Pulmonary Sessions: Progress and Perspectives, featuring leading experts in the field

Cardiopulmonary exercise testing and unexplained dyspnoea: new insights

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Département "R3S" — Respiration, Réanimation, Réhabilitation, Sommeil —

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UMRS 1158 « Neurophysiologie Respiratoire Expérimentale et Clinique »
INSERM - Sorbonne Université

Paris, France

Conflicts of interest

• **Pr Laveneziana is** an employee of *Sorbonne Université* and *Assistance Publique – Hôpitaux de Paris;* he is also director of the “Dyspnoea and Exercise” programme at the Respiratory Department of the University Hospital "Pitié-Salpêtrière" and at the research unit UMRS 1158 at Sorbonne Université in Paris.

The content of this presentation is NOT endorsed by these institutions.

- **Pr Laveneziana has no conflict of interest to disclose regarding this presentation**

- **Outside the presentation, Pr Laveneziana reports the following conflicts of interest:**
    - **on an individual basis**
        - *advisory and teaching activities*

          Chiesi, Trudell Medical International

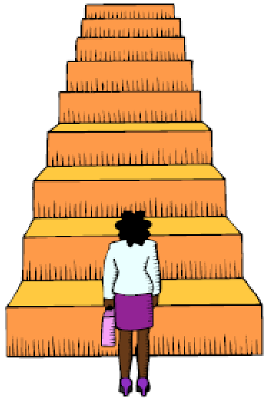
Clinical Utility of CardioPulmonary Exercise Testing (CPET)

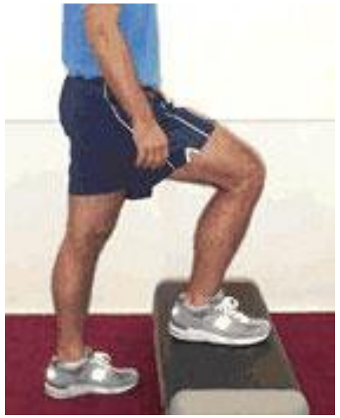
Exercise testing

- to determine peak oxygen consumption ($V'O_2$) and level of disability
- to identify factors contributing to dyspnoea and exercise limitation
- to objectively evaluate the impact of therapeutic interventions:
  - ✓ Oxygen
  - ✓ Bronchodilators
  - ✓ Vasodilators
  - ✓ Exercise training
- to assist in planning individualized exercise training
- to generate prognostic information:
  - ✓ surgical risk
  - ✓ survival
  - ✓ time to clinical worsening
  - ✓ exacerbations
- to screen for coexistent ischemic heart disease, peripheral vascular disease, arterial hypoxemia

EXERCISE MODALITIES

- Stair Climbing
- Master Two-Step Test
- 6 Minute Walk Test
- Treadmill
- Cycle Ergometer
- Shuttle Walking





Cardiopulmonary exercise testing (CPET)

Maximal incremental test
Constant work rate test

Treadmill test
Cycle ergometer test

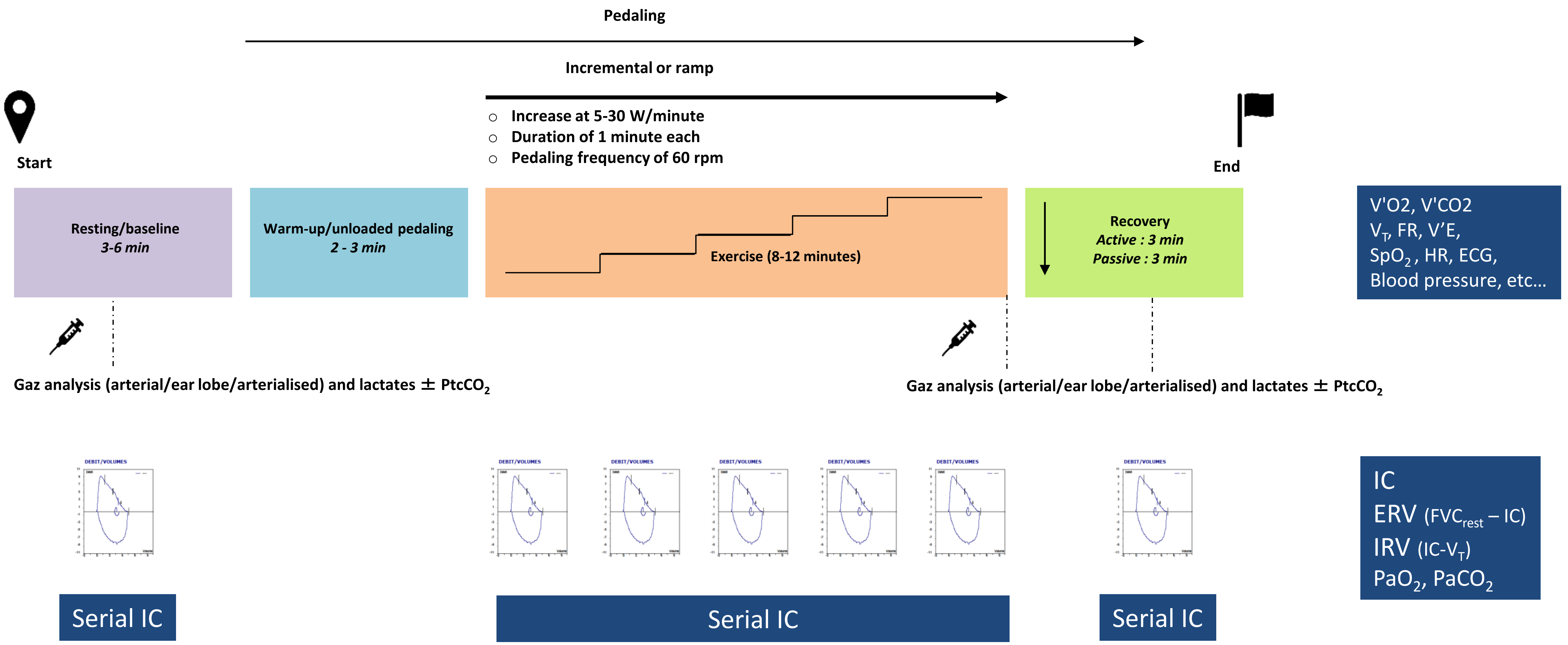
Cardiopulmonary variables

- VO_2
- VCO_2
- V’E
- Breathing reserve (VE/MVV)
- EKG
- Heart rate (HR)
- Blood Pressure (BP)
- LT
- VE/VCO_2
- Oxygen Pulse (VO_2/HR)
- Work efficiency (VO_2/watt)
- TLIM

Exercise Equipment: Cycle Ergometer versus Treadmill

	Cycle	Treadmill
$\dot{V}O_2max$	lower	higher
Work rate measurement	yes	no
Blood gas collection	easier	more difficult
Noise and artifacts	less	more
Safety	safer	less safe?
Weight bearing in obese	less	more
Degree of leg muscle training	less	more
More appropriate for:	patients	active normal subjects

How to run an incremental exercise testing



Dyspnoea and leg discomfort/fatigue at rest, every minute during exercise, at peak + descriptors of reasons for stopping exercise at the end

Laveneziana P, Eur Respir Monograph 2018

Commonly (but avoidable) mistakes

- Known nothing about the patient and his/her clinical history
- Ignore symptoms and reasons for stopping exercise
- Don’t pay attention to CPET comments from who is running the CPET
- Focus ONLY on numbers (see please next two slides)
- Rely (almost exclusively) on predefined algorithms to interpret CPET

The key variables and their meaning

Quantitative approach

(“give me a number please”….
% predicted….

