al. N Engl J Med 2013;368:795-805.

The NEW ENGLAND JOURNAL of MEDICINE

Combinations of FiO_2 and PEEP Or Mean Airway Pressure Used to Adjust Ventilators.

Table 2. Usual Combinations of the Fraction of Inspired Oxygen (FiO_2) and Positive End-Expiratory Pressure (PEEP) or Mean Airway Pressure Used to Adjust Ventilators.

HFOV		Control Ventilation	
FiO_2	Mean Airway Pressure *cm of water*	FiO_2	PEEP *cm of water*
0.4	20	0.3	5
0.4	22	0.3	8
0.4	24	0.3	10
0.4	26	0.4	10
0.4	28	0.4	12
0.4	30	0.4	14
0.5	30	0.4	16
0.6	30	0.4	18
0.6	32	0.5	18
0.6	34	0.5	20
0.7	34	0.6	20
0.8	34	0.7	20
0.9	34	0.8	20
1.0	34	0.8	22
1.0	36	0.9	22
1.0	38	1.0	22
		1.0	24

HFO

f ~ 6.8 Hz

NO CUFF LEAK

High mPaw

CMV
High PEEP

Ferguson ND et al. N Engl J Med 2013;368:795-805.

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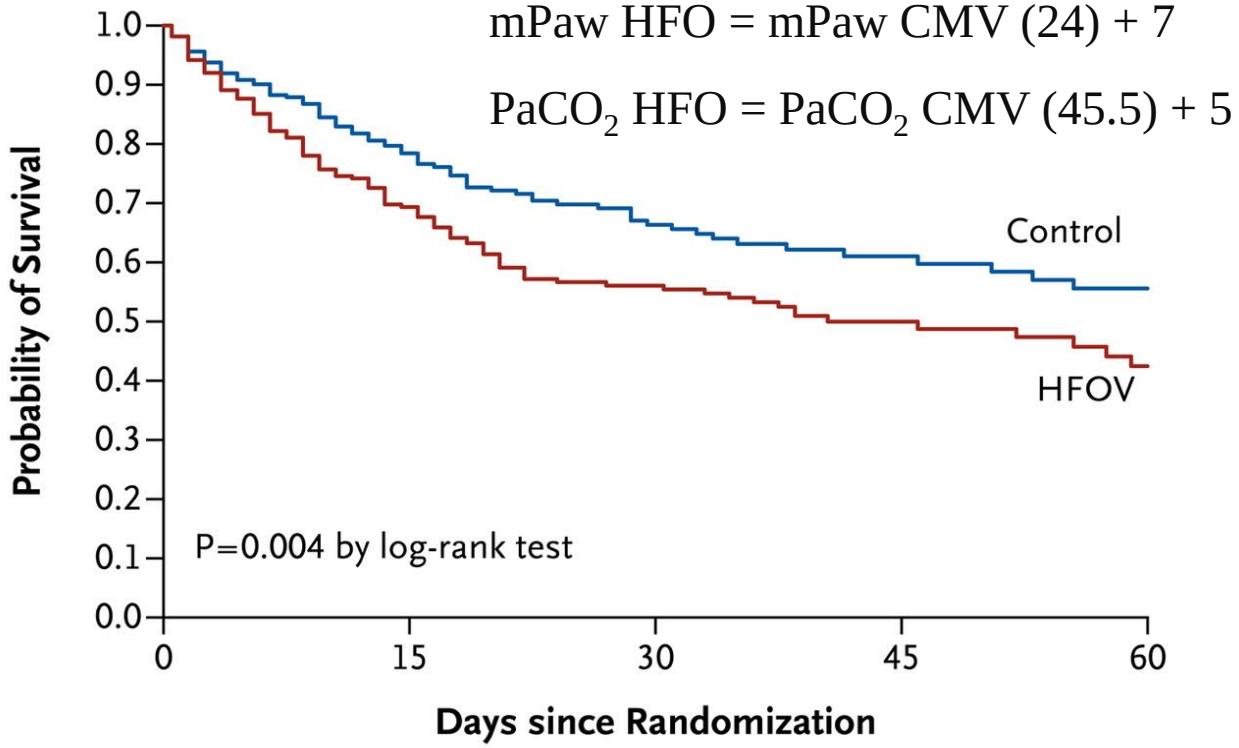
Probability of Survival from the Day of Randomization to Day 60 in the HFOV and Control Groups.



No. at Risk					
HFOV	275	169	98	54	26
Control	273	181	92	54	39

Ferguson ND et al. N Engl J Med 2013;368:795-805.

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Young et al Trial; Ventilatory Variables during the First 3 Study Days.

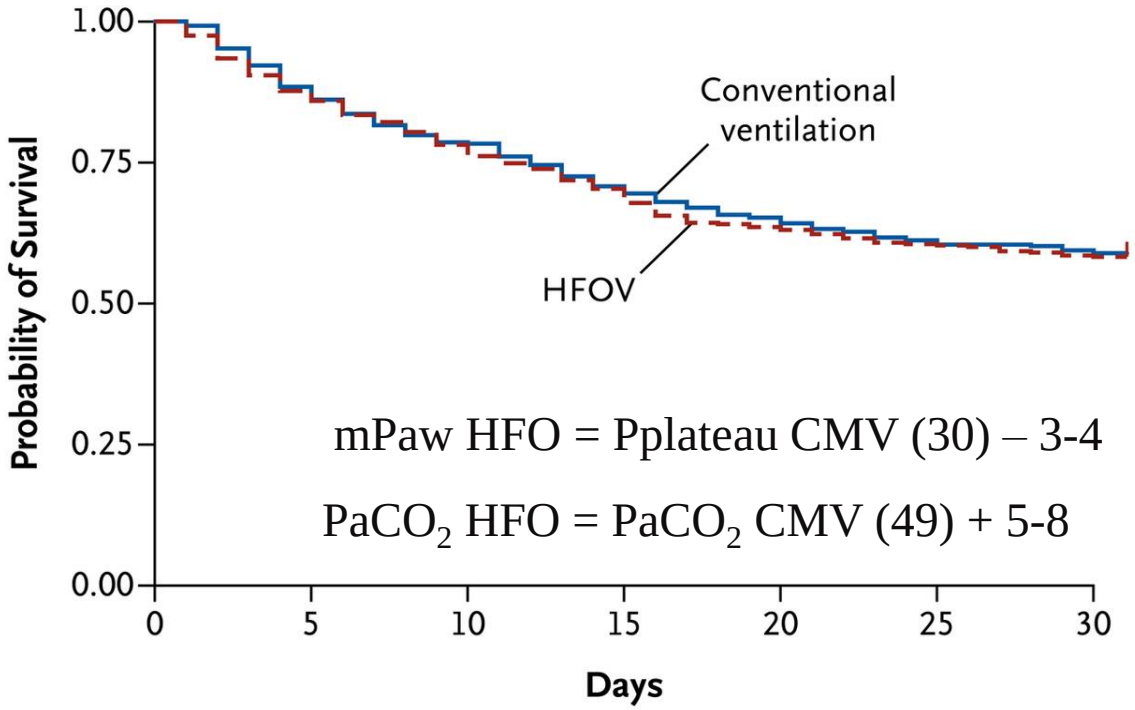
Table 2. Ventilatory Variables during the First 3 Study Days.*

Variable	Day 1		Day 2		Day 3	
	HFOV	Conventional Ventilation	HFOV	Conventional Ventilation	HFOV	Conventional Ventilation
No. of patients	370	392	326	374	240	348
Mean airway pressure (HFOV) or plateau pressure (conventional ventilation) — cm of water	26.9±6.2	30.9±11.0	25.3±5.5	29.5±10.7	25.1±5.4	28.5±11.2
Total respiratory frequency — Hz (HFOV) or breaths/min (conventional ventilation)	7.8±1.8	21.7±8.4	7.5±1.8	22.7±9.0	7.2±1.8	23.3±8.2
Cycle volume (HFOV) or tidal volume (conventional ventilation) — ml (HFOV) or ml/kg of ideal body weight (conventional ventilation)	213±72	8.3±2.9	228±75	8.2±2.5	240±75	8.3±3.0
Positive end-expiratory pressure — cm of water (conventional ventilation only)	NA	11.4±3.6	NA	11.0±3.6	NA	10.5±3.7
Pa_{O_2}:Fi_{O_2} ratio — mm Hg	192±77	154±61	212±69	163±66	217±69	166±63
Pa_{CO_2} — mm Hg	55±17	50±19	56±16	49±13	56±17	48±13
Arterial pH	7.30±0.10	7.35±0.10	7.32±0.09	7.37±0.10	7.34±0.10	7.39±0.09
Medication use — no. (%)†						
Neuromuscular-blocking agent	209 (52.5)	165 (41.6)	147 (36.9)	115 (29.0)	110 (27.6)	77 (19.4)
Vasoactive or inotropic agent	173 (43.5)	177 (44.6)	158 (40.0)	146 (36.8)	126 (31.7)	112 (28.2)
Sedative agent	390 (98.0)	388 (97.7)	371 (93.2)	363 (91.4)	341 (85.7)	335 (84.4)

Young D et al. N Engl J Med 2013;368:806-813.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Survival Estimates during the First 30 Study Days.



No. at Risk							
Conventional ventilation	397	351	312	281	259	243	236
HFOV	398	349	311	280	253	241	233

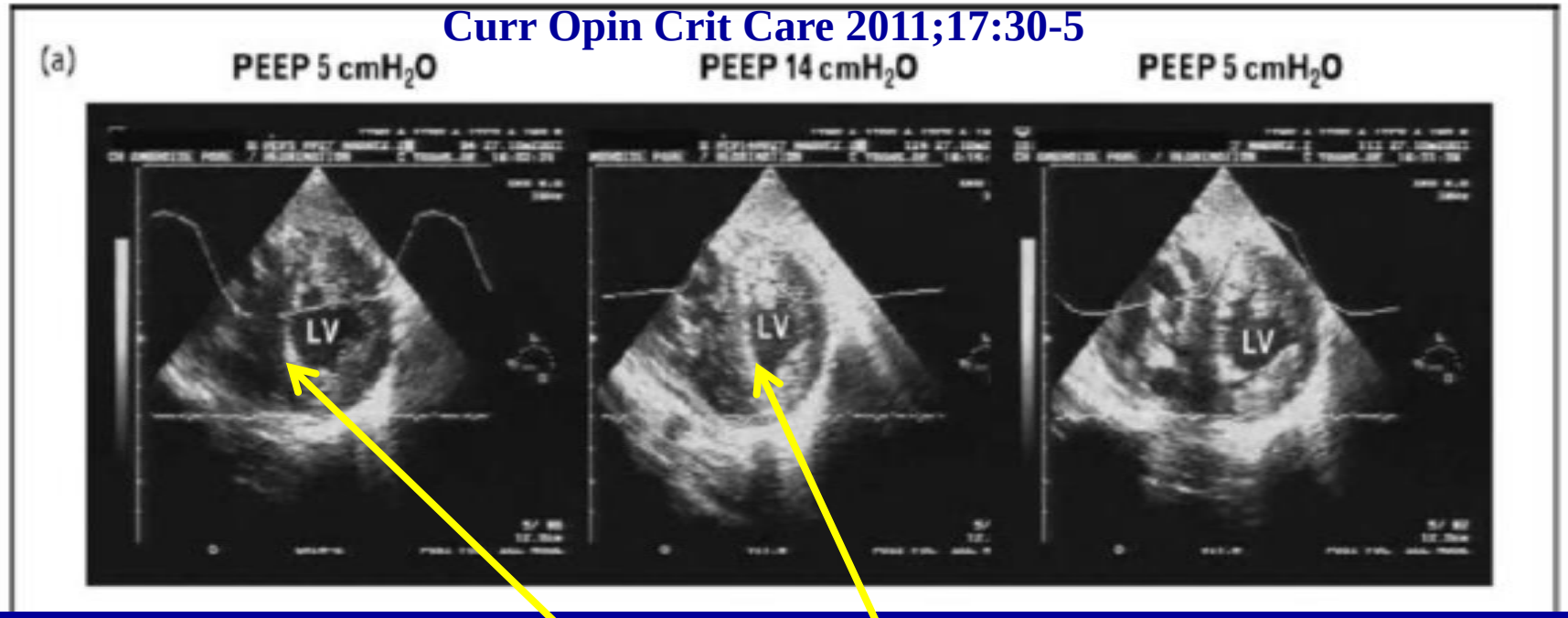
Young D et al. N Engl J Med 2013;368:806-813.

The NEW ENGLAND JOURNAL of MEDICINE

Can High Ventilation Pressures cause Right Ventricular Dysfunciton and Impact Patient Outcomes?

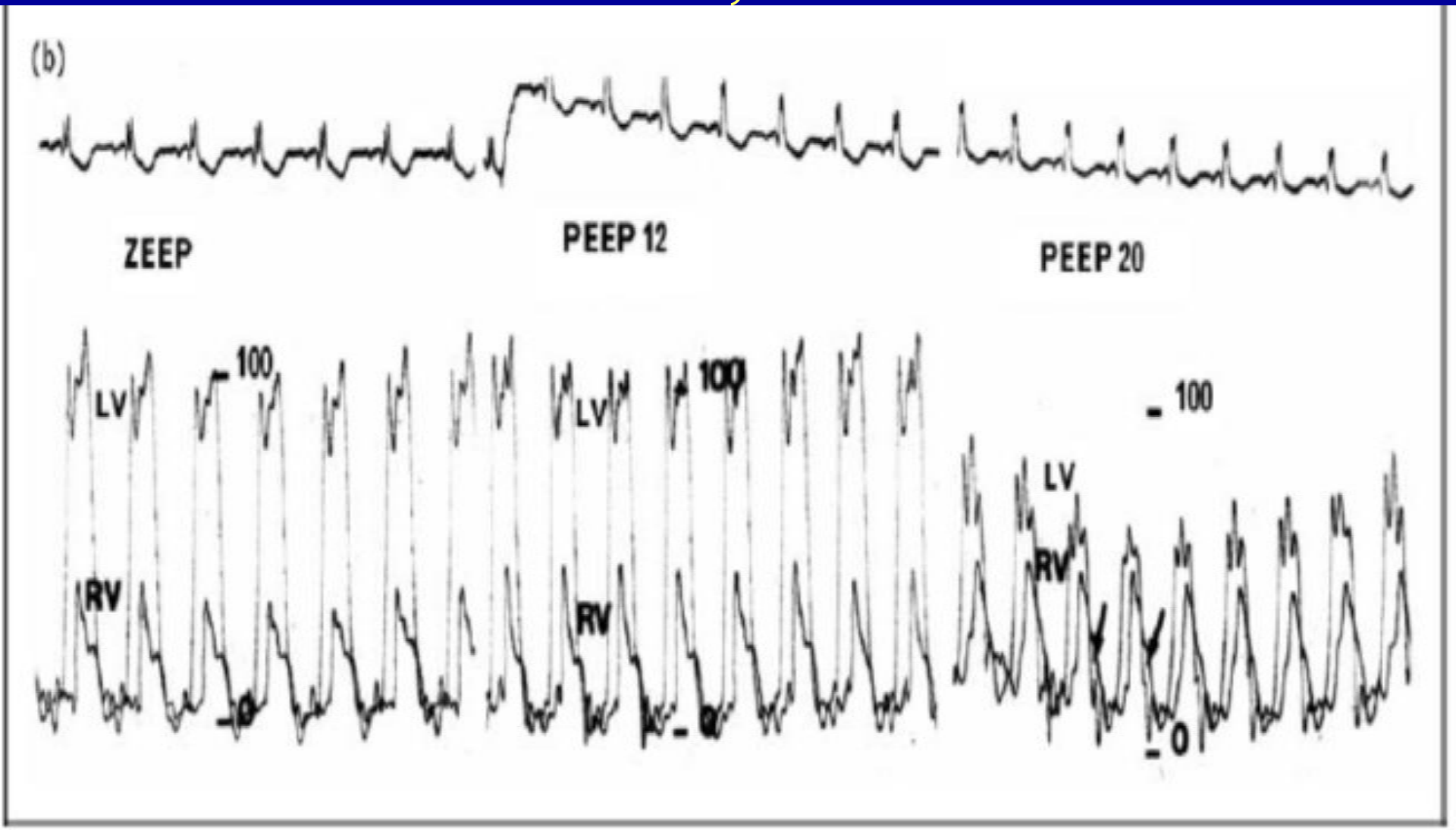
Figure 5 Effects of increasing positive end-expiratory pressure on right ventricular systolic function

Curr Opin Crit Care 2011;17:30-5



Transgastric TEE View: IVS and its Leftward Shift caused by PEEP increase

Inversion of RV to LV end-systolic pressure gradient with increasing PEEP NEJM 1981;304:387-92



Intensive Care Med (2009) 35:1850–1858
DOI 10.1007/s00134-009-1569-2

ORIGINAL

Armand Mekontso Dessap
Cyril Charron
Jérôme Devaquet
Jérôme Aboab
François Jardin
Laurent Brochard
Antoine Vieillard-Baron

Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome

Table 3 Echocardiographic variables

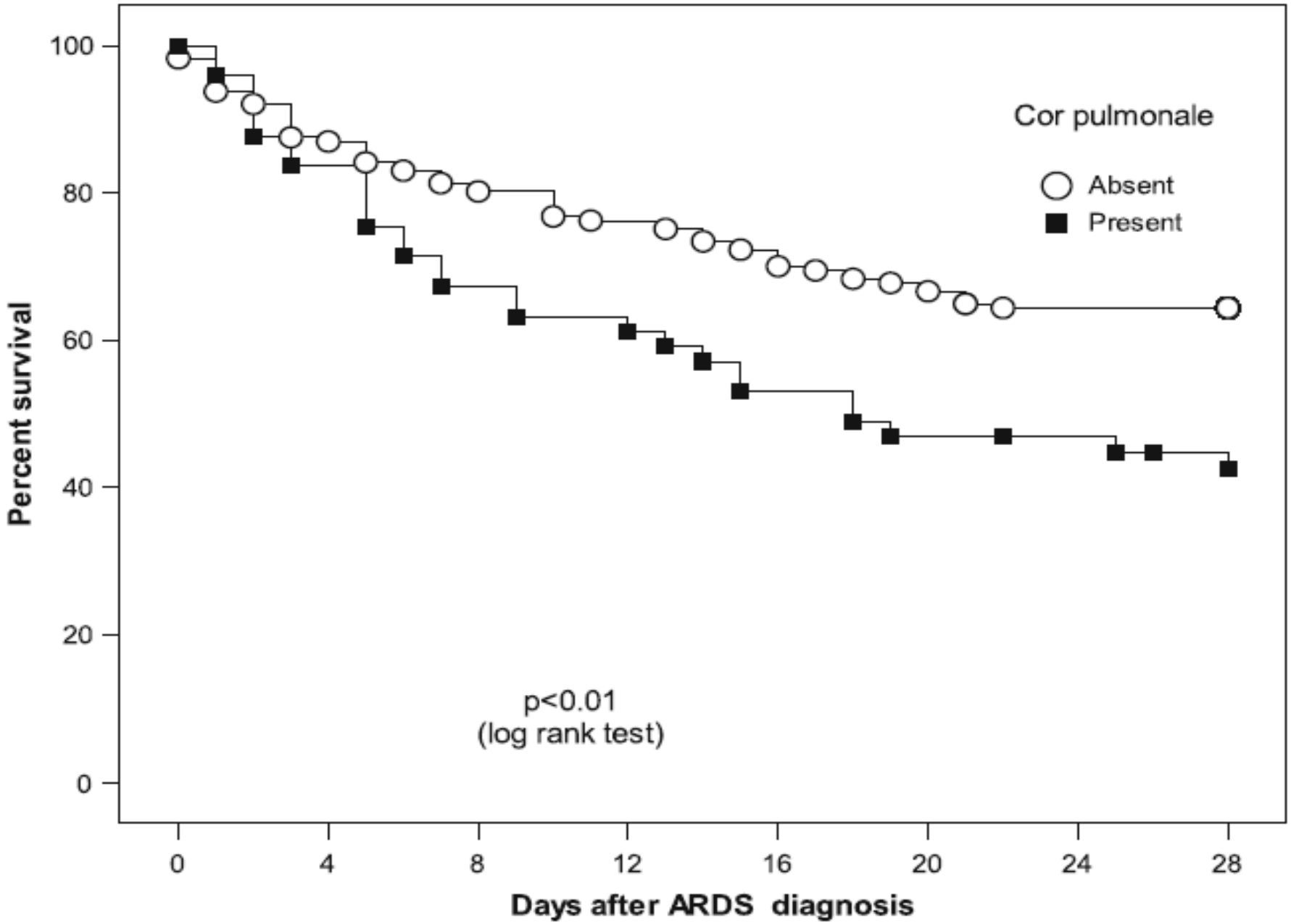
	LP strategy	HP/HR strategy	HP/LR strategy
LV ejection fraction (%)	62 (57–71)	64 (49–67)	59 (53–66)
LV fractional area contraction (%)	58 (55–65)	57 (53–70)	62 (54–65)
LV maximal systolic elastance (mmHg/mL)	5.5 (3.9–6.3)	5.2 (4.1–6.6)	5.4 (4.3–7.2)
Superior vena cava collapsibility index (%)	0 (0–26)	0 (0–8)	0 (0–23)
RV stroke index (cm^3/m^2)	22 (20–32)	17 (10–26)*	16 (11–27)*
Cardiac index ($L/min/m^2$)	2.60 (1.53–3.54)	1.87 (1.16–2.98)*	1.89 (1.38–3.35)*
End-systolic eccentricity index	1.10 (1.02–1.25)	1.19 (1.07–1.54)*	1.28 (1.00–1.52)*
End-diastolic RV/LV area ratio	0.64 (0.56–0.77)	0.85 (0.62–1.10)*	1.0 (0.69–1.20)*,#
End-diastolic RV/LV area ratio >0.6	7 (64%)	9 (82%)	9 (82%)

Data are medians (interquartile range)

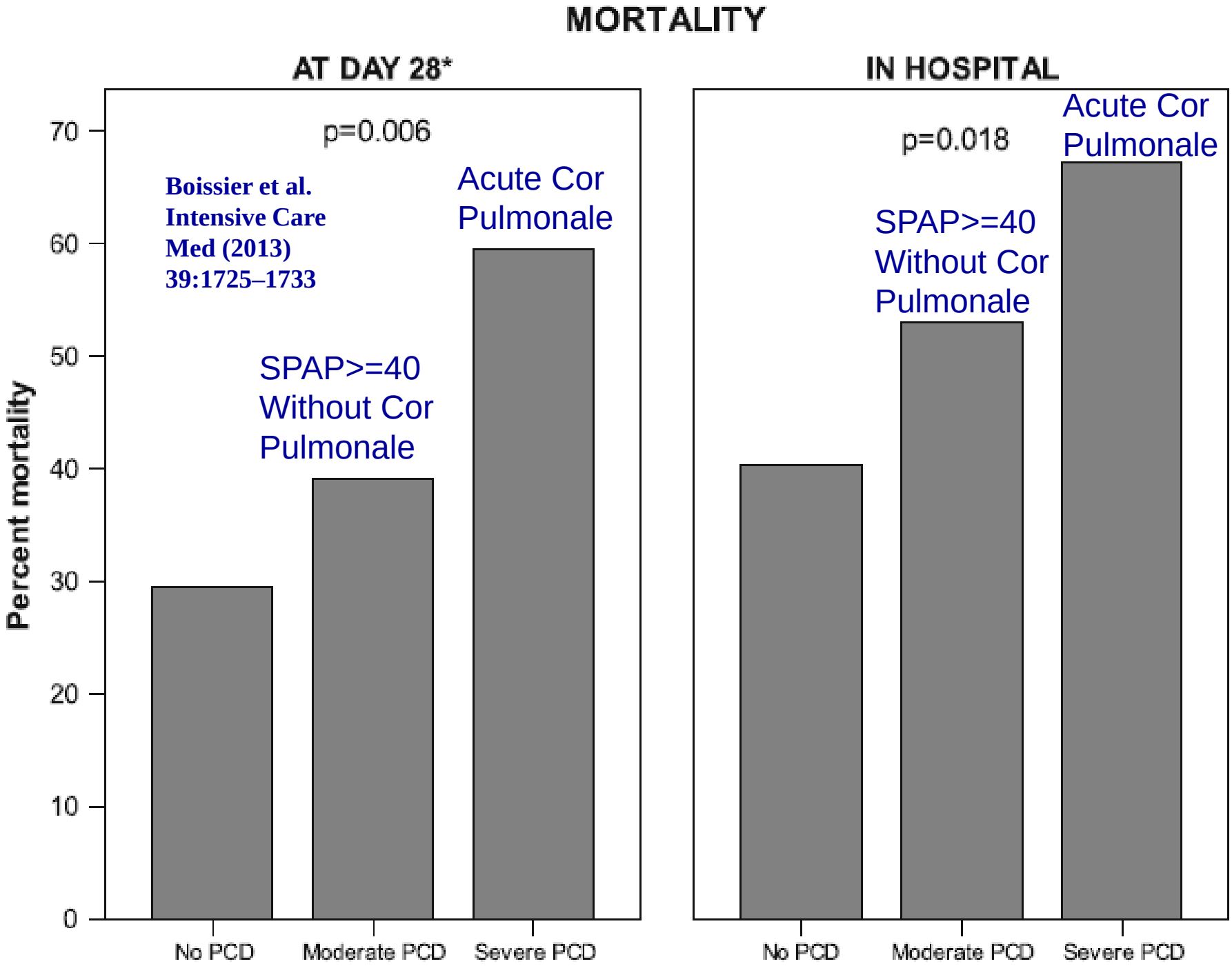
LP low positive end-expiratory pressure, *HP* high positive end-expiratory pressure, *HR* high respiratory rate, *LR* low respiratory rate, *LV* left ventricle, *RV* right ventricle, see text for definitions

* $p < 0.05$ compared to the LP strategy

\# $p < 0.05$ compared to the HP/HR strategy



Number at risk								
Cor pulmonale								
No	177	154	143	135	127	119	113	112
Yes	49	41	33	31	26	23	22	19

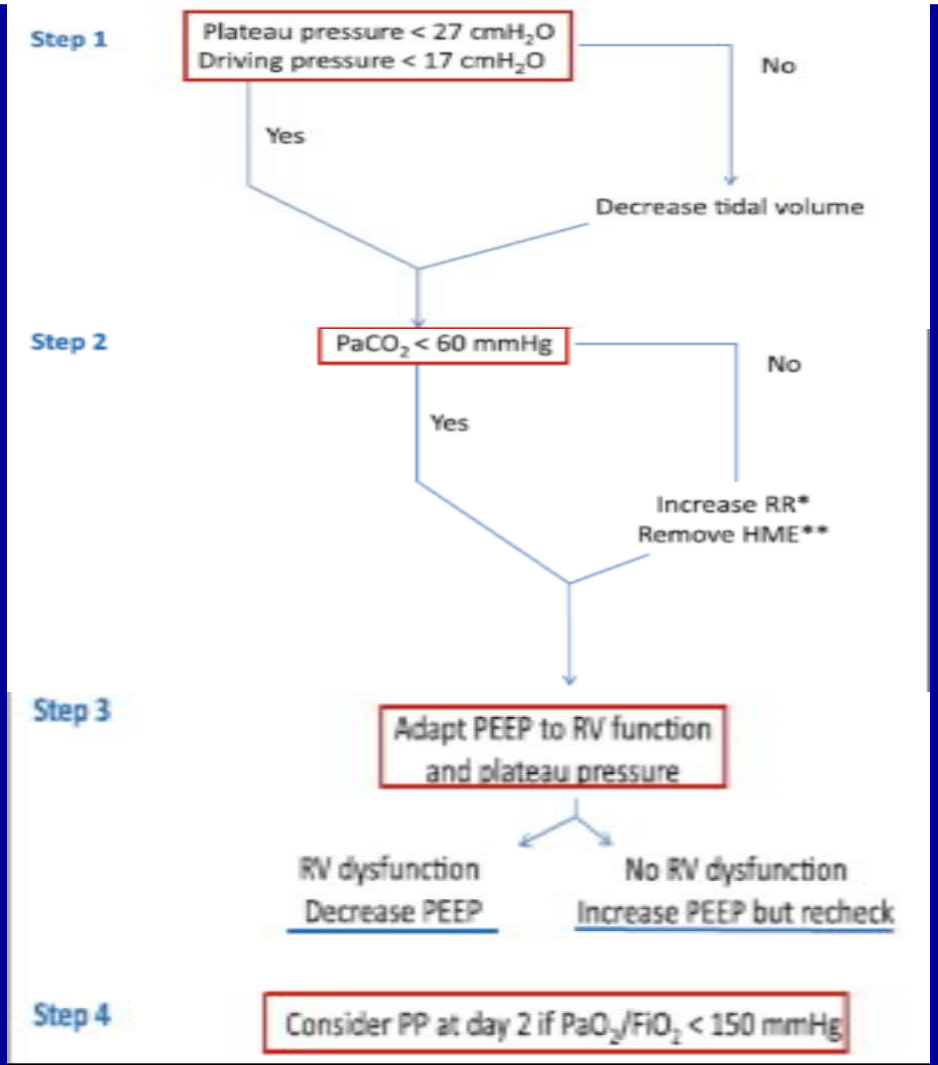

MORTALITY
AT DAY 28*
IN HOSPITAL
Percent mortality
0
10
20
30
40
50
60
70
p=0.006
p=0.018
Boissier et al.
Intensive Care
Med (2013)
39:1725–1733
Acute Cor
Pulmonale
SPAP>=40
Without Cor
Pulmonale
No PCD
Moderate PCD
Severe PCD

Intensive Care Med (2013) 39:1836–1838
DOI 10.1007/s00134-013-3045-2

WHAT'S NEW IN INTENSIVE CARE

A. Vieillard-Baron
L. C. Price
M. A. Matthay

Acute cor pulmonale in ARDS



Intensive Care Med (2013) 39:1836–1838
DOI 10.1007/s00134-013-3045-2

WHAT'S NEW IN INTENSIVE CARE

A. Vieillard-Baron
L. C. Price
M. A. Matthay

Acute cor pulmonale in ARDS

- RV function should be monitored in moderate to severe ARDS
- PROSEVA positive results: Prone position may unload the RV by reversing hypoxemia (without PEEP increase) and reducing $PaCO_2$
- OSCILLATE negative results: HFO-associated RV failure

Guervilly et al. Right ventricular function during HFO in ARDS. Crit Care Med 2012; 40:1539–1545