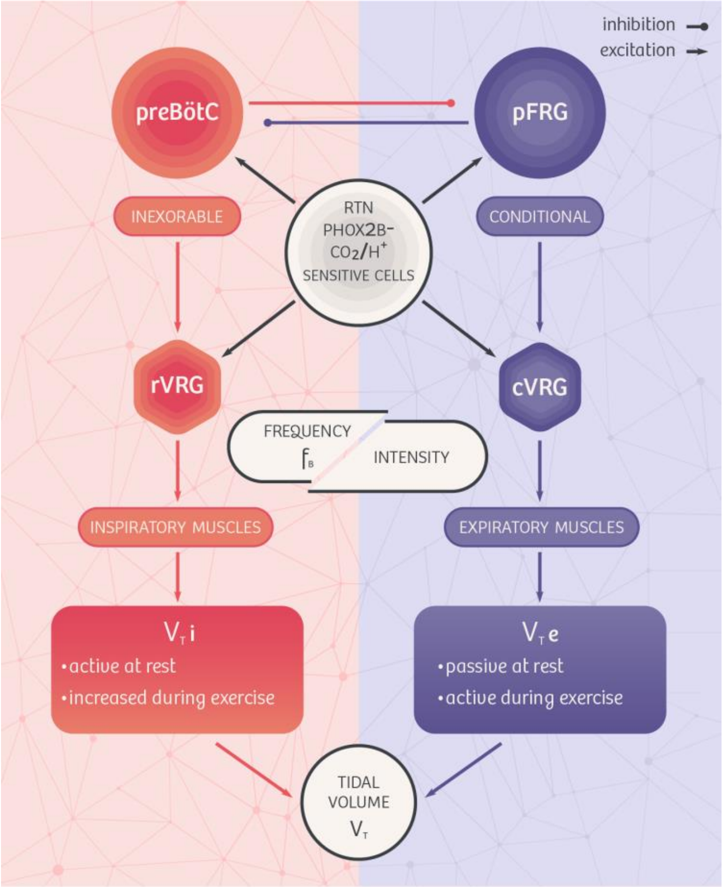
Qualitative approach

(response profile and or kinetics)

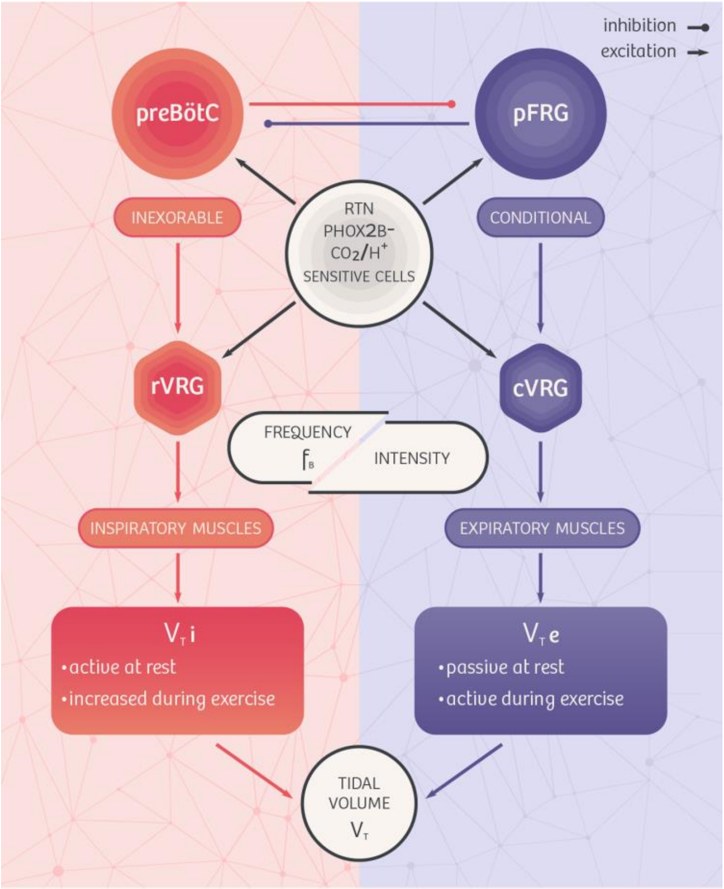
Defective exercise-related expiratory muscle recruitment in patients with PHOX2B mutations: A clue to neural determinants of the congenital central hypoventilation syndrome.

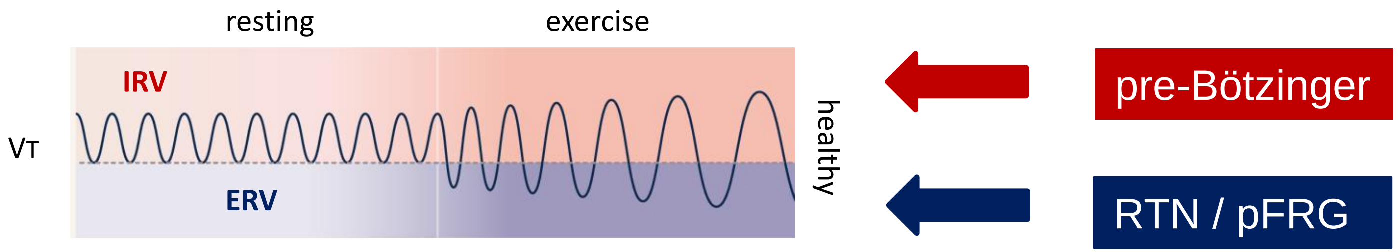
Laveneziana P, Fossé Q, Bret M, Patout M, Dudoignon B, Llontop C, Morélot-Panzini C, Cayetanot F, Bodineau L, Straus C, Similowski T.

Pulmonology. 2025 Dec 31;31(1):2416790. doi: 10.1016/j.pulmoe.2024.01.005. Epub 2024 Oct 24.

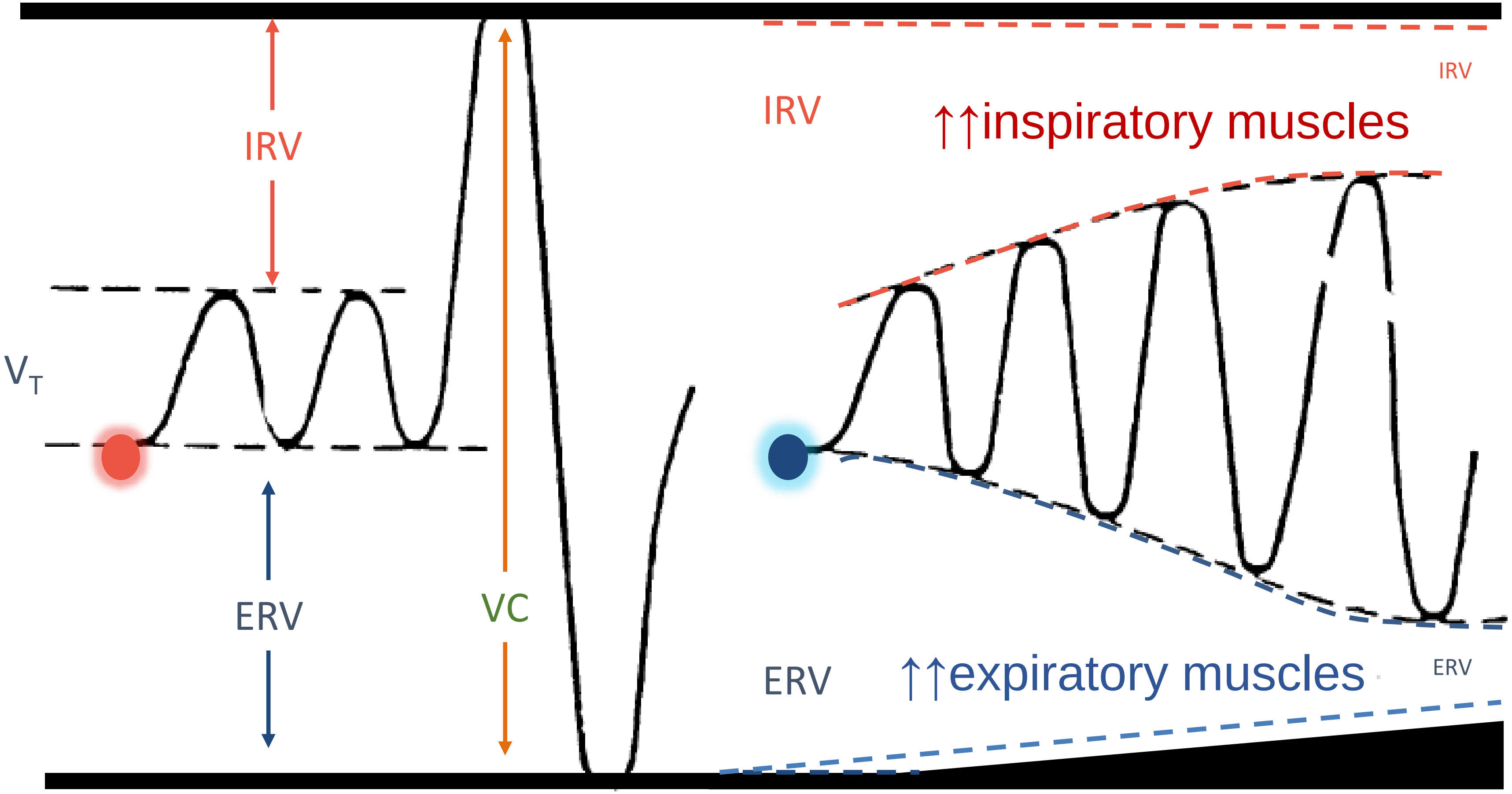


inhibition
excitation
preBötC
pFRG
INEXORABLE
RTN
PHOX2B-
CO2/H+
SENSITIVE CELLS
CONDITIONAL
rVRG
cVRG
FREQUENCY
fB
INTENSITY
INSPIRATORY MUSCLES
EXPIRATORY MUSCLES
VT i
•active at rest
•increased during exercise
VT e
•passive at rest
•active during exercise
TIDAL
VOLUME
VT





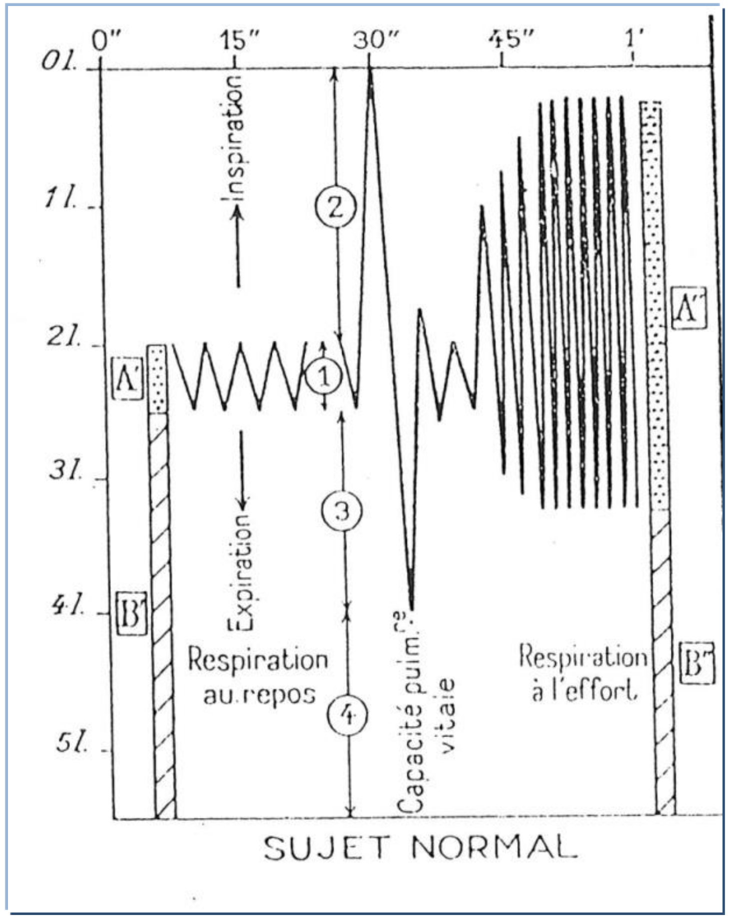
(Laveneziana et al., AJRCCM 2011 ; Laveneziana et al., RESPNB 2014)