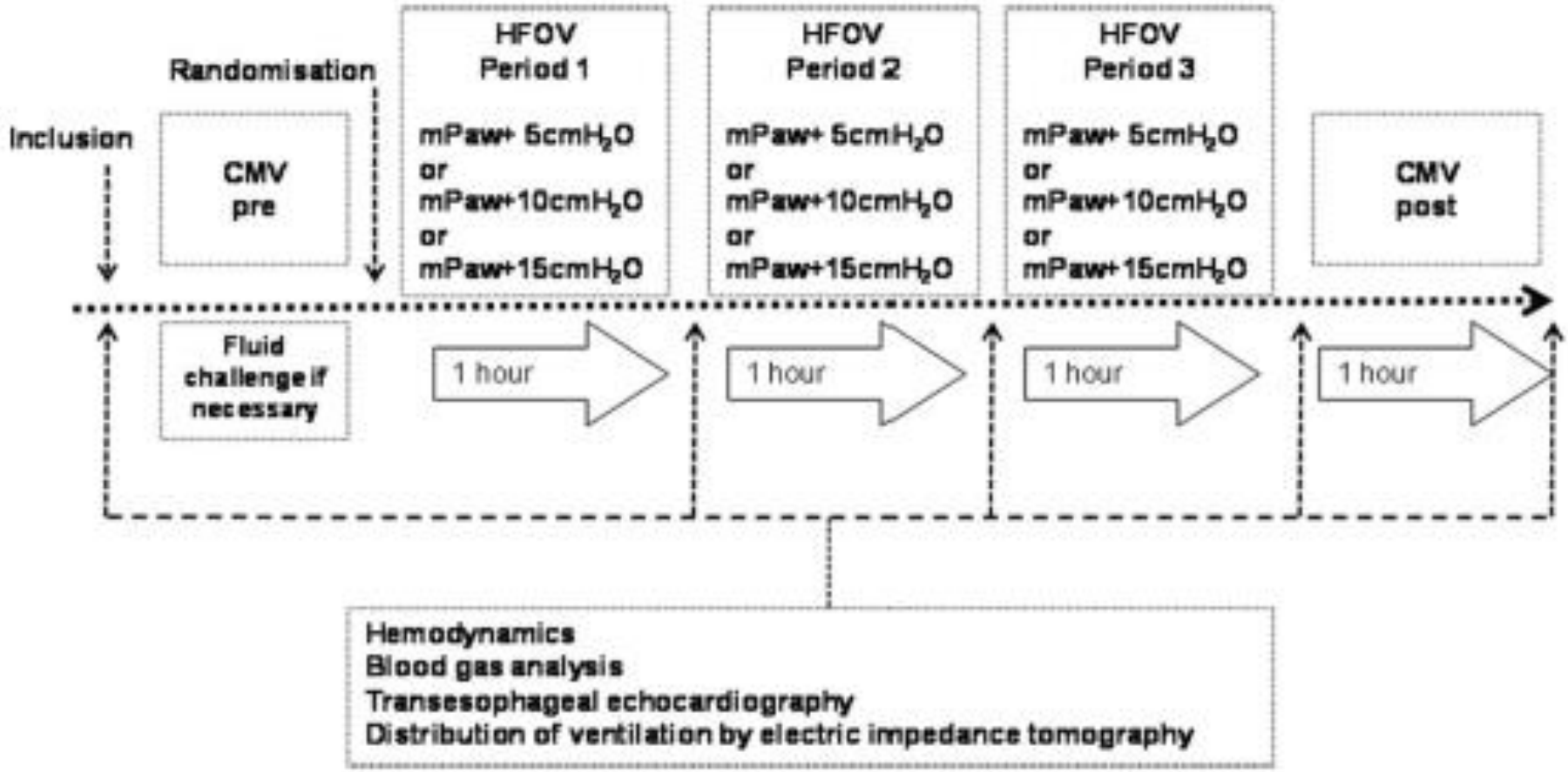
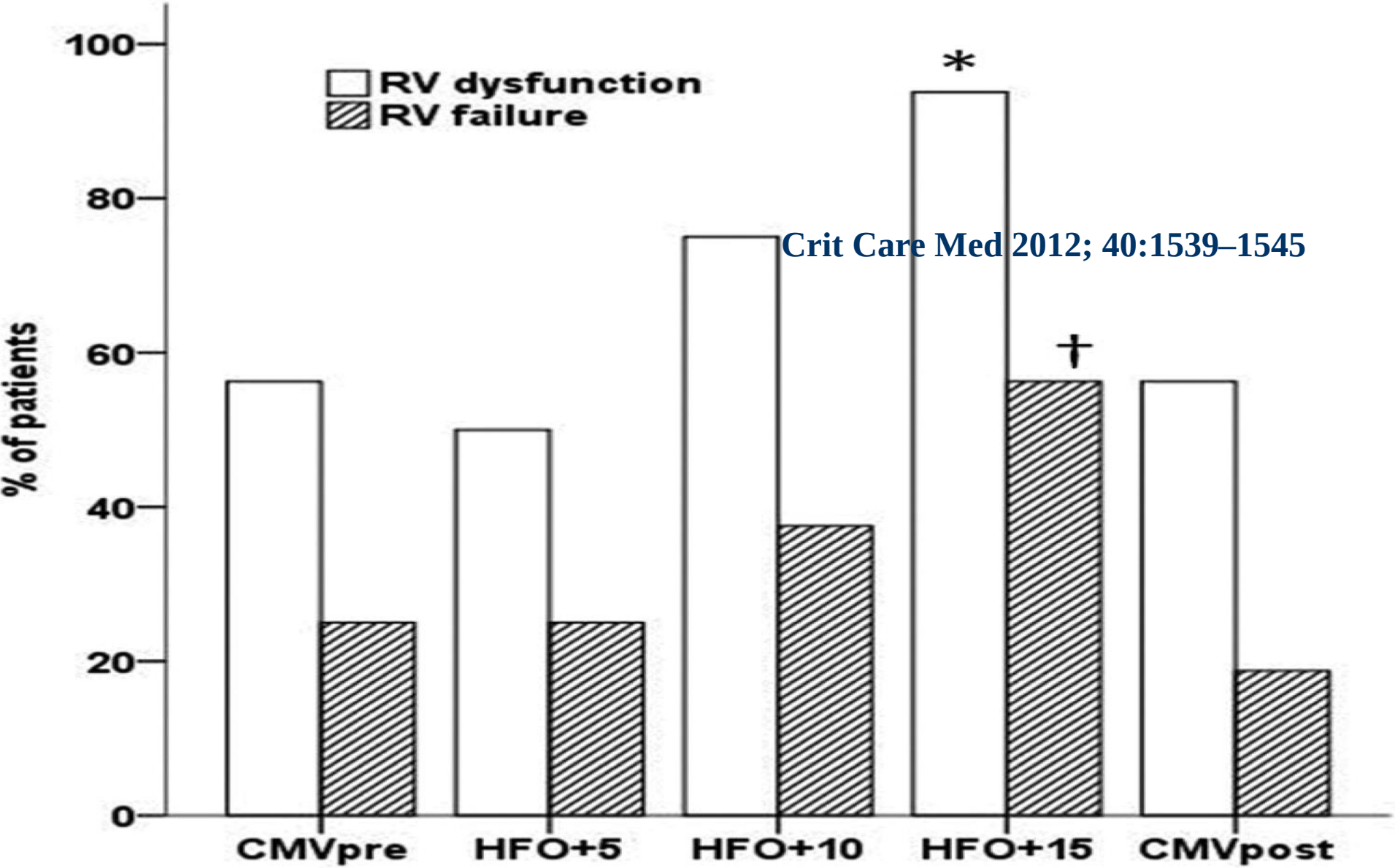


Figure 1. Study design. *CMV*, conventional mechanical ventilation; *HFOV*, high-frequency oscillatory ventilation; *mPaw*, mean airway pressure.

Age (yrs)	63 ± 13
Gender (male), n (%)	10 (62)
Body mass index ($kg \cdot m^{-2}$)	30 ± 9
Simplified Acute Physiology Score II at admission	48 ± 20
Sequential Organ Failure Assessment the admission	9 ± 4
Intensive care unit mortality, n (%)	9 (56)
Direct lung injury, n (%)	14 (87)
Computed tomography scan or radiograph presentation (lobar/diffuse), n	9 of 7
Pao_2/Fio_2 ratio (mm Hg)	127 ± 46
Fio_2	0.73 ± 0.18
$Paco_2$ (mm Hg)	45 ± 8
Positive end-expiratory pressure (cm H_2O)	13 ± 3
Tidal volume (mL/mL/kg)	407 ± 55/6.6 ± 0.8
Respiratory rate (cycleg·min^{-1})	24 ± 5
Plateau airway pressure (cm H_2O)	25 ± 3
Mean airway pressure (cm H_2O)	18 ± 3

Variable	Conventional Mechanical Ventilation Pre	HFO + 5	HFO + 10	HFO + 15	Conventional Mechanical Ventilation Post	p
Transesophageal echocardiography data						
RVEDA/LVEDA ratio	0.64 [0.46–0.92][b]	0.60 [0.52–0.87][b]	0.91 [0.57–1.15]	0.90 [0.73–1.55]	0.64 [0.49–0.85][b]	<.001
RVEDA/LVEDA ratio >0.6, n(%)	9 (56)[b]	8 (50)[b]	12 (75)	15 (93)	9 (56)[b]	
RVEDA/LVEDA ratio >0.9, n(%)	4 (25)[a]	4 (25)[a]	6 (37)	9 (56)	3 (19)[a]	
End-diastolic eccentricity index	1.03 [0.99–1.09][b]	1.13 [1.02–1.19][a]	1.13 [1.08–1.21]	1.28 [1.16–1.41]	1.09 [1.04–1.19][b]	.001
Hemodynamics						
Heart rate, beats/min	86 ± 19	89 ± 20	89 ± 21	89 ± 21	86 ± 18	.99
Mean arterial pressure, mm Hg	80 ± 11	79 ± 13	79 ± 11	76 ± 11	80 ± 13	.92
Right atrial pressure, mm Hg	11 ± 4	12 ± 4	13 ± 5	15 ± 7	12 ± 5	.20
Mean pulmonary arterial pressure, mm Hg	28 ± 7[a]	29 ± 7	33 ± 9	36 ± 9	27 ± 7[a]	.015
Pulmonary artery occlusion pressure, mm Hg	13 ± 4	13 ± 4	15 ± 5	17 ± 5	11 ± 5[a]	.017
Cardiac index (L/min/m^2)	3.2 [2.6–4.1][a]	3.2 [2.4–4.1][a]	3.1 [2.2–3.7]	2.7 [2–3.6]	3.1 [2.4–3.5][a]	.003
Systemic vascular resistances index (dynes-sec-cm^{-5}-m^{-2})	1519 [1210–2145]	1513 [1228–2191]	1682 [1400–2400]	1743 [1188–2960]	1800 [1187–2509]	.39
Pulmonary vascular resistances index (dynes-sec-cm^{-5}-m^{-2})	327 [240–412][b]	390 [281–554][b]	438 [267–600]	489 [311–838]	313 [274–514][b]	.001
Mixed venous oxygen saturation (%)	70 ± 6	70 ± 8	68 ± 8	65 ± 7	69 ± 5	.24

Guervilly et al. Right ventricular function during HFO in ARDS



Crit Care Med 2012; 40:1539–1545

Guervilly et al. Right ventricular function during HFO in ARDS

- RV stress was greater when HFO did not seem to recruit the posterior parts of the lungs as shown by electrical impedance tomography.

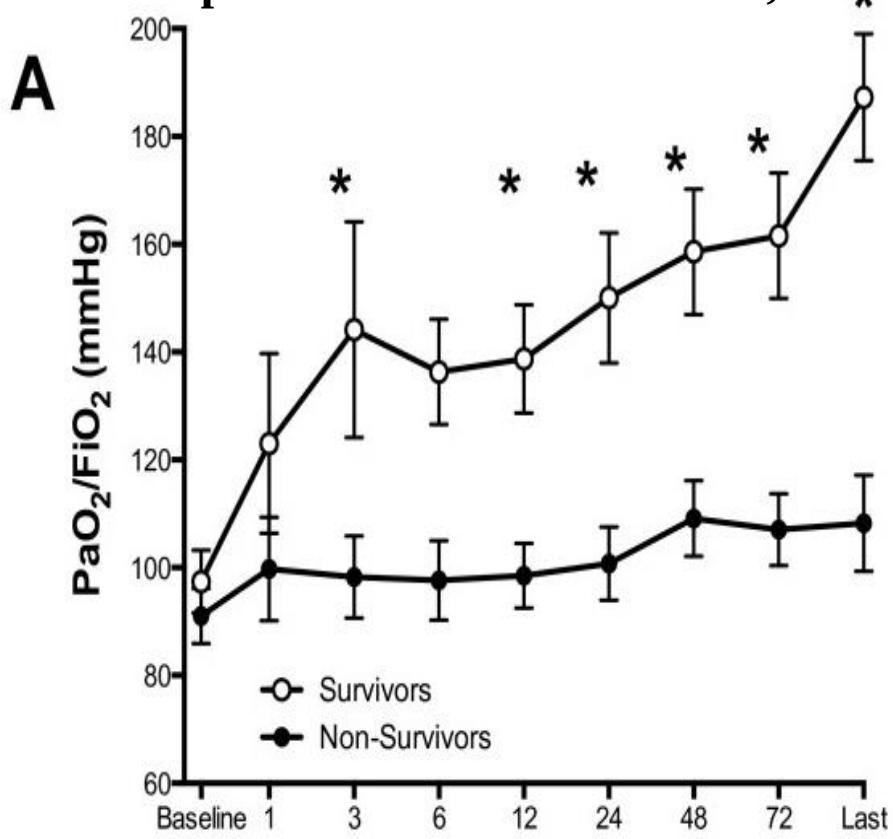
Guervilly et al, Conclusions

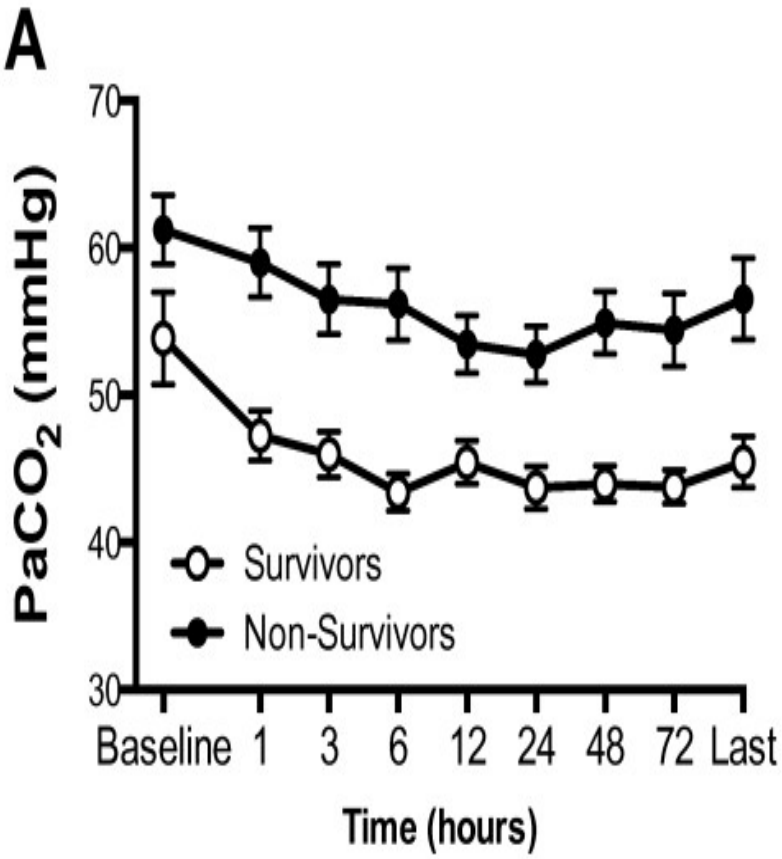
In pulmonary ARDS, using high mPaw under HFO can worsen right ventricular function when compared with protective conventional mechanical ventilation, notably in patients in whom HFO produced less alveolar recruitment of the posterior parts of the lungs.

This study highlights the interest of monitoring right ventricular function during HFO.

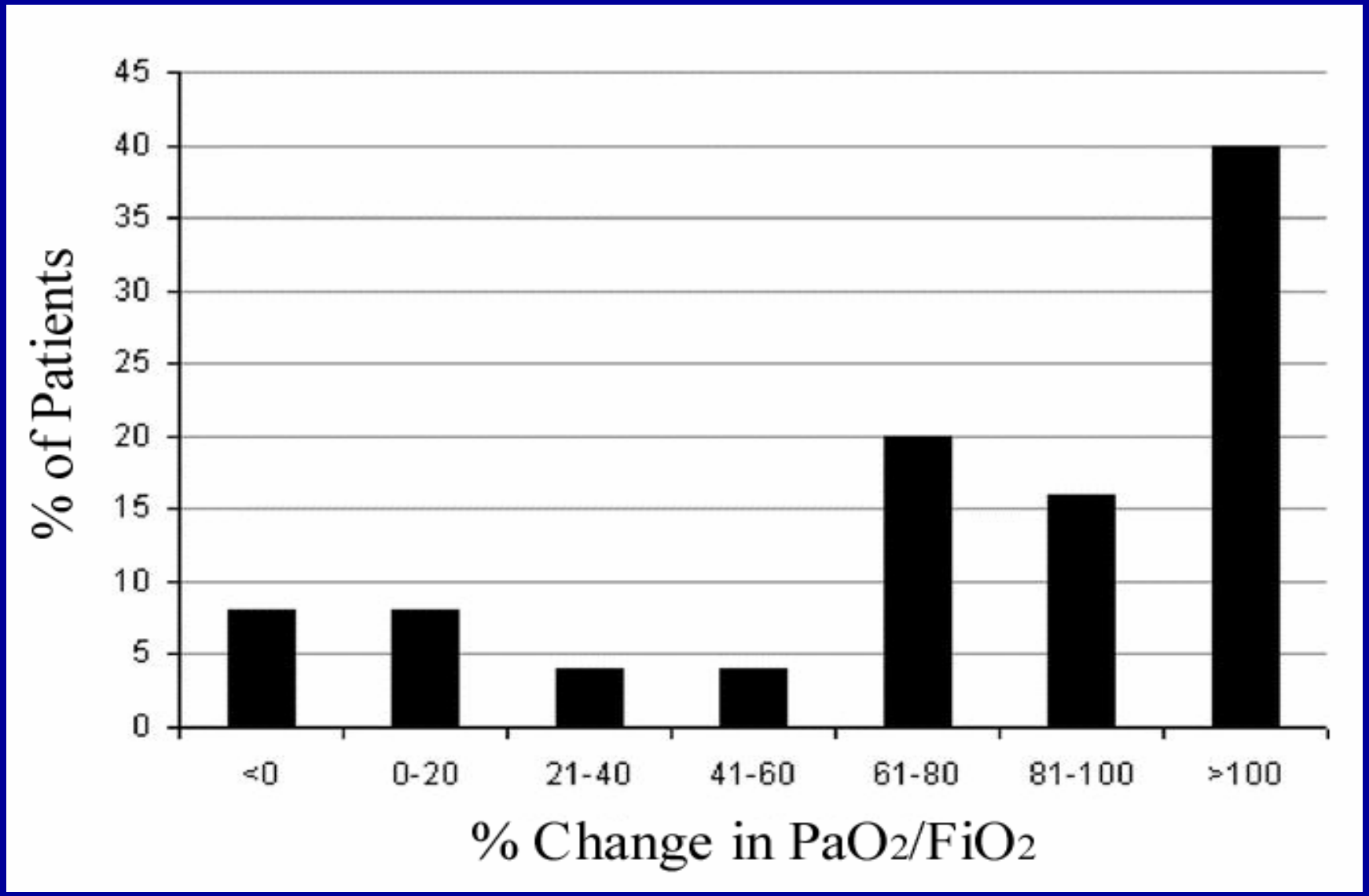
Survivors of ARDS patients treated with HFO have better gas-exchange than non-survivors; this is also consistent with less RV stress/dysfunction

Camporota et al. Crit Care 2013;17:R40





HFO + RMs



Ferguson et al. Crit Care Med 2005;33:479-486

HFO-RMs combined with Tracheal Gas Insufflation (TGI)

- mPaw = CMV mPaw + 6-10 cmH_2O
- F ~ 4 Hz→Vt ~ 200 mL (~3 mL/Kg PBW)
- ΔP = 85-90 cmH_2O
- Cuff leak = 3-5 cmH_2O
- Bias flow = 40-60 L/min
- TGI ~ 6 L/min

Cuff leak

- ↑ CO_2 clearance
- ↓ Mean Tracheal Pressure by 5-6 cmH2O relative to the set mPaw
- ↓ Risk of HFO-TGI-induced hyperinflation

Mentzelopoulos et al. Crit Care Med 2007;35:1500-8

Mentzelopoulos et al. Intensive Care Med. 2011 ;37:990-9.