Resting

Incremental exercise

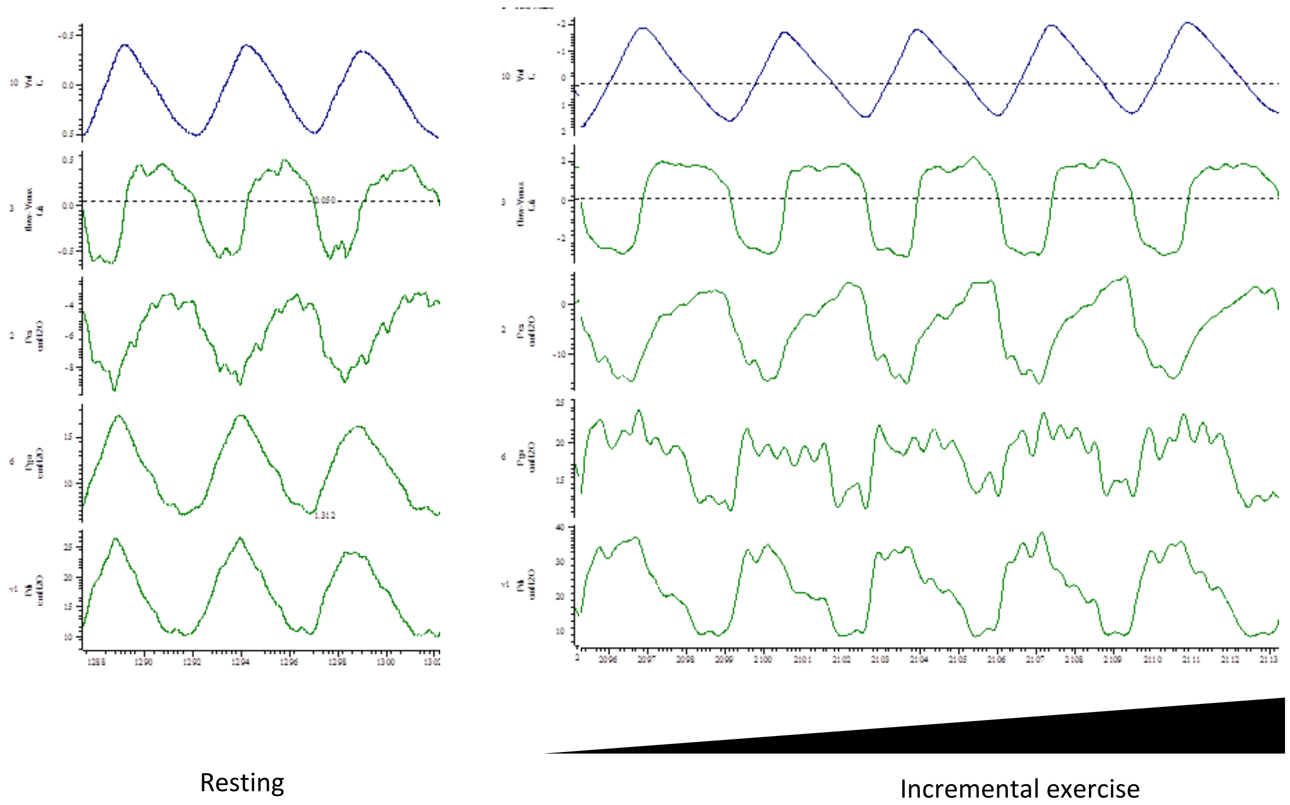
27 Décembre 1947

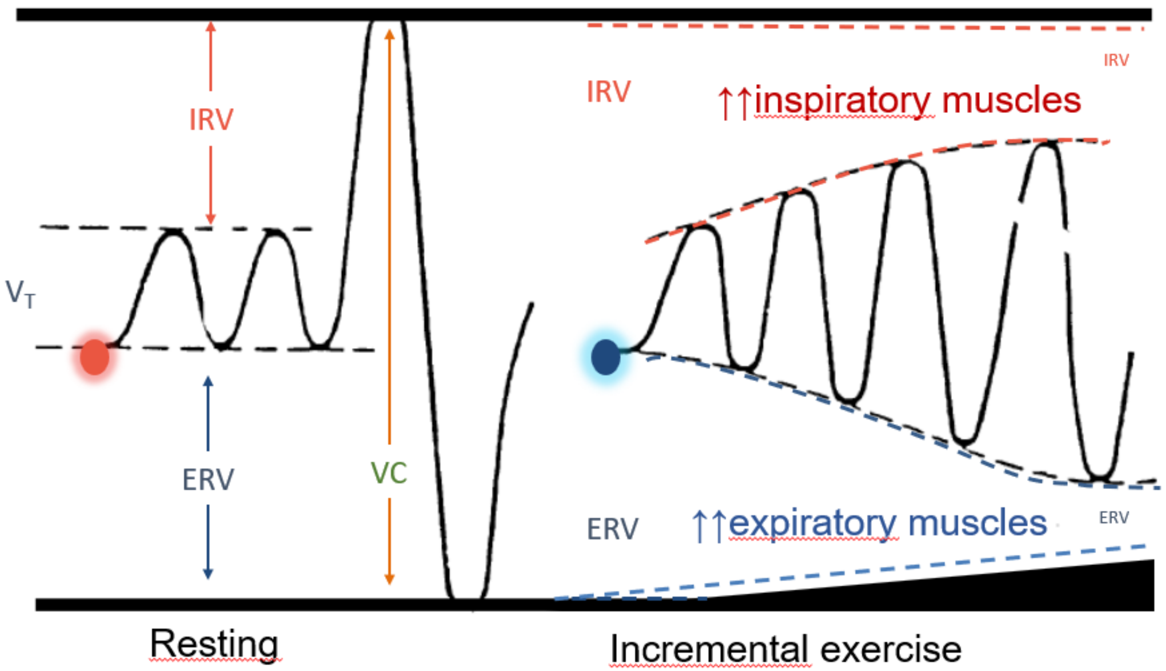


AIR CIRCULANT ET AIR CAPTIF DANS L'EXPLORATION DE LA FONCTION VENTILATRICE PULMONAIRE

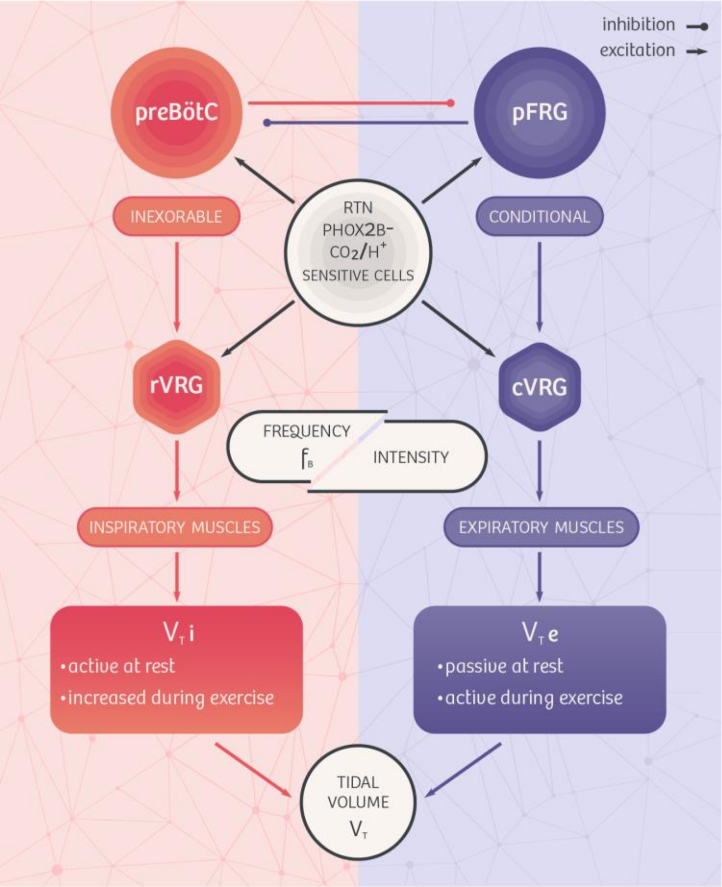
PAR

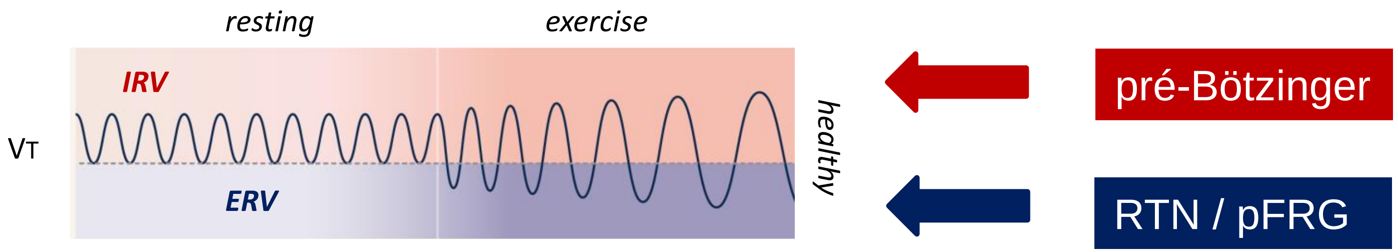
Robert TIFFENEAU et PINELLI





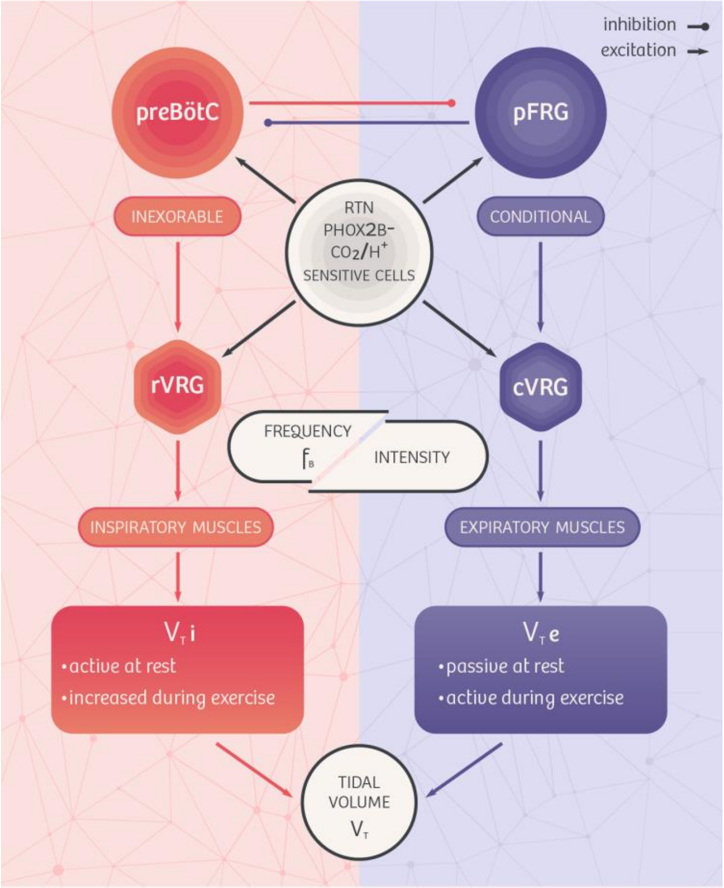
(Laveneziana et al., AJRCCM 2011 ; Laveneziana et al., RESPNB 2014)

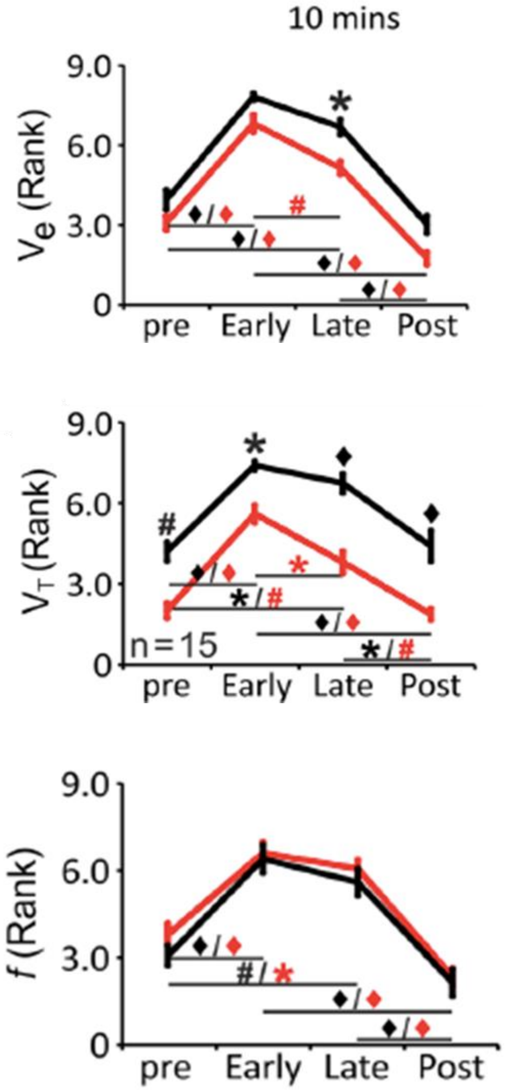




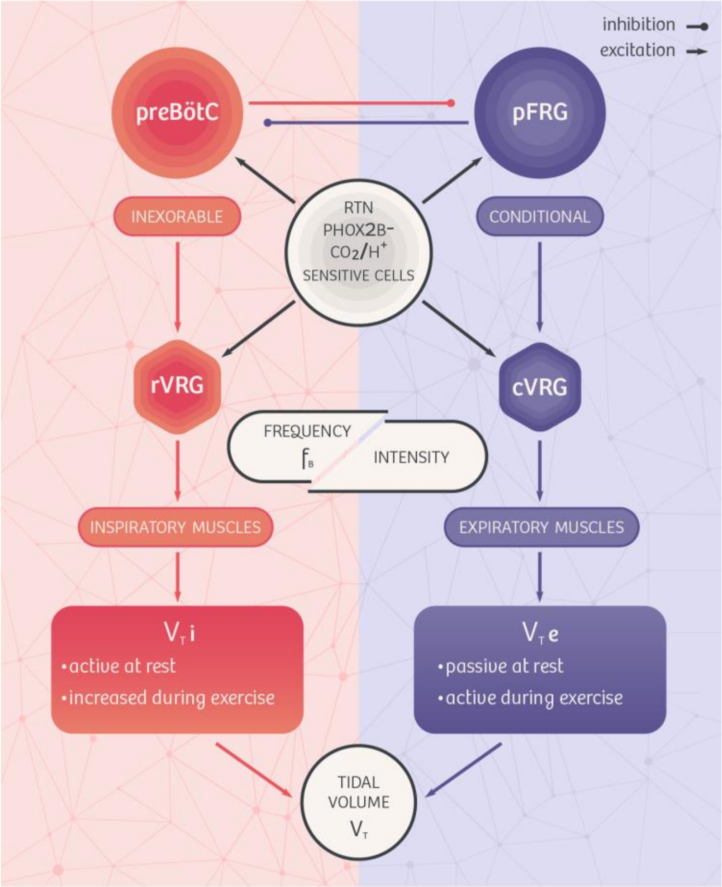
$\uparrow\uparrow V_T \rightarrow \uparrow\uparrow V'_E$

(Laveneziana et al., AJRCCM 2011 ; Laveneziana et al., RESPNB 2014)



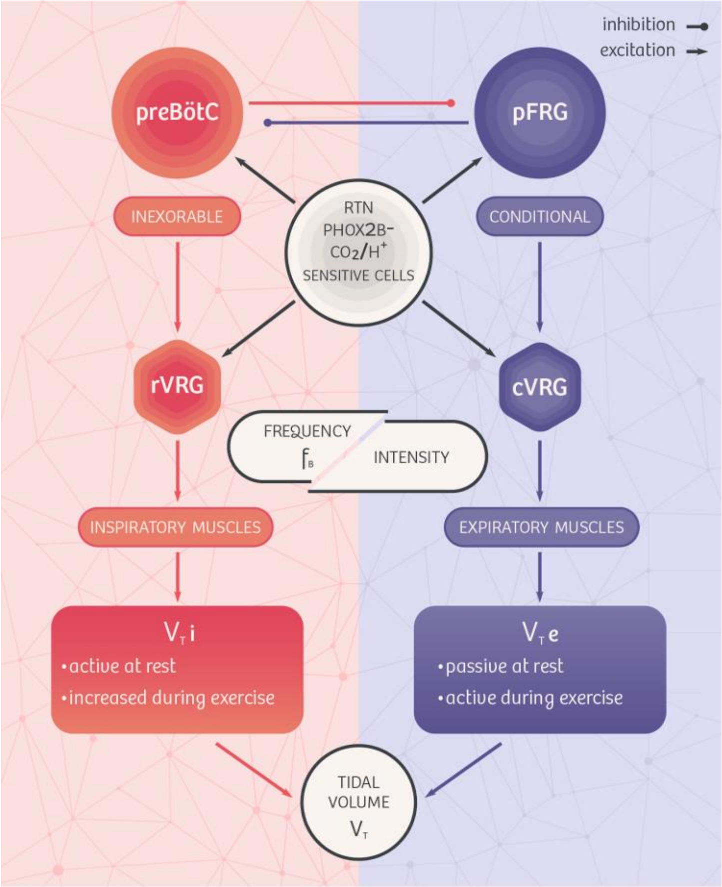


(Korsak et al. 2018)



if dysfunction of RTN/pFRG in CCHS patients

(Laveneziana et al. Pulmonology 2025)



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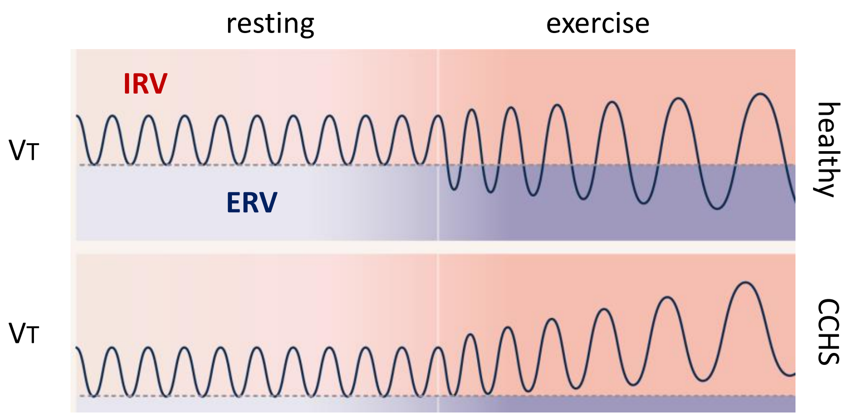


?

(Laveneziana et al. Pulmonology 2025)

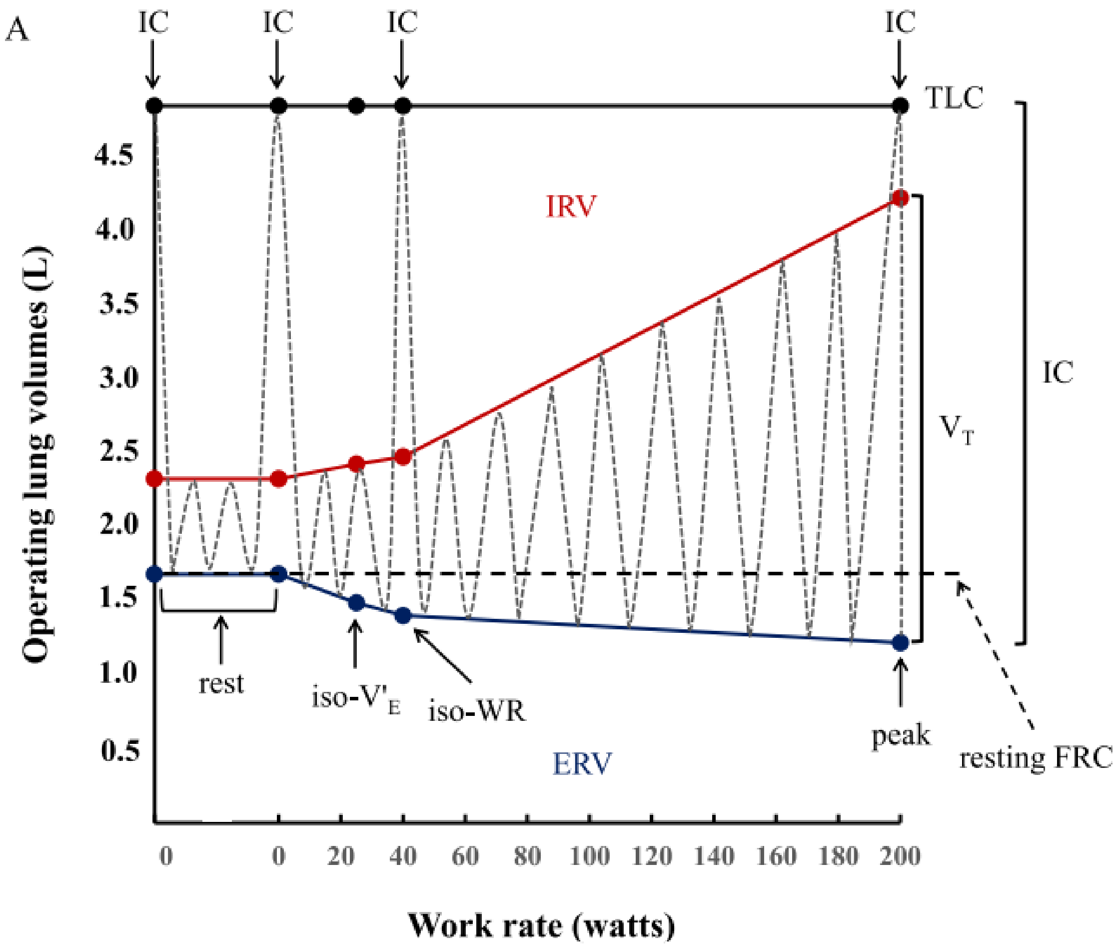
Table 1 CCHS and healthy subjects' characteristics and resting lung function.