TGI improves Gas-exchange

- ↑CO_2 clearance
- PEEP effect by impeding expiration
- Inspiratory, high-velocity Jet stream

Mentzelopoulos et al. Crit Care Med 2007;35:1500-8

Mentzelopoulos et al. Intensive Care Med. 2011 ;37:990-9.

Table 4. Gas exchange

Ventilatory Strategy	Pa_{O_2}/Fi_{O_2}, mm Hg	Pa_{CO_2}, mm Hg	pHa	Pv_{O_2}, mm Hg	Sv_{O_2}, %	Pv_{CO_2}, mm Hg	Shunt Fraction	Oxygenation Index
ARDS Network 1	105.0 ± 3.7	53.1 ± 2.6	7.34 ± 0.02	43.3 ± 0.9	71.8 ± 1.3	57.8 ± 2.7	0.45 ± 0.01	20.6 ± 1.2
HFO-TGI	174.5 ± 10.4[a]	55.1 ± 2.1	7.33 ± 0.01	50.1 ± 1.5[a]	77.8 ± 1.2[a]	60.2 ± 2.1	0.36 ± 0.01[a]	17.1 ± 1.3
HFO	136.0 ± 10.0[a,b]	52.9 ± 2.5	7.34 ± 0.01	47.5 ± 1.3	75.9 ± 1.1	57.8 ± 2.5	0.42 ± 0.01	22.3 ± 1.7[b]
ARDS Network 2A	129.4 ± 8.0[b]	53.7 ± 2.6	7.34 ± 0.01	46.1 ± 1.2	73.7 ± 1.2	58.3 ± 2.6	0.39 ± 0.01	17.4 ± 1.3[c]
ARDS Network 2B	105.6 ± 3.3[b,d]	53.9 ± 2.6	7.34 ± 0.01	44.6 ± 1.0[b]	72.4 ± 1.3[b]	58.4 ± 2.7	0.45 ± 0.01[b]	20.1 ± 1.1

pHa, arterial pH; Pv_{O_2}, mixed venous partial pressure of oxygen; Sv_{O_2}, mixed venous oxygen saturation; Pv_{CO_2}, mixed venous partial pressure of CO_2; ARDS Network, Acute Respiratory Distress Syndrome Network; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; 2A and 2B, measurements performed within 30–36 mins and 150–156 mins after HFO, respectively.

[a] $p < .05$ vs. ARDS Network 1; [b] $p < .05$ vs. HFO-TGI; [c] $p = .07$ vs. HFO; [d] $p < .05$ vs. HFO. Values are mean± SE.

Table 5. Hemodynamics

Mentzelopoulos et al. Crit Care Med 2007;35:1500-8

Ventilatory Strategy	HR, Beats/Min	MAP, mm Hg	CVP, mm Hg	MPAP, mm Hg	PAWP, mm Hg	CI, $L \cdot min^{-1} \cdot m^{-2}$	SVRI, $dynes \cdot sec \cdot cm^{-5} \cdot m^{-2}$	PVRI, $dynes \cdot sec \cdot cm^{-5} \cdot m^{-2}$	Do_2I, $mL \cdot min^{-1} \cdot m^{-2}$
ARDS Network 1	104 ± 3	83 ± 2	12 ± 1	31 ± 1	15 ± 1	4.0 ± 0.2	1502 ± 68	328 ± 25	418 ± 19
HFO-TGI	106 ± 3	89 ± 3	12 ± 1	32 ± 1	16 ± 1	4.3 ± 0.2	1484 ± 73	311 ± 24	473 ± 19
HFO	103 ± 3	88 ± 3	12 ± 1	31 ± 1	16 ± 1	4.2 ± 0.2	1503 ± 76	316 ± 25	449 ± 20
ARDS Network 2A	104 ± 3	87 ± 2	11 ± 1	30 ± 1	15 ± 1	4.0 ± 0.2	1552 ± 65	320 ± 27	430 ± 19
ARDS Network 2B	105 ± 3	86 ± 2	12 ± 1	30 ± 1	15 ± 1	4.0 ± 0.2	1546 ± 66	324 ± 26	418 ± 18

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; Do_2I, oxygen delivery index; ARDS Network, Acute Respiratory Distress Syndrome Network; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; 2A and 2B, measurements performed within 30–36 mins and 150–156 mins after HFO, respectively.

Values are mean ± SE.

Table 3 Hemodynamics, central-venous oxygen saturation, and shunt fraction

Ventilatory strategy	Heart rate (beats/min)	MAP (mmHg)	CVP (mmHg)	Cardiac index (L min^{-1} m^{-2})	$ScvO_2$ (%)	Shunt fraction	VO_2I (L min^{-1} m^{-2})
CMV pre-high	101 ± 3	83 ± 2	15 ± 1	4.1 ± 0.2	74.3 ± 1.3	0.37 ± 0.02	0.14 ± 0.01
HFO-high P_{aw}	100 ± 3	87 ± 2	15 ± 1	4.3 ± 0.2	78.6 ± 1.8	0.34 ± 0.01	0.13 ± 0.01
HFO-TGI-high P_{aw}	102 ± 4	85 ± 2	15 ± 1	4.3 ± 0.2	78.4 ± 1.9	0.28 ± 0.02*	0.14 ± 0.01
CMV post-high	102 ± 4	82 ± 2	15 ± 1	4.5 ± 0.2	75.7 ± 1.5	0.36 ± 0.02#	0.14 ± 0.01
CMV pre-low	102 ± 3	82 ± 2	14 ± 1	4.1 ± 0.2	72.9 ± 1.1	0.34 ± 0.02	0.14 ± 0.01
HFO-low P_{aw}	98 ± 4	89 ± 2	15 ± 1	4.4 ± 0.2	78.7 ± 1.7	0.38 ± 0.02#	0.13 ± 0.01
HFO-TGI-low P_{aw}	101 ± 4	87 ± 3	15 ± 1	4.4 ± 0.2	79.8 ± 1.8*	0.32 ± 0.02	0.13 ± 0.01
CMV post-low	101 ± 3	83 ± 2	14 ± 1	4.1 ± 0.2	72.9 ± 1.1¶	0.31 ± 0.02	0.14 ± 0.01

Values are mean ± SEM. For the computation of shunt fraction, we used blood-gas values obtained from central-venous blood *CMV* conventional mechanical ventilation, *HFO* high-frequency oscillation, *TGI* tracheal gas insufflation, P_{aw} mean airway pressure, *CMV pre-/post-high* CMV preceding/following HFO-/HFO-TGI-high P_{aw}, *CMV pre-/post-low* CMV preceding/following HFO-/HFO-TGI-low P_{aw}, *MAP* mean arterial pressure, *CVP* central venous pressure, *CI* cardiac index, VO_2I O_2 consumption index, $ScvO_2$ central-venous oxygen saturation

* $P < 0.05$ versus preceding CMV; # $P < 0.05$ versus HFO-TGI-high P_{aw}; ¶ $P < 0.05$ versus HFO-TGI-low P_{aw}

Mentzelopoulos et al. Intensive Care Med. 2011 ;37:990-9.

Low Frequency, high Bias Flow/ΔP HFO-TGI with cuff leak

- May ↓ Right Ventricular stress compared to HFO mainly by:

  1] Augmenting Ventilation Pressure Drop at the level of the Trachea

  and

  2] Improving CO_2 clearance

- A Vt of ~ 200 mL should still be considered as lung protective

Eur Respir J 2012; 39: 635–647
DOI: 10.1183/09031936.00158810
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Intermittent recruitment with high-frequency oscillation/tracheal gas insufflation in acute respiratory distress syndrome

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HFO + RMs + TGI vs. CMV + RMs

- 125 patients
- $PaO_2/FiO_2 < 150$ mm Hg & PEEP ≥ 8 cmH_2O
- 61 patients: During Days 1-10 postrandomization: Sessions of HFO-TGI until the reversal of the severe oxygenation disturbance i.e. $PaO_2/FiO_2 > 150$ mm Hg
- 64 patients: Protective CMV: Vt 5.5-7.5 mL/kg, Pplateau target: 30 cmH_2O (<35 cmH_2O)

Mentzelopoulos et al. Eur Respir J. 2012;39:635-47.

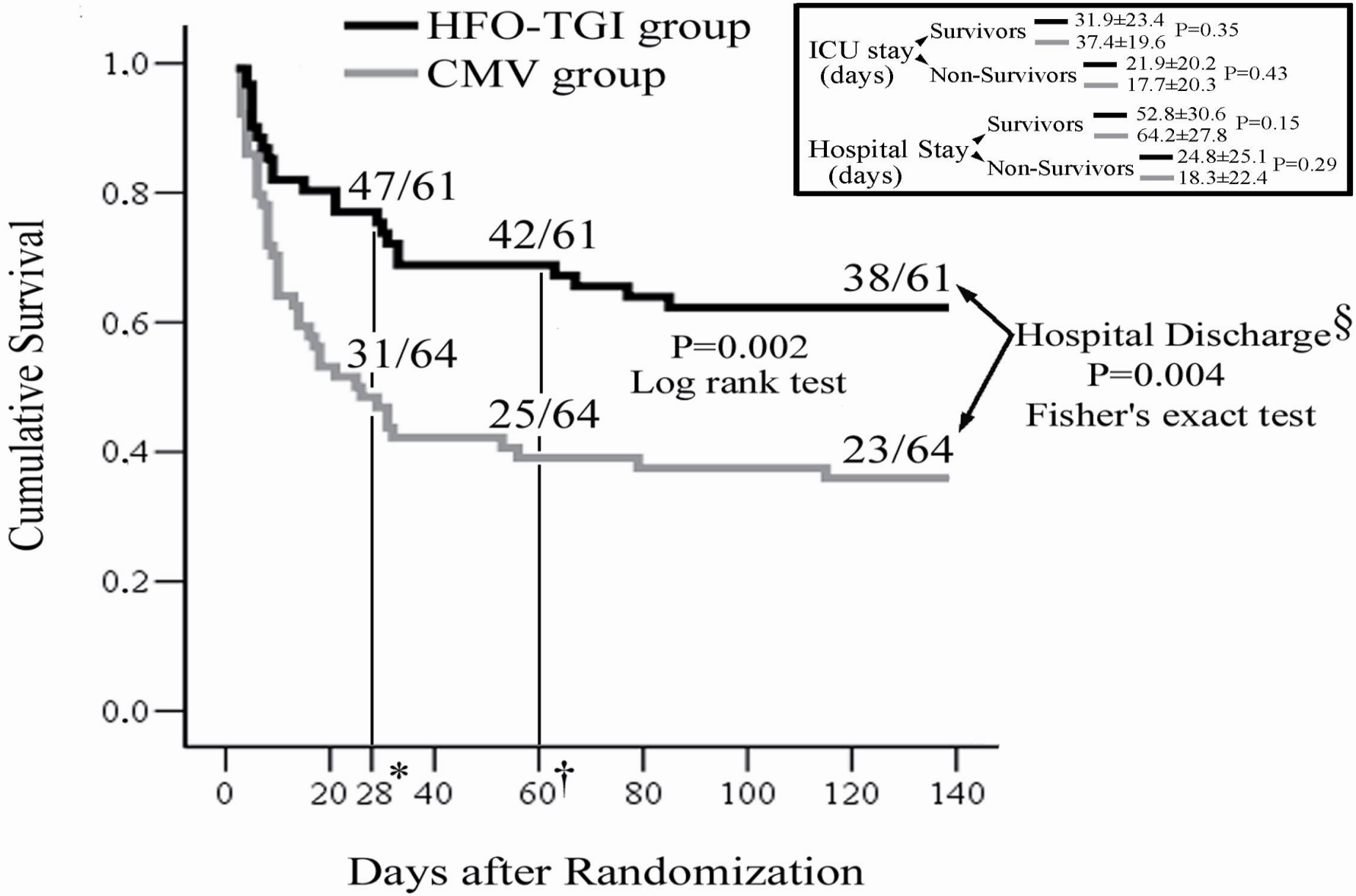
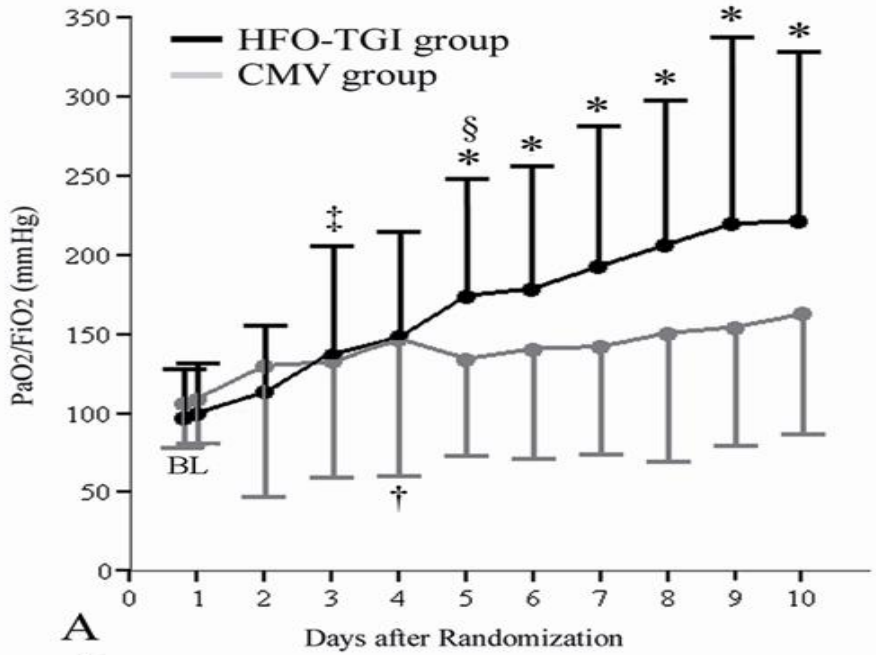
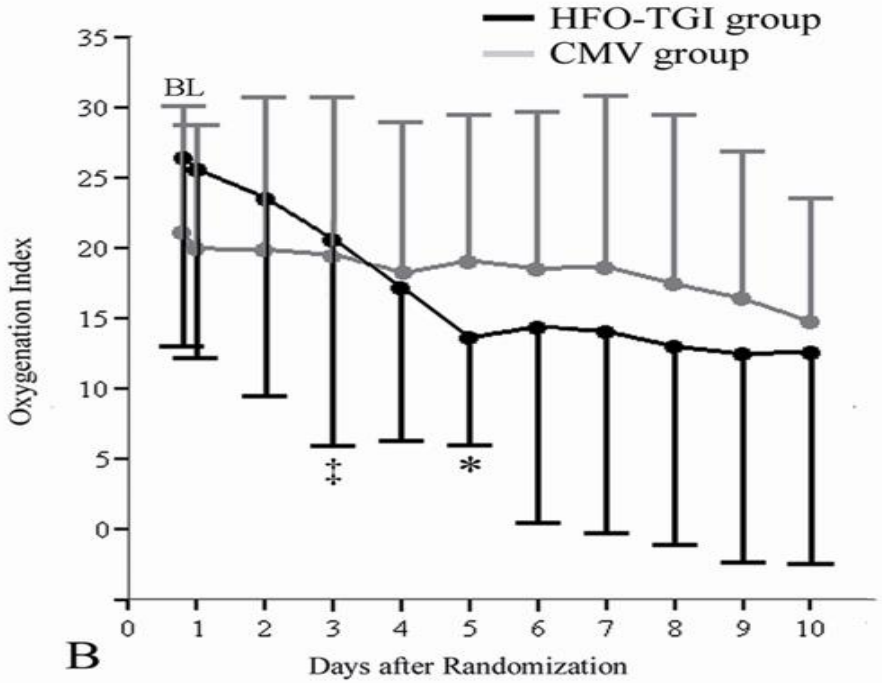
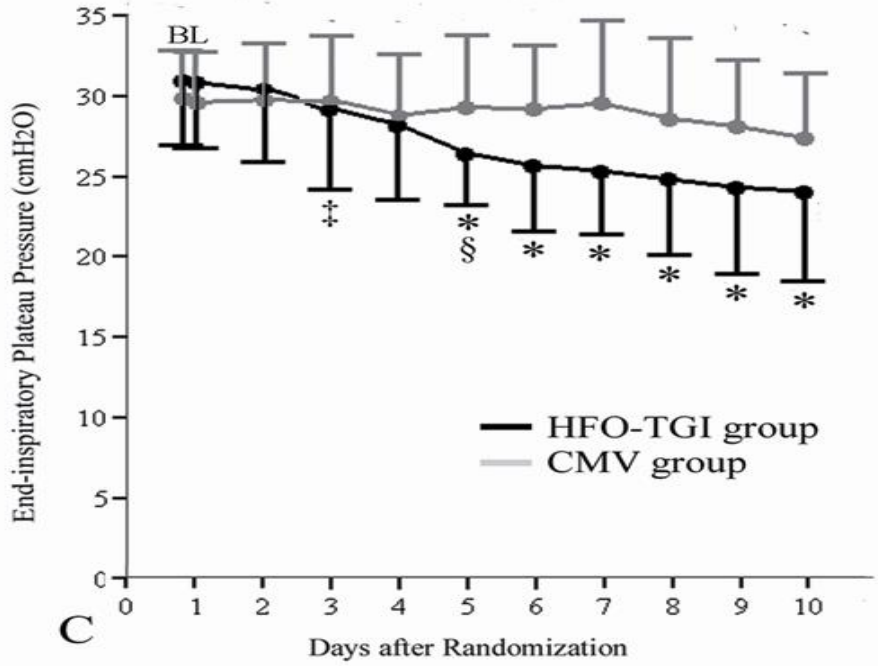
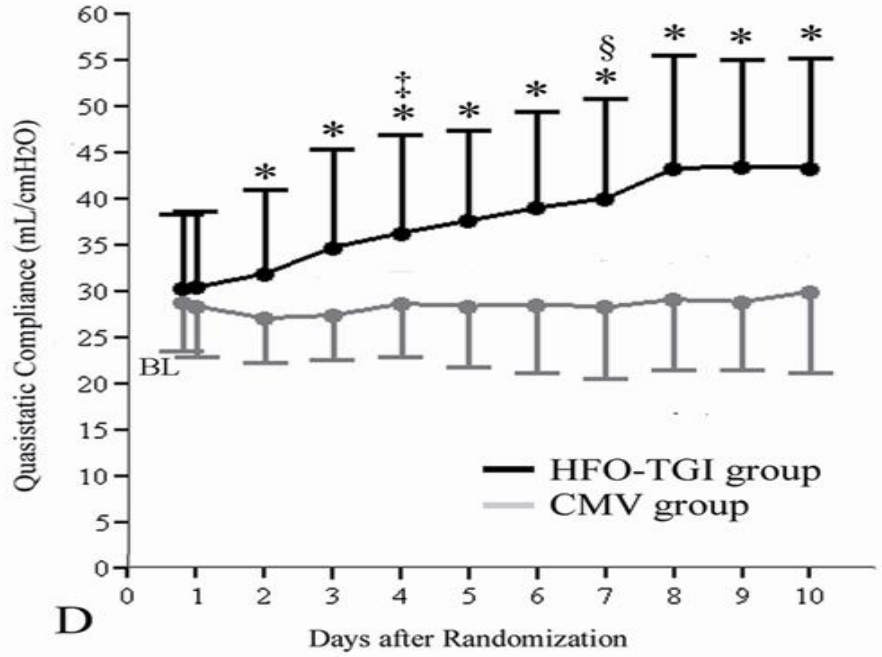