	CCHS	Healthy
Sex Female/Male, *n*	7/6	5/8
Age, *years*	24 (19 – 32)	27 (25 – 39)
Height, *cm*	172 (164 – 176)	172 (167 – 176)
Weight, *kg*	65 (55 – 82)	67 (62 – 75)
BMI, kg/m^2	22 (19 – 26)	23 (20 – 26)
PHOX2B mutation – n° subjects	13	/
PARM – n° subjects	12	/
NPARM – n° subjects	1	/
Lung function tests		
FEV_1, *L*	3.54 (3.32 – 4.29)	4.06 (3.76 – 4.16)
FEV_1, *% predicted*	98 (84 – 110)	106 (104 – 116)
VC max, *L*	4.35 (3.56 – 5.07)	4.96 (4.61 – 5.29)
VC max, *% predicted*	91 (85 – 110)	106 (101 – 116)
FEV_1/VC max, *%*	81 (75 – 92)	81 (80 – 87)
TLC, *L*	5.95 (4.99 –7.01)	6.33 (5.79 – 7.58)
TLC, *% predicted*	96 (89 – 104)	106 (98 – 111)
FRC, *L*	2.85 (2.35 – 3.21)	3.23 (2.97 – 4.07)
FRC, *% predicted*	103 (86 – 113)	111 (97 – 116)
RV, *L*	1.51 (1.26 – 1.93)	1.47 (1.37 – 2.00)
RV, *% predicted*	103 (79 – 119)	93 (88 – 107)
IC, *L*	2.71 (2.13 – 3.31)	3.20 (2.76 – 3.55)
ERV, *L*	1.43 (1.15 – 1.59)	1.53 (1.45 – 1.78)
pH	7.43 (7.41 – 7.48)	/
PaO_2, *mmHg*	105 (94 – 115)	/
$PaCO_2$, *mmHg*	36 (29 – 40)	/
SaO_2 (%)	99 (97 – 99)	/
Ventilatory response to CO_2 (re-breathing method), *L*/min/*mmHg*	0.37 (0.26 – 0.58)	/

(Laveneziana et al. Pulmonology 2025)

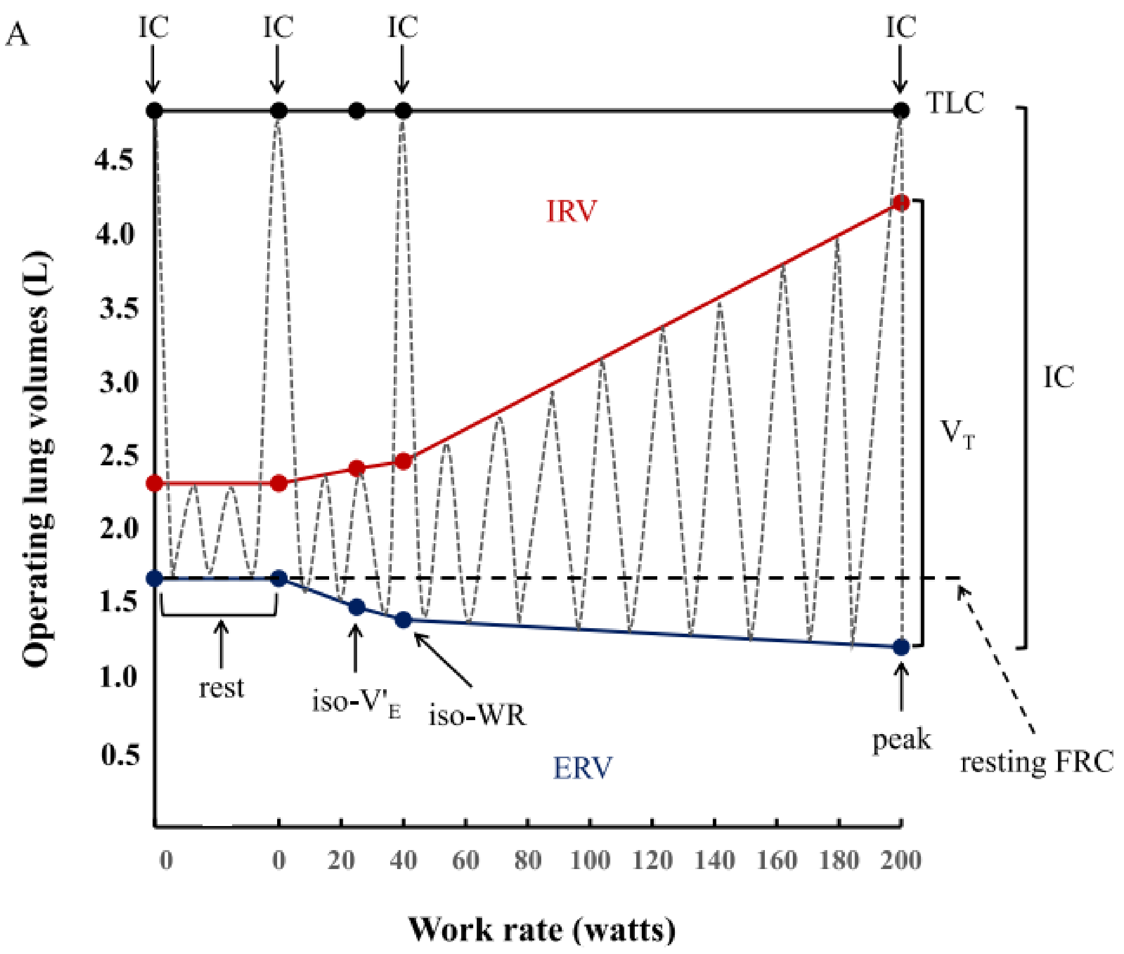
Healthy subjects (n=13, 5F/8M)

CCHS patients (n=13, 7F/6M)

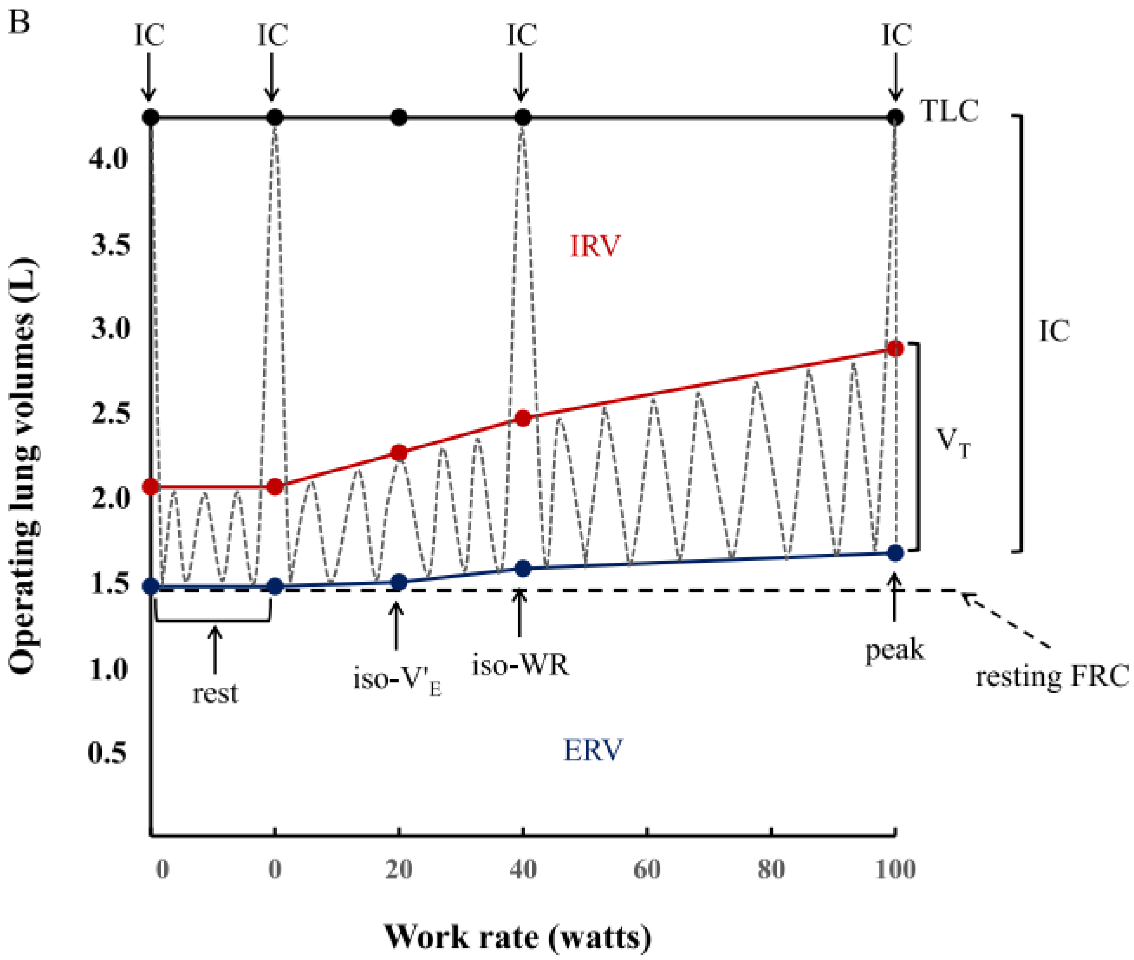


(Laveneziana et al. Pulmonology 2025)

Healthy subjects (n=13, 5F/8M)



CCHS patients (n=13, 7F/6M)



(Laveneziana et al. Pulmonology 2025)

Table 2 Physiological responses to cardiopulmonary exercise testing at rest and at peak in CCHS and healthy subjects.

	Rest		Peak	
Variables	CCHS	Healthy	CCHS	Healthy
Work rate, watts	0 (0 – 0)	0 (0 – 0)	90 (80 – 130)***	190 (155 – 240)
$V'O_2$, L/min	0.321 (0.296 – 0.352)	0.282 (0.273 – 0.303)	1.472 (1.160 – 1.790)***	2.555 (2.070 – 2.890)
$V'O_2$, % pred	15 (13 – 16)	12 (11 – 14)	68 (44 – 80)***	99 (98 – 102)
SpO_2, %	98 (96 – 99)	99 (99 – 99)	91 (86 – 95)***	99 (98 – 99)
PaO_2, mmHg	105 (94 – 115)	/	78 (71 – 91)	/
$PaCO_2$, mmHg	36 (29 – 40)	/	54 (48 – 60)	/
$P_{ET}CO_2$, mmHg	33 (28 – 36)	39 (38 – 40)	59 (50 – 65)***	40 (37 – 42)
V'_E, L/min	9.8 (9.2 – 11.9)	9.9 (9.0 – 10.2)	26.3 (20.6 – 40.9)***	106.5 (97.2 – 110.5)
V_T, L	0.58 (0.48 – 0.71)	0.60 (0.58 – 0.68)	1.21 (0.92 – 1.40)***	2.94 (2.73 – 3.05)
B_f, breaths/min	17 (15 – 22)	15 (15 – 17)	27 (19 – 30)***	37 (32 – 40)
IRV, L	1.89 (1.69 – 2.77)	2.59 (2.31 – 2.78)	1.36 (0.84 – 1.94)***	0.59 (0.40 – 0.77)
Δ IRV, L	0 (0 – 0)	0 (0 – 0)	−0.95 (−1.06 – −0.39)***	−1.85 (−2.16 – −1.44)
ERV, L	1.40 (1.03 – 1.63)	1.83 (1.34 – 2.08)	1.86 (1.04 – 2.09)*	1.44 (0.89 – 1.50)
Δ ERV, L	0 (0 – 0)	0 (0 – 0)	0.06 (−0.06 – 0.53)*	−0.45 (−0.60 – −0.39)
IC, L	2.51 (2.13 – 3.44)	3.20 (2.90 – 3.36)	2.50 (2.02 – 3.29)***	3.62 (3.42 – 3.83)
Δ IC, L	0 (0 – 0)	0 (0 – 0)	−0.06 (−0.53 – 0.06)***	0.45 (0.39 – 0.60)

(Laveneziana et al. Pulmonology 2025)

Table 3 Physiological responses to cardiopulmonary exercise testing at iso-WR (40 W) and iso-V'_E (15 L/min) in CCHS and healthy subjects.

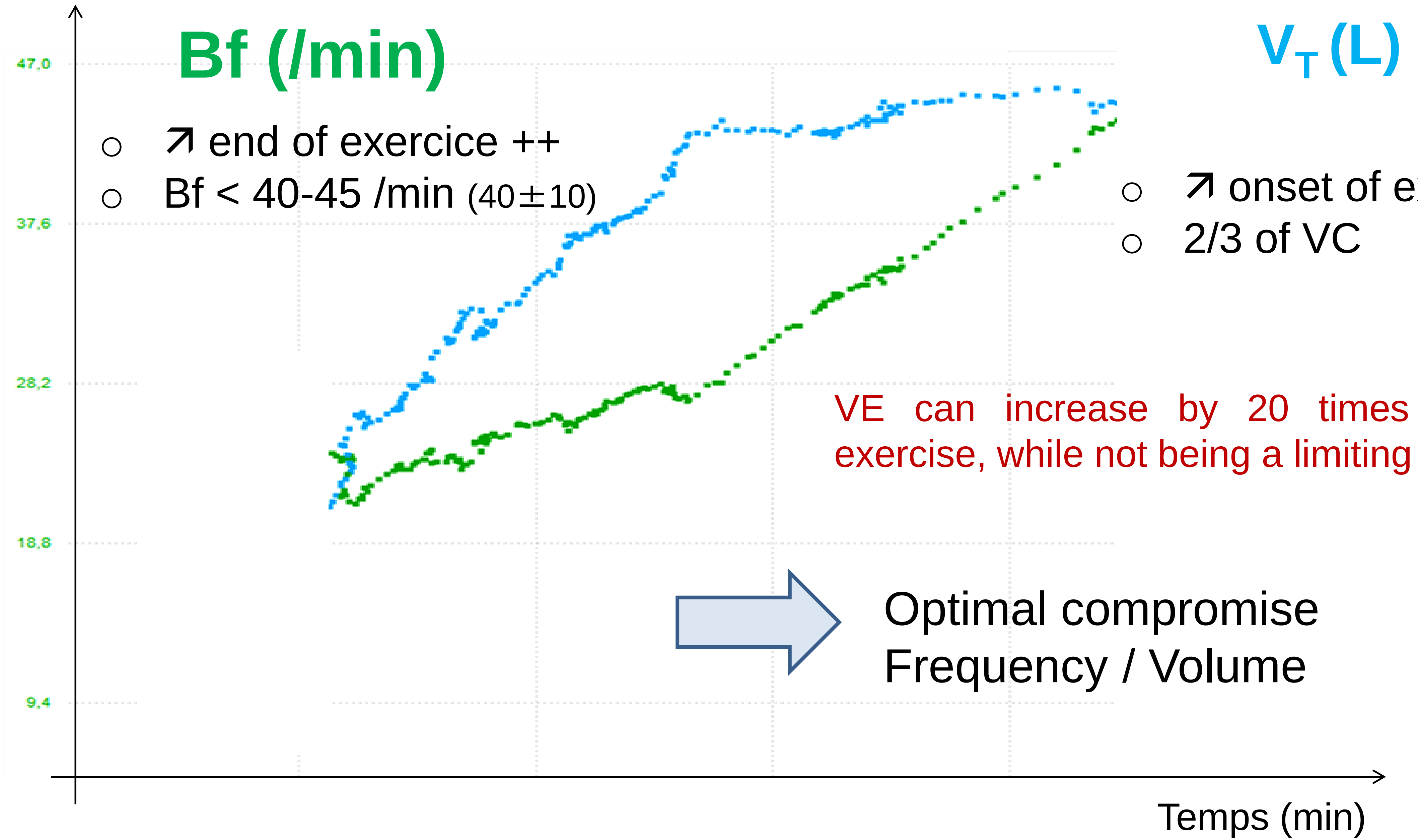
	iso-V'_E (15 L/min)		iso-WR (40 W)	
Variables	CCHS	Healthy	CCHS	Healthy
Work rate, watts	16 (14 – 30)	26 (19 – 29)	40	40
$V'O_2$, L/min	0.613 (0.491 – 0.670)	0.499 (0.443 – 0.545)	0.841 (0.750 – 0.912)*	0.660 (0.603 – 0.785)
$V'O_2$, % pred	28 (20 – 33)	21 (20 – 23)	35 (26 – 42)*	27 (25 – 31)
SpO_2,%	96 (92 – 98)*	99 (99 – 99)	96 (93 – 98)*	99 (99 – 99)
$P_{ET}CO_2$, mmHg	38 (34 – 46)	41 (40 – 42)	45 (38 – 51)	41 (40 – 42)
V'_E, L/min	15.0	15.0	17.6 (15.4 – 22.0)	17.4 (17.1 – 19.4)
V_T, L	0.72 (0.68 – 0.80)*	0.93 (0.76 – 0.97)	0.92 (0.73 – 1.01)*	1.04 (0.94 – 1.12)
B_f, breaths/min	21 (19 – 22)*	16 (16 – 20)	21 (18 – 23)*	17 (15 – 19)
IRV, L	1.68 (1.37 – 2.73)	2.54 (1.96 – 2.75)	1.74 (1.45 – 2.52)	2.40 (1.93 – 2.71)
Δ IRV, L	−0.14 (−0.19 – −0.02)**	−0.06 (−0.17 – 0.01)	−0.28 (−0.47 – −0.24)**	−0.15 (−0.24 – −0.01)
ERV, L	1.45 (1.06 – 1.60)	1.69 (1.03 – 1.85)	1.52 (1.29 – 2.08)	1.64 (0.96 – 1.76)
Δ ERV, L	0.00 (−0.04 – 0.04)**	−0.14 (−0.31 – −0.10)	−0.02 (−0.07 – 0.20)**	−0.24 (−0.32 – −0.19)
IC, L	2.51 (2.15 – 3.45)**	3.36 (3.18 – 3.48)	2.62 (2.18 – 3.52)**	3.43 (3.34 – 3.62)
Δ IC, L	0.00 (−0.04 – 0.04)**	0.14 (0.10 – 0.31)	0.02 (−0.20 – 0.07)**	0.24 (0.19 – 0.32)