HFO-TGI group
CMV group
ICU stay (days)
Survivors
31.9±23.4
37.4±19.6
P=0.35
Non-Survivors
21.9±20.2
17.7±20.3
P=0.43
Hospital Stay (days)
Survivors
52.8±30.6
64.2±27.8
P=0.15
Non-Survivors
24.8±25.1
18.3±22.4
P=0.29
47/61
42/61
38/61
31/64
25/64
23/64
P=0.002
Log rank test
Hospital Discharge§
P=0.004
Fisher's exact test
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
28*
40
60†
80
100
120
140
Days after Randomization

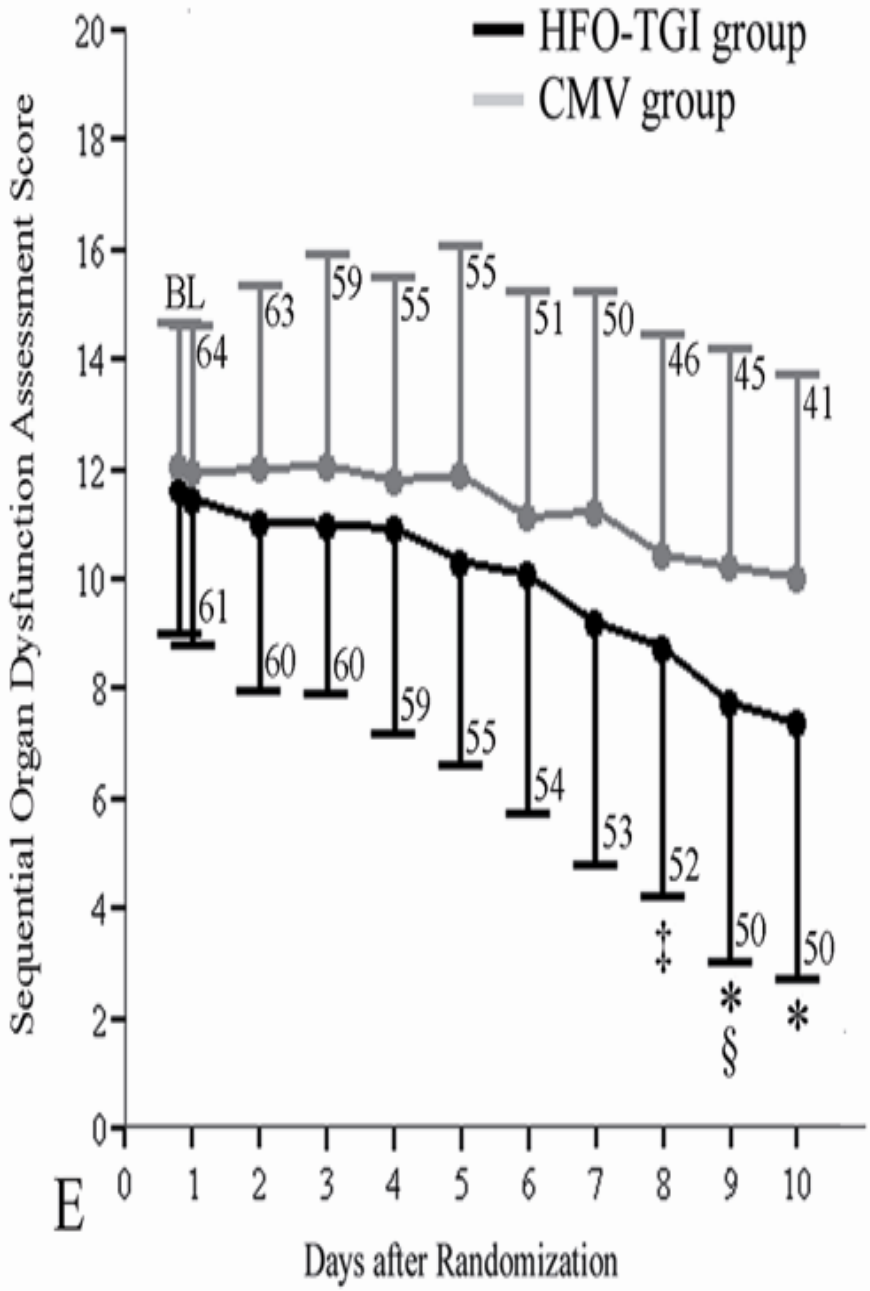
Figure 4

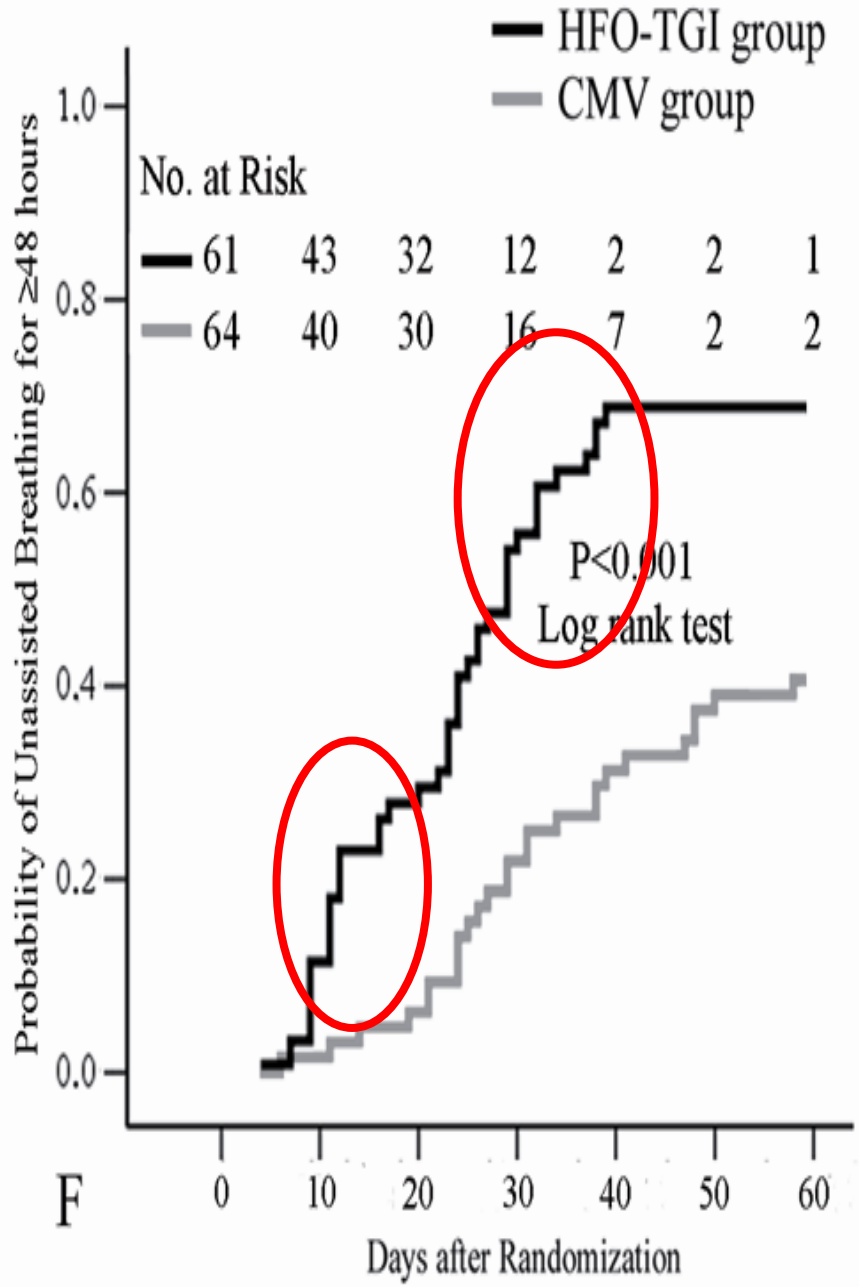

HFO-TGI group
CMV group
PaO2/FiO2 (mmHg)
Days after Randomization
BL
A


HFO-TGI group
CMV group
Oxygenation Index
Days after Randomization
BL
B

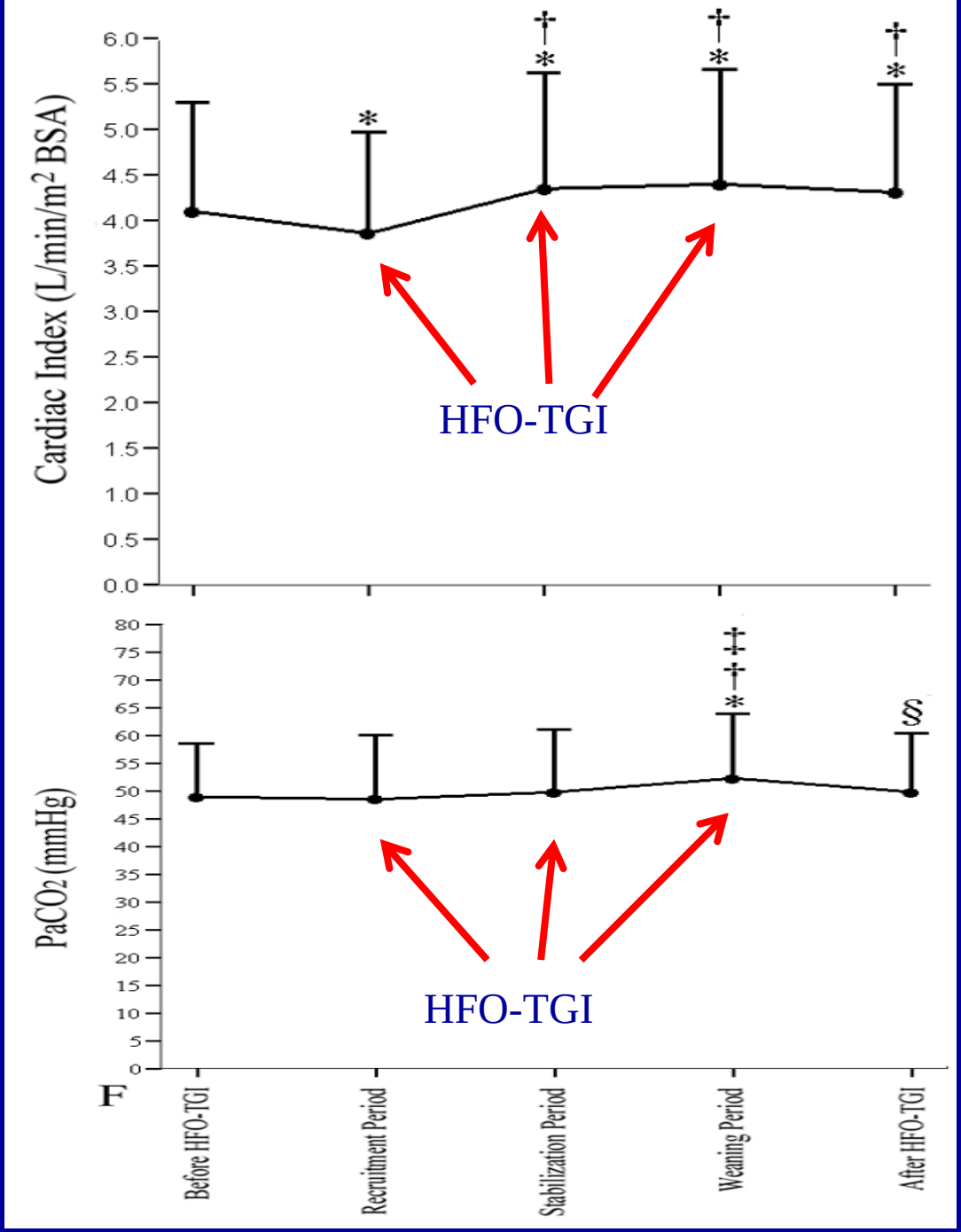

HFO-TGI group
CMV group
End-inspiratory Plateau Pressure (cmH2O)
Days after Randomization
BL
C


HFO-TGI group
CMV group
Quasistatic Compliance (mL/cmH2O)
Days after Randomization
BL
D


HFO-TGI group
CMV group
Sequential Organ Dysfunction Assessment Score
BL
64
63
59
55
55
51
50
46
45
41
61
60
60
59
55
54
53
52
50
50
‡
*
§
*
E
Days after Randomization


HFO-TGI group
CMV group
No. at Risk
61 43 32 12 2 2 1
64 40 30 16 7 2 2
Probability of Unassisted Breathing for ≥48 hours
P<0.001
Log rank test
F
Days after Randomization

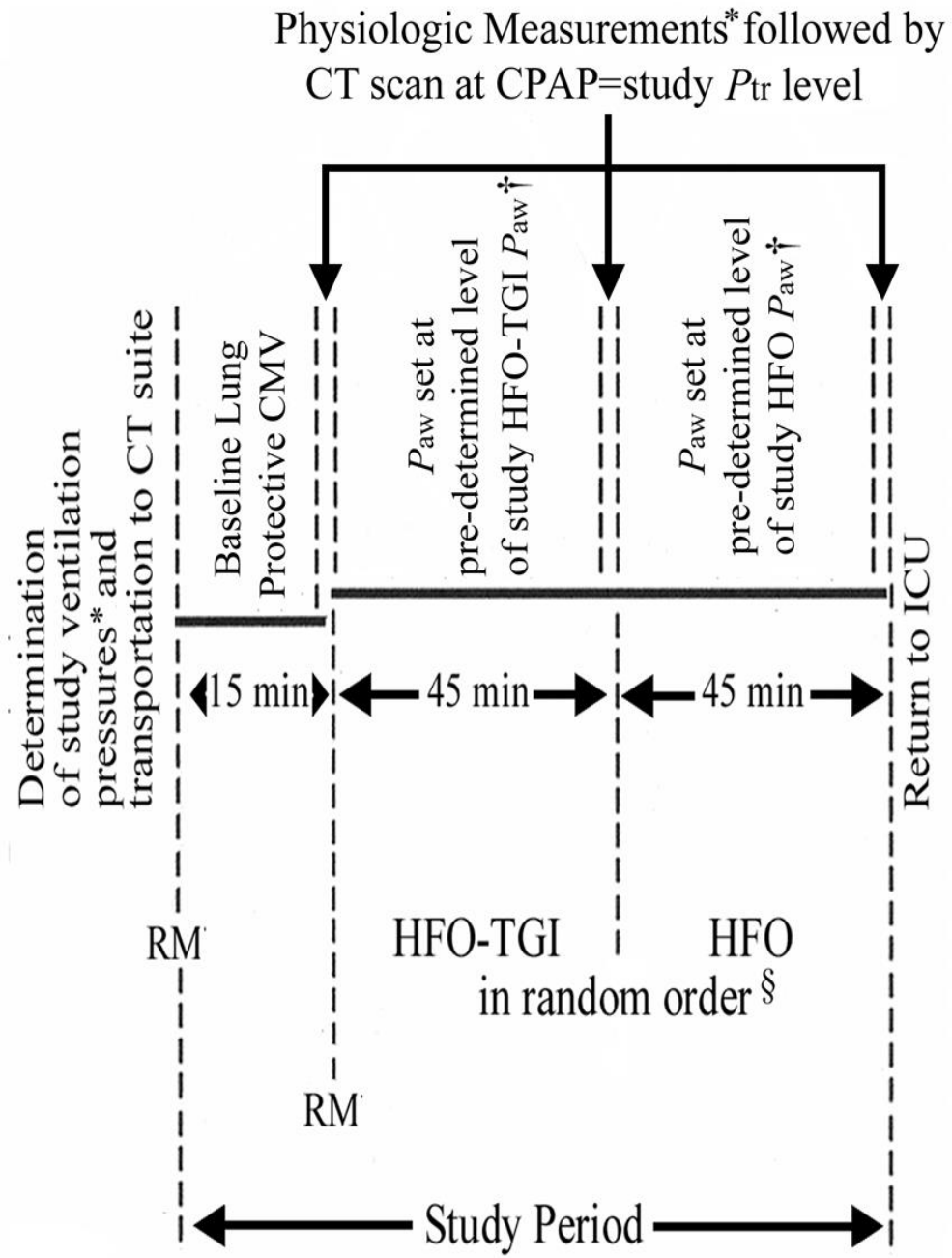
mPaw of approx. 30 cmH_2O, corresponding to a Mean Tracheal Pressure of 24-25 cmH_2O



Scanographic Comparison HFO-TGI vs. HFO and CMV

- 15 patients
- $PaO_2/FiO_2 \leq 200$ mm Hg & PEEP ≥ 8 cmH_2O
- Comparison of thoracic CT findings and gas-exhange among CMV, HFO and HFO-TGI

Mentzelopoulos et al. Intensive Care Med. 2011 ;37:990-9.


Physiologic Measurements* followed by
CT scan at CPAP=study Ptr level
Determination of study ventilation pressures* and transportation to CT suite
Baseline Lung Protective CMV
Paw set at pre-determined level of study HFO-TGI Paw†
Paw set at pre-determined level of study HFO Paw†
Return to ICU
15 min
45 min
45 min
RM
HFO-TGI
HFO
in random order §
RM
Study Period

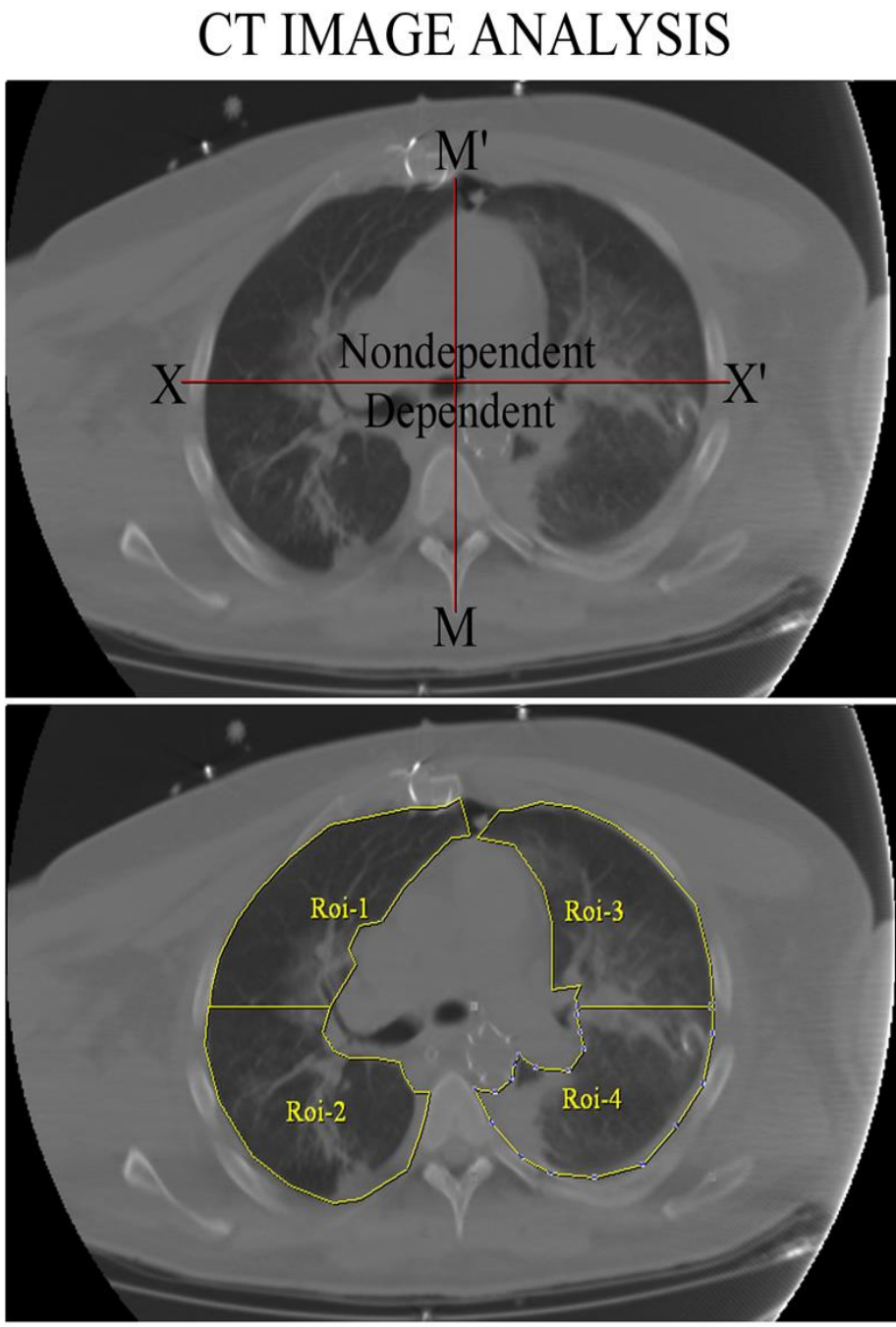
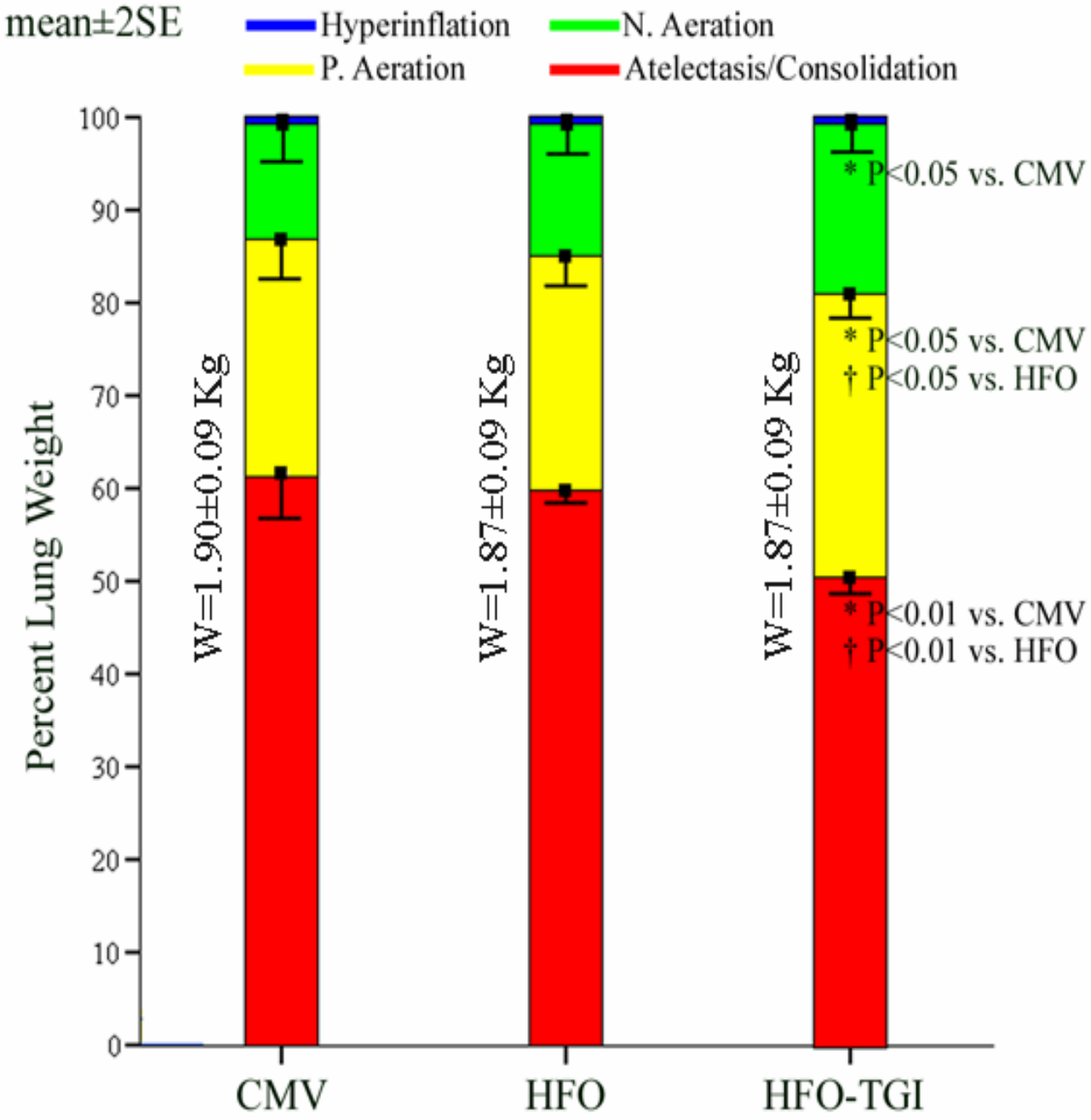
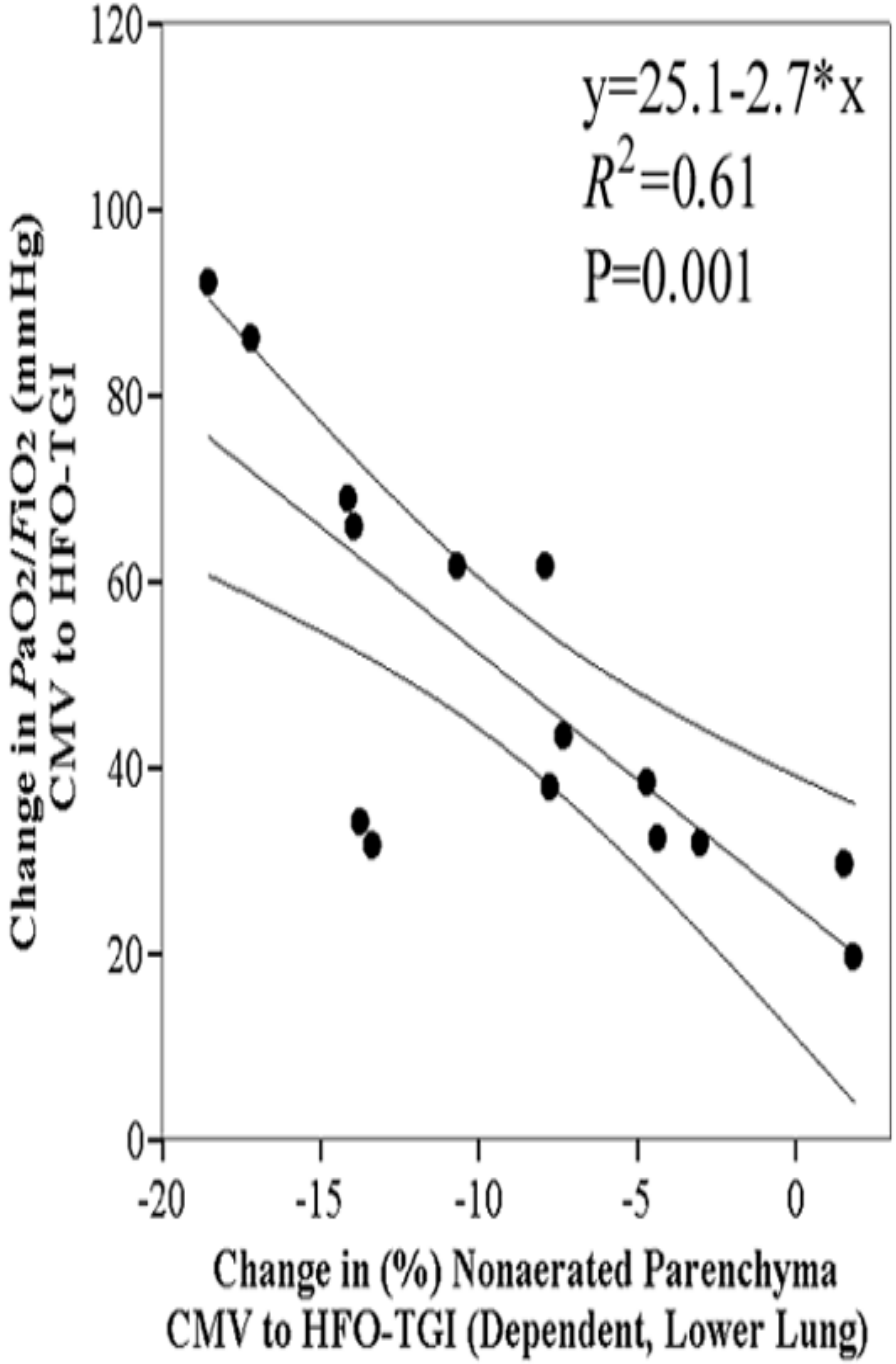
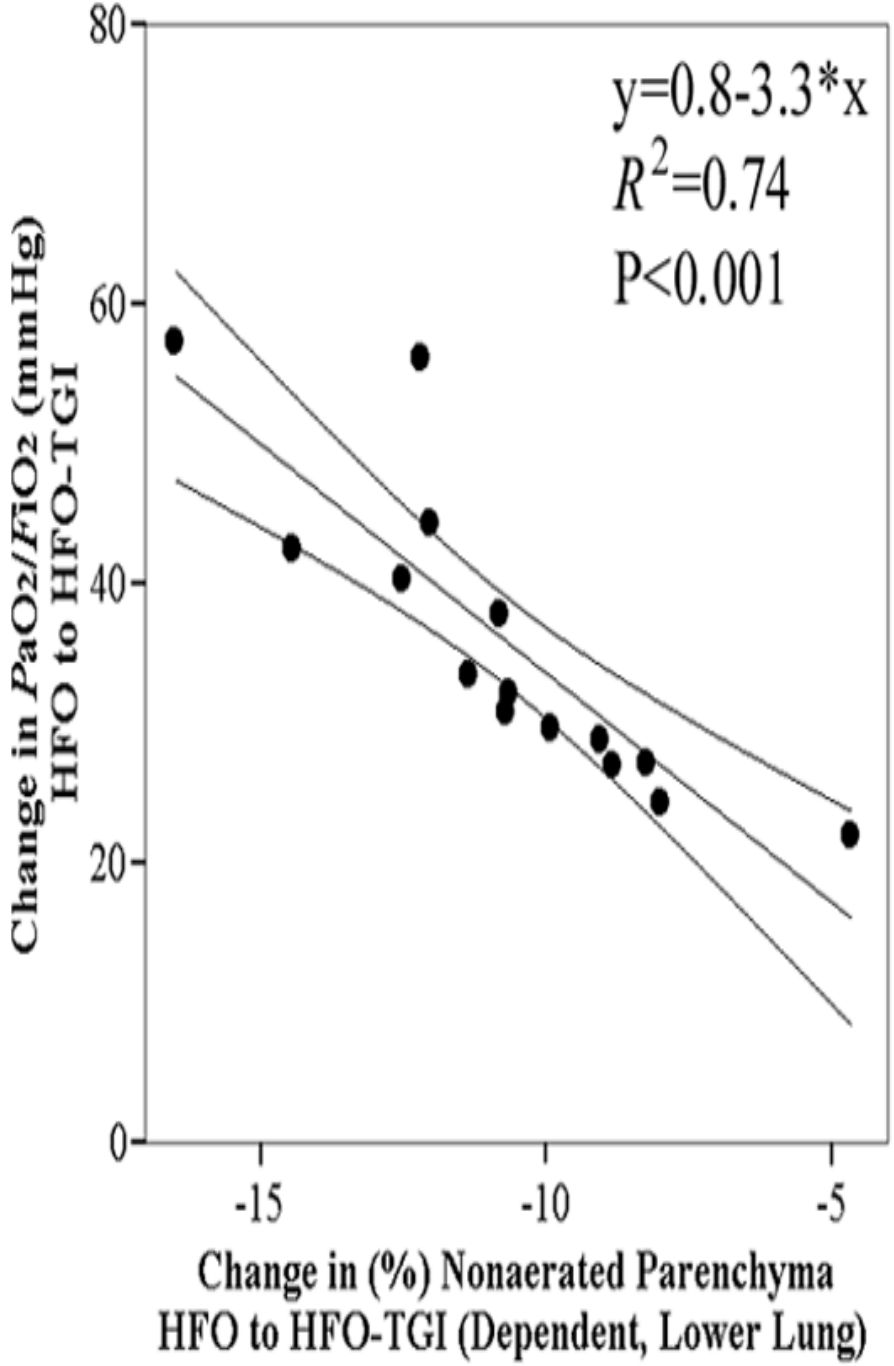

CT IMAGE ANALYSIS
M'
X
Nondependent
Dependent
X'
M
Roi-1
Roi-3
Roi-2
Roi-4

Figure 1


mean±2SE
Hyperinflation
N. Aeration
P. Aeration
Atelectasis/Consolidation
Percent Lung Weight
100
90
80
70
60
50
40
30
20
10
0
W=1.90±0.09 Kg
W=1.87±0.09 Kg
W=1.87±0.09 Kg
* P<0.05 vs. CMV
* P<0.05 vs. CMV
† P<0.05 vs. HFO
* P<0.01 vs. CMV
† P<0.01 vs. HFO
CMV
HFO
HFO-TGI


y=25.1-2.7*x
R^2=0.61
P=0.001
Change in PaO2/FiO2 (mmHg)
CMV to HFO-TGI
Change in (%) Nonaerated Parenchyma
CMV to HFO-TGI (Dependent, Lower Lung)
120
100
80
60
40
20
0
-20
-15
-10
-5
0


y=0.8-3.3*x
R^2=0.74
P<0.001
Change in PaO2/FiO2 (mmHg)
HFO to HFO-TGI
Change in (%) Nonaerated Parenchyma
HFO to HFO-TGI (Dependent, Lower Lung)
80
60
40
20
0
-15
-10
-5

Vrettou et al. HFO-TGI in 13 TBI/ARDS patients. Crit Care 2013;17:R136

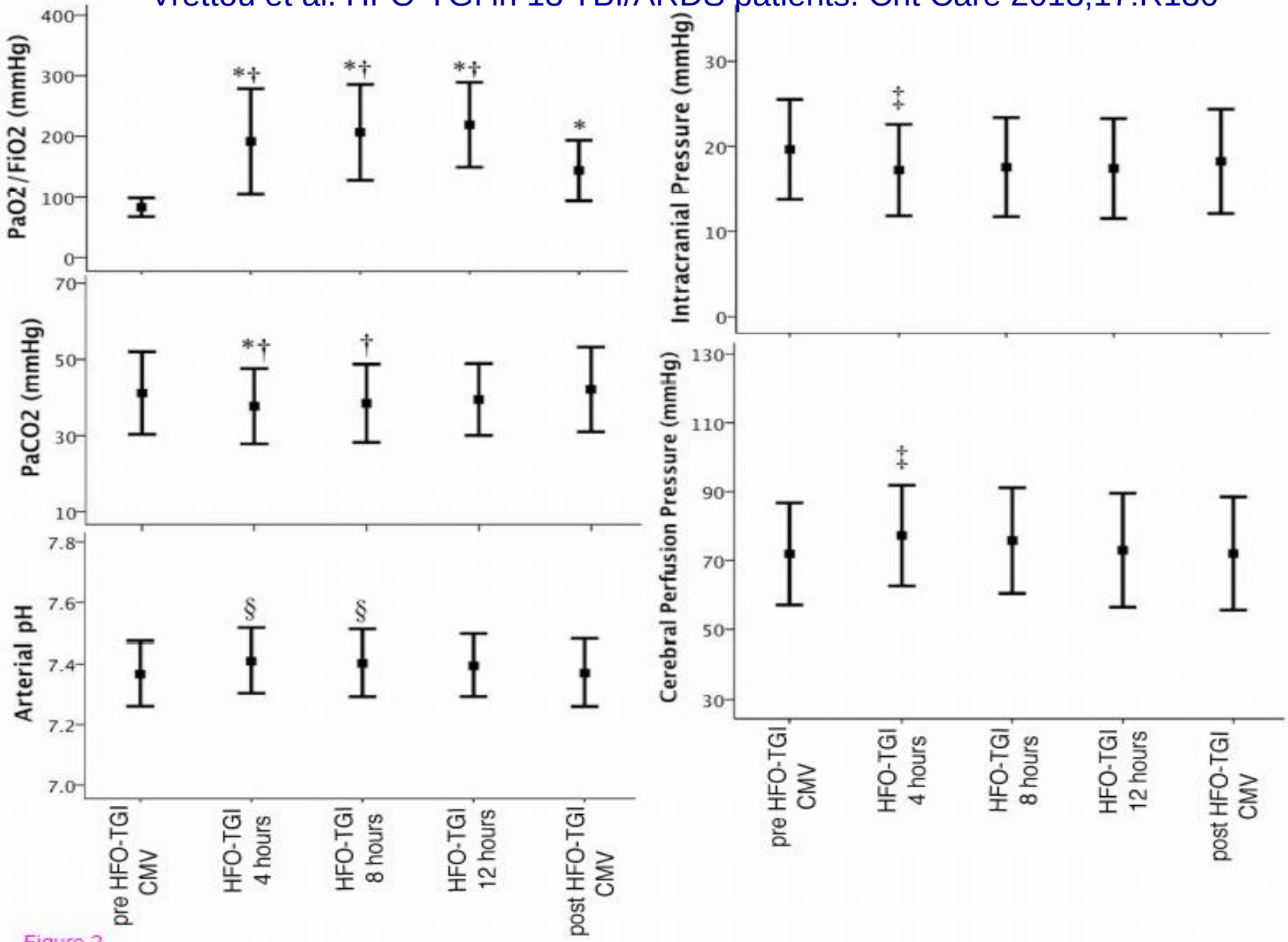


Figure 2

Vrettou et al. HFO-TGI in 13 TBI/ARDS patients. Crit Care 2013;17:R136

Table 3 Shunt fraction, peripheral perfusion indices, and hemodynamics

Ventilatory strategy	Shunt fraction	$ScvO_2$ (%)	Heart rate (beats/min)	MAP (mm Hg)
Pre HFO-TGI CMV	0.49 ± 0.09	70.1 ± 6.2	95 ± 24	92 ± 12
HFO-TGI (4 hours)	0.31 ± 0.09*	74.0 ± 3.9 *,§	92 ± 23	94 ± 13
HFO-TGI (8 hours)	0.29 ± 0.06*	74.6 ± 4.1 *,§	92 ± 23	93 ± 14
HFO-TGI (12 hours)	0.29 ± 0.06*	75.0 ± 4.1 *,§	92 ± 22	90 ± 15
Post HFO-TGI CMV	0.33 ± 0.14	70.5 ± 6.2	92 ± 22	90 ± 14
Ventilatory strategy	**Cardiac Index (L/min/m^2 BSA)**	**DO_2 Index (ml/min/m^2 BSA)**	**Arterial blood lactate (mM)**	**CVP (mm Hg)**
Pre HFO-TGI CMV	4.8 ± 1.3	510 ± 119	1.72 ± 0.70	12 ± 3.4
HFO-TGI (4 hours)	4.7 ± 1.1	541 ± 119 §	1.82 ± 0.68	12 ± 3.0
HFO-TGI (8 hours)	4.8 ± 1.1	553 ± 114 *,§	1.85 ± 0.68	12 ± 2.9
HFO-TGI (12 hours)	4.7 ± 1.2	551 ± 119 *,§	1.82 ± 0.69	12 ± 2.8
Post HFO-TGI CMV	4.5 ± 1.1	513 ± 106	1.81 ± 0.74	11.5 ± 3.3

Values are mean ± SD. CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; TGI, tracheal gas insufflation; pre-HFO-TGI CMV, corresponds to either the baseline CMV period of study day 1, or the 60-minute period that followed the 11-hour period of post-HFO-TGI CMV of the preceding study day (see also Figure 1 and corresponding legend); $ScvO_2$, central venous O_2 saturation; MAP, mean arterial pressure; BSA, body surface area; DO_2, peripheral O_2 delivery; CVP, central venous pressure.

* $P < 0.01$ versus pre-HFO-TGI CMV

§ $P < 0.05$ versus post-HFO-TGI CMV

Is low-frequency HFO-TGI with cuff leak RV protective?

- Data from 4 studies of HFO-TGI use (n=100) indicate no adverse effect on hemodynamics or $PaCO_2$

Mentzelopoulos et al. Crit Care Med 2007;35:1500-8 ; (HFO-TGI use, n=14).

Mentzelopoulos et al. Intensive Care Med. 2011 ;37:990-9; (HFO-TGI use, n=22).

Mentzelopoulos et al. Eur Respir J. 2012;39:635-47. (HFO-TGI use, n=61).

Vrettou et al. Crit Care 2013;17:R136; (HFO-TGI use, n=13).

- Current study: TEE Comparison: Low frequency HFO (with cuff leak)

vs.

- High frequency HFO (without cuff leak)
- ClinicalTrials.gov Identifier: NCT02027129

RHGAS,

Kliniki Entatikis Therapei 6T
06/12/13 19:00:07 ADM Cardiac3

MI 0.32
TIs 0.3

--:--:--
08/01/14 12:49:27

HR 55

1 A 17.76 cm2

hfo 4 hz

RVEDA=17.76 CM^2

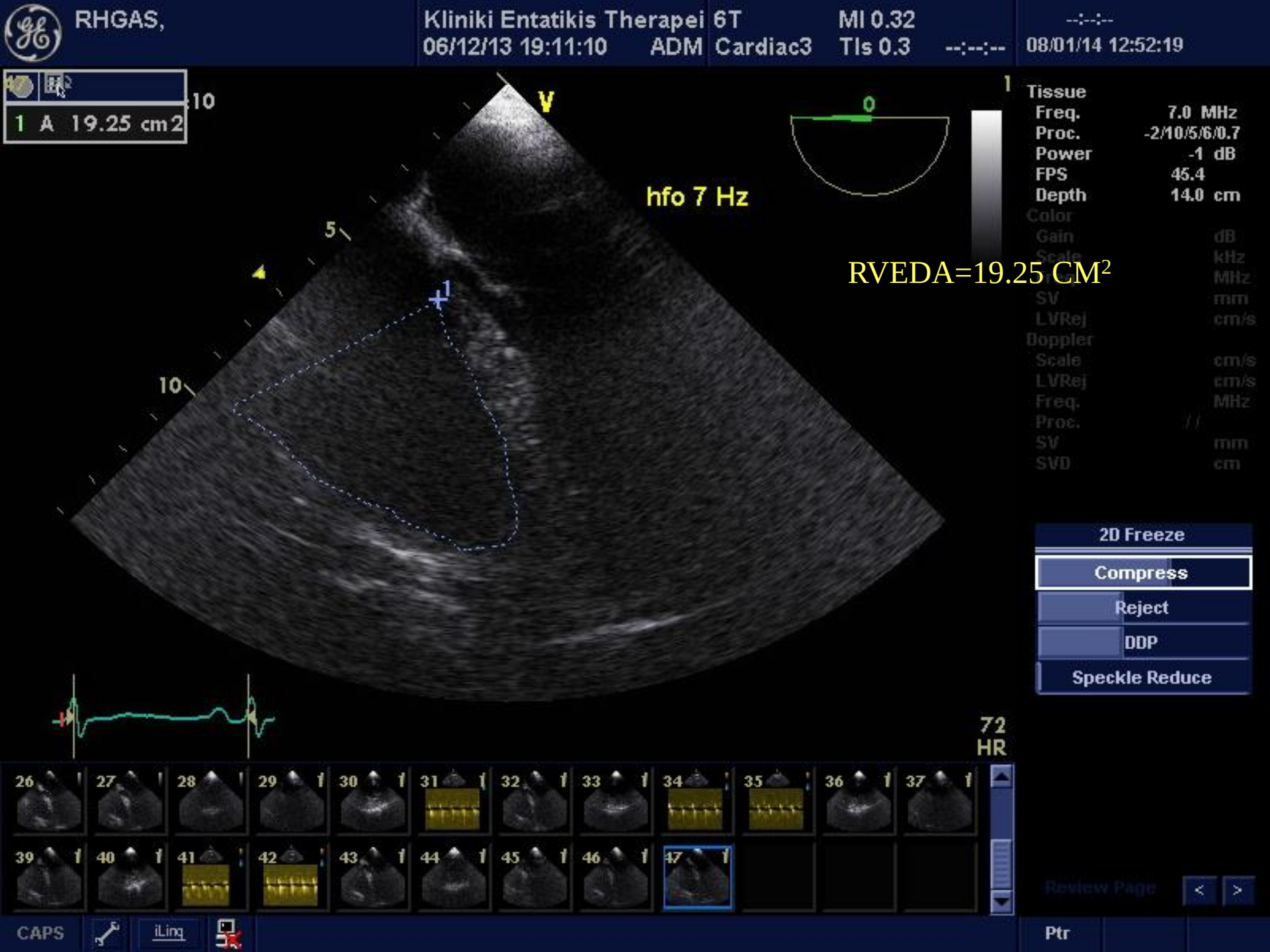
Tissue
Freq. 7.0 MHz
Proc. -2/10/5/6/0.7
Power -1 dB
FPS 45.4
Depth 14.0 cm
Color
Gain dB
Scale kHz
MHz
SV mm
LVRej cm/s
Doppler
Scale cm/s
LVRej cm/s
Freq. MHz
Proc. / /
SV mm
SVD cm

2D Freeze
Compress
Reject
DDP
Speckle Reduce

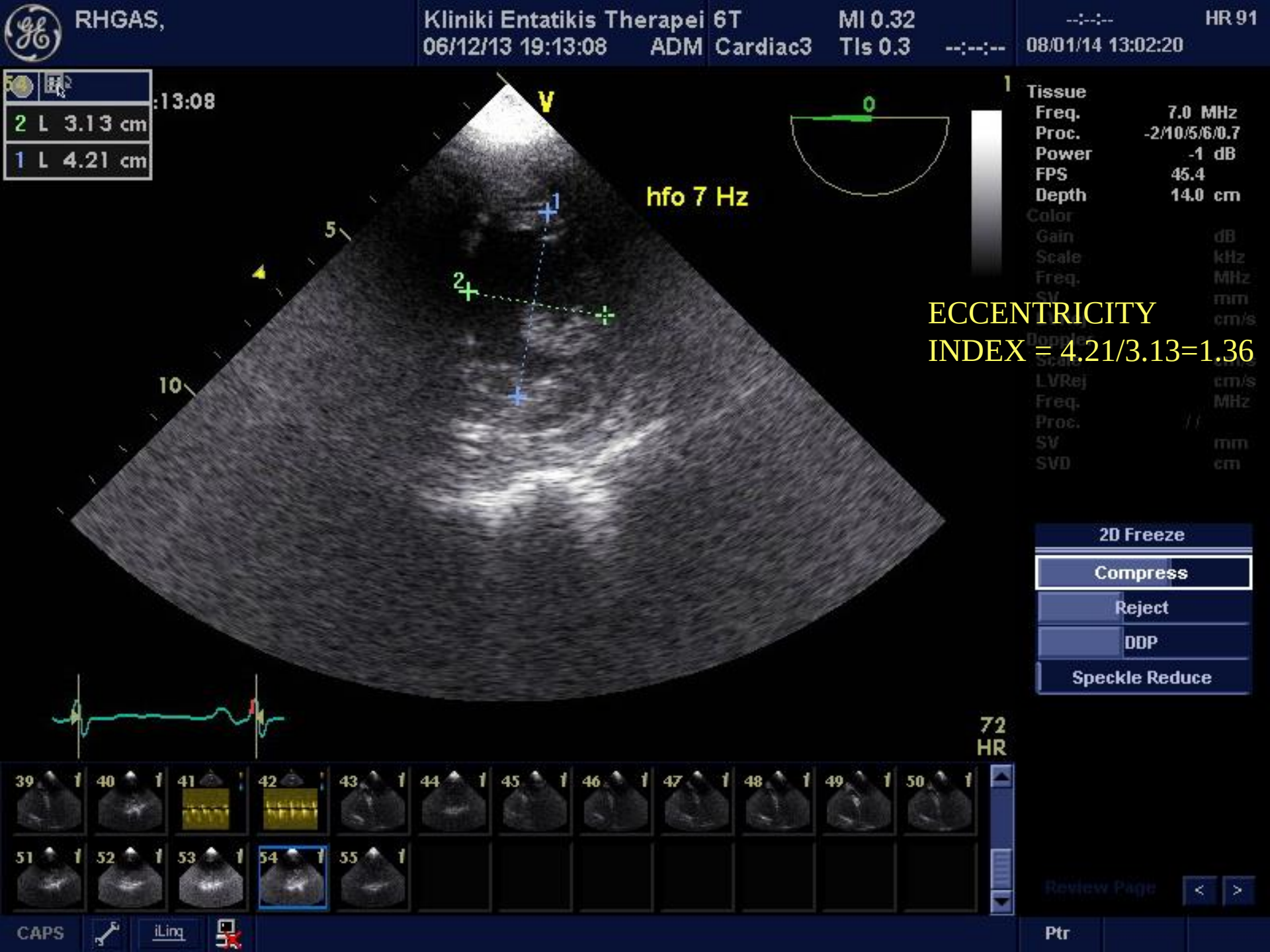
70
HR

Review Page < >

CAPS iLinq Ptr


RHGAS,
Kliniki Entatikis Therapei 6T
06/12/13 19:11:10 ADM Cardiac3
MI 0.32
TIs 0.3
--:--:--
08/01/14 12:52:19
1 A 19.25 cm2
hfo 7 Hz
RVEDA=19.25 CM2
Tissue
Freq. 7.0 MHz
Proc. -2/10/5/6/0.7
Power -1 dB
FPS 45.4
Depth 14.0 cm
Color
Gain dB
Scale kHz
MHz
SV mm
LVRej cm/s
Doppler
Scale cm/s
LVRej cm/s
Freq. MHz
Proc.
SV mm
SVD cm
2D Freeze
Compress
Reject
DDP
Speckle Reduce
72
HR
Review Page
CAPS
iLinq
Ptr

RHGAS,
Kliniki Entatikis Therapei 6T
06/12/13 18:55:24 ADM Cardiac3
MI 0.32
TIs 0.3
--:--:--
08/01/14 13:02:15
HR 73
:55:24
2 L 3.26 cm
1 L 4.10 cm
hfo 4 hz
Tissue
Freq. 7.0 MHz
Proc. -2/10/5/6/0.7
Power -1 dB
FPS 45.4
Depth 14.0 cm
Color
Gain dB
Scale kHz
Freq. MHz
SV mm
cm/s
LVRej cm/s
Freq. MHz
Proc.
SV mm
SVD cm
ECCENTRICITY
INDEX = 4.10/3.26=1.26
2D Freeze
Compress
Reject
DDP
Speckle Reduce
71
HR
Review Page
CAPS
iLinq
Ptr



ECCENTRICITY INDEX = 4.21/3.13=1.36

Severity of Hypoxemia and Effect of High Frequency Oscillatory Ventilation in ARDS

Maureen O Meade[1], Du… …homas E Bachman[3], Casper Bollen[4], Arthur S Sluts… …9, Spyros D Mentzelopoulos[10], Deb… …12, B Taylor Thompson[13], Sanjoy Shah[14], Alex Ste… …uson[5,7,8,16]

Meade et al, AJRCCM. 2017 Feb 28. doi: 10.1164/rccm.201609-1938OC

At A Glance Commentary:

Scientific Knowledge on the Subject

High frequency oscillatory ventilation (HFOV) is theoretically lung protective in ARDS but results of clinical trials are inconsistent, with study-level meta-analyses suggesting no effect on mortality.

What This Study Adds to the Field

We found a convincing relationship between severity of ARDS and impact of therapy: HFOV was harmful in patients with moderate ARDS while showing possible benefit in patients with severe hypoxemia. This heterogeneity of treatment effect implies that HFOV should be avoided in mild and moderate ARDS; clinicians might consider HFOV in patients with severe ARDS who remain hypoxic after optimizing conventional lung-protective ventilation and for whom other approaches (e.g. proning, extracorporeal support) are either contraindicated or unavailable.

IPDMA Design

- N=1552 patients from 4 trials of HFOV vs. CMV [MOAT, 148; eMOAT, 61, OSCILLATE, 548; OSCAR, 795]
- Standardized Database with uniform data definitions
- Primary Outcome: 30-day mortality
- Multilevel, mixed-effects Logistic Regression
- Adjusted for Age, APACHE II score, baseline duration of Mechanical Ventilation

Subgroup Analyses

Patient Variables

- PaO_2/FiO_2
- Respiratory Compliance
- Body Mass Index

Hospital Variable

- Day-1 Vt

↑ HFO Experience → ↓ Mortality?

HFO effect on barotrauma

Characteristic	HFOV (n = 785)	Control (n = 767)	Missing (%)
Age - yr	54±17	54±17	0.2
Male sex - no. of patients (%)	492 (63)	451 (59)	0
APACHE II score#	23±8	24±8	2.6
Duration of mechanical ventilation – days, me dian (IQR)	2 (1, 4)	2 (1, 3)	0
Pneumonia - no. of patients (%)	430 (55)	418 (55)	0
Aspiration - no. of patients (%)	80 (11)	83 (12)	9.5
Barotrauma - no. of patients (%)	53 (7)	41 (5)	1.2
Respiratory measures			
PaO_2:FiO_2 - mm Hg	114±38	115±40	2.0
PaO_2:FiO_2 ≤ 100 mm Hg - no. (%)	299 (39)	298 (39)	2.0
FiO_2	0.74±0.18	0.73±0.17	1.5
PaO_2 - mm Hg	79±21	80±23	1.8
Set PEEP - cm H_2O	12±4	13±4	2.6
Plateau pressure - cm H_2O	32±8	32±9	4.6
Tidal volume - mL/kg of predicted body weight	8.0±2.7	7.8±2.5	5.0
Respiratory rate - breaths/minute	23±7	23±7	9.9
Prone positioning - no. of patients (%)	27 (4)	26 (4)	9.5
Inhaled nitric oxide - no. of patients (%)	31 (4)	25 (4)	9.5

TABLE 4 Physiological variables, haemodynamic support and organ failure assessment for days 1–10 post-randomisation

Variable	Baseline	Day 1	Day 5	Day 10	Missing values %	p-value		
						Group	Time	Group × time
$P_{a,O_2}/F_{I,O_2}$ mmHg						0.007	<0.001	<0.001
HFO-TGI group	96.5 ± 31.3	99.5 ± 31.6	175.2 ± 74.1*,+,§	222.9 ± 108.1*,+,§	8.3			
CMV group	106.9 ± 27.7	110.5 ± 28.2	135.0 ± 61.6	163.5 ± 76.1	15.8			
P_{a,CO_2} mmHg						0.03	0.048	0.14
HFO-TGI group	47.6 ± 8.4	47.2 ± 8.2	46.9 ± 8.3	46.3 ± 10.7	8.3			
CMV group	47.5 ± 8.0	47.4 ± 8.0	50.0 ± 9.9	50.3 ± 18.9+,§	15.8			
Tidal volume						<0.001	<0.001	<0.001
L								
HFO-TGI group	0.46 ± 0.05	0.46 ± 0.05	0.47 ± 0.06	0.50 ± 0.07	15.2			
CMV group	0.45 ± 0.06	0.44 ± 0.06	0.45 ± 0.05	0.46 ± 0.07	18.2			
$mL \cdot kg^{-1}$ PBW								
HFO-TGI group	6.5 ± 0.6	6.4 ± 0.6	6.7 ± 0.7§	7.2 ± 1.2*,+,§,f	15.2			
CMV group	6.5 ± 0.5	6.4 ± 0.5	6.3 ± 0.4	6.4 ± 0.6	18.2			
PEEP, cm H_2O		13 (4) [n = 725]			14 (5) [n = 690]			12 (4) [n = 646]
Plateau pressure, cm H_2O		30 (9) [n = 686]			29 (9) [n = 650]			28 (10) [n = 595]
Tidal volume, mL/kg of predicted body weight		7.6 (2.3) [n = 705]			7.7 (2.4) [n = 678]			7.9 (2.8) [n = 636]

- NMBas, approx. 40%
- Prone ventilation in OSCAR, 10% of HFO group vs. 20% of Controls
- HFO was used in 3-18% of Controls [MOAT, 18%; OSCILLATE, EMOAT, 12%; OSCAR, 3%]
- 6% of patients received iNO

	Successive patients within each quartile	Mortality (95% CI)	p-value
First quartile	1st - 3rd	36% (28 – 45)	< 0.02
Second quartile	4th - 6th	41% (32 - 51)	
Third quartile	7th – 12th	49% (39 - 58)	
Fourth quartile	13th – final	53% (42 - 64)	

Major differences between included studies and the HFO-TGI study

- Intermittent vs. Continuous intervention according to oxygenation criteria → 12-24 h / over days 1-4 in less severe ARDS
- Low f, high ΔP & Bias Flow; Cuff leak; TGI → Effective $PaCO_2$ Control
- Cuff leak → ↓ mean Ptr & risk of Barotrauma

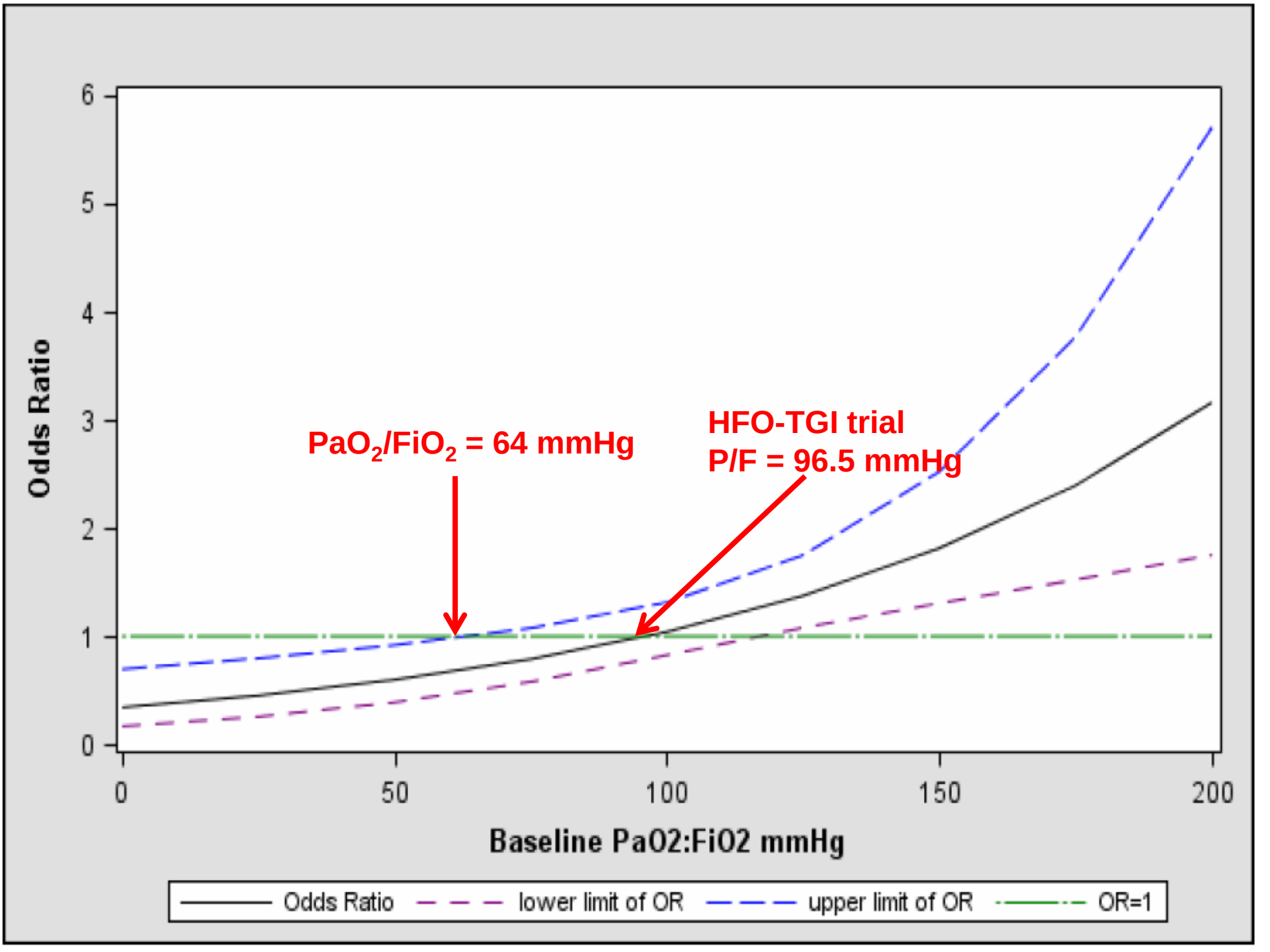
30-day Mortality

- HFO vs. Control, 321/785 (40.9%) vs. 288/767 (37.6%); OR=1.17, 95% CI, 0.94-1.46, P=0.16

- 614 patients with $PaO_2/FiO_2 < 100$ mmHg
- HFO vs. Control, OR=0.83, 95% CI, 0.58-1.19, P=0.30
- HFO-TGI $PaO_2/FiO_2 = 96.5$ mmHg @ PEEP = 14.3 cmH_2O
- HFO-TGI vs. Control, HR=0.38, 95% CI, 0.22-0.66, P=0.01

Barotrauma

- HFO vs. Control, OR=1.87, 95% CI, 1.06-3.28, P=0.03;
- HFO-TGI vs. Control, 9.8 vs. 14.1%, P=0.59


Odds Ratio
6
5
4
3
2
1
0
0
50
100
150
200
Baseline PaO2:FiO2 mmHg
PaO2/FiO2 = 64 mmHg
HFO-TGI trial
P/F = 96.5 mmHg
Odds Ratio
lower limit of OR
upper limit of OR
OR=1

Conclusions

hypoxemia.(19) Our results suggest that this expansion of clinical indication should be reversed and HFOV generally should not be used for patients with mild or moderate ARDS. The results of this study also indicate that there remains a potential role for HFOV in a restricted subgroup of severe ARDS. In particular, clinicians caring for patients with severely hypoxic patients with ARDS and who have optimized conventional lung-protective ventilation might consider initiation of HFOV, especially when other approaches (e.g. proning, extracorporeal support) are contraindicated or unavailable.

Conclusions

- In light of combined HFO RCT findings, available data on HFO - TGI + RMs + cuff leak [f~4 Hz] are encouraging, but further study is needed to demonstrate generalizability .
- Low f, high-bias flow HFO-TGI with cuff leak might protect the right ventricle from the combination of increased intrathoracic pressures and hypercapnia.
- New Proposal: For Severe ARDS: Combine Alternating Sessions of Prone Lung-Protective Conventional Ventilation and Supine HFO-TGI.