(Laveneziana et al. Pulmonology 2025)

Assuming a similar organization of respiratory rhythmogenesis in humans and rodents, the lack of exercise-related expiratory recruitment observed in our CCHS patients is compatible with a PHOX2B-related defect of a neural structure that would be analogous to the rodents' RTN.

Provided corroboration, ERV recruitment could serve as a physiological outcome in studies aiming at correcting breathing control in CCHS.

(Laveneziana et al. Pulmonology 2025)



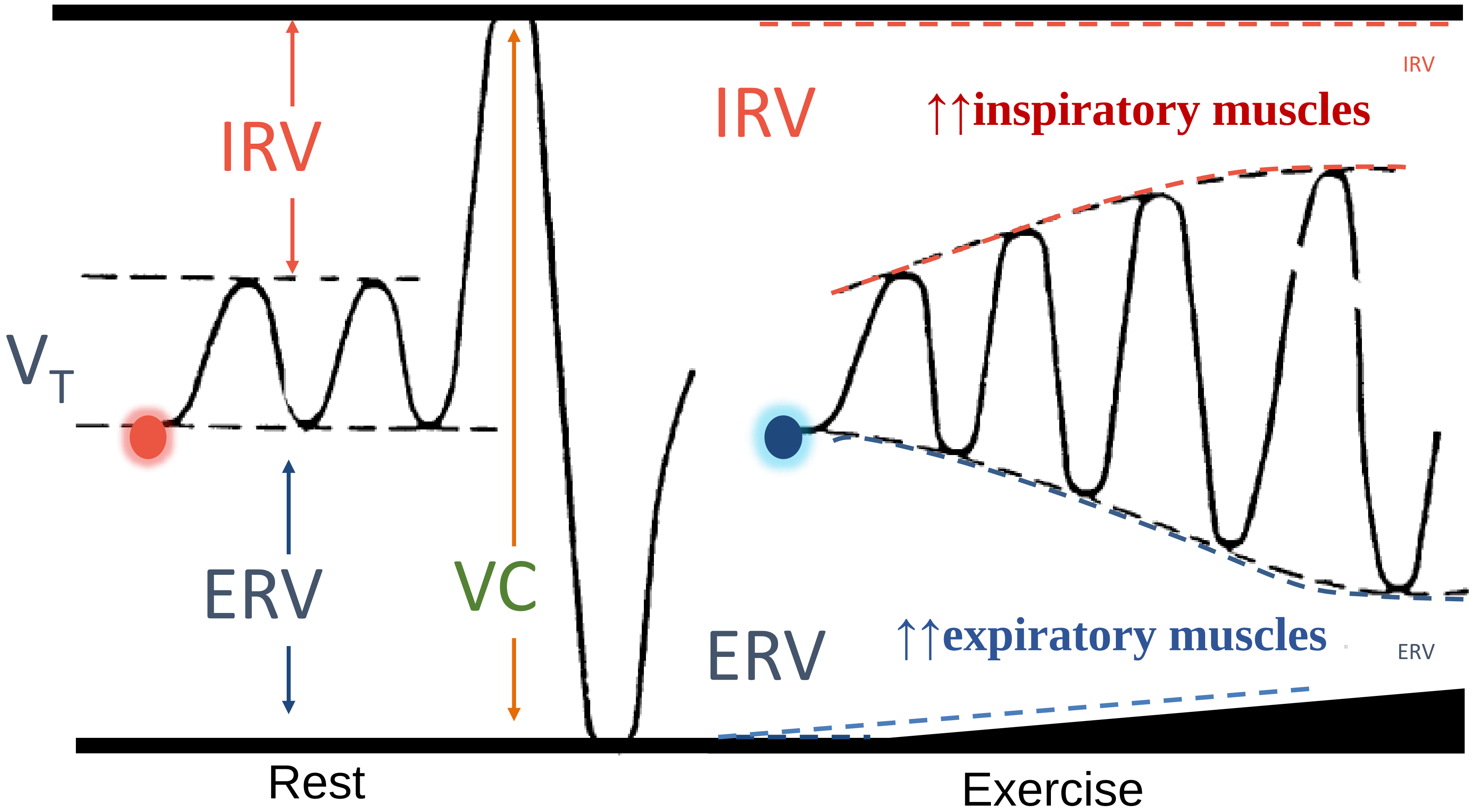
- ↗ end of exercice ++
- Bf < 40-45 /min (40±10)

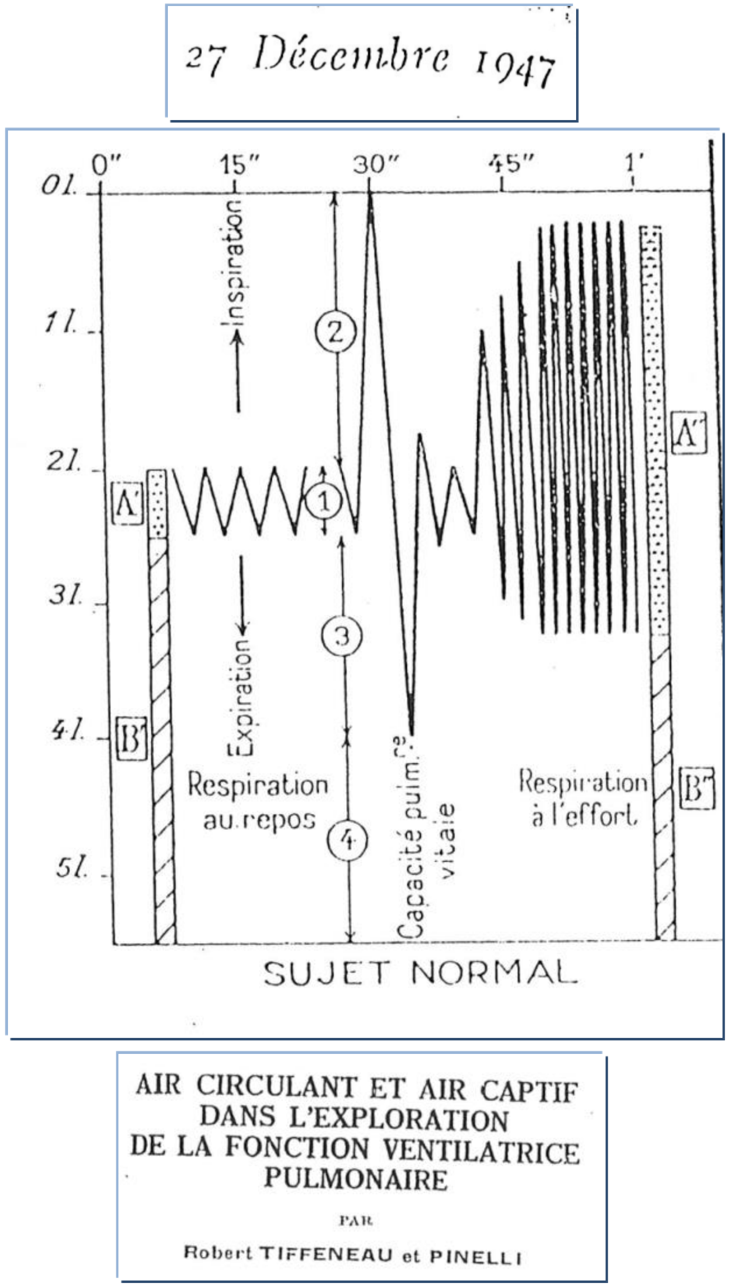
- ↗ onset of exercice
- 2/3 of VC

VE can increase by 20 times during exercise, while not being a limiting factor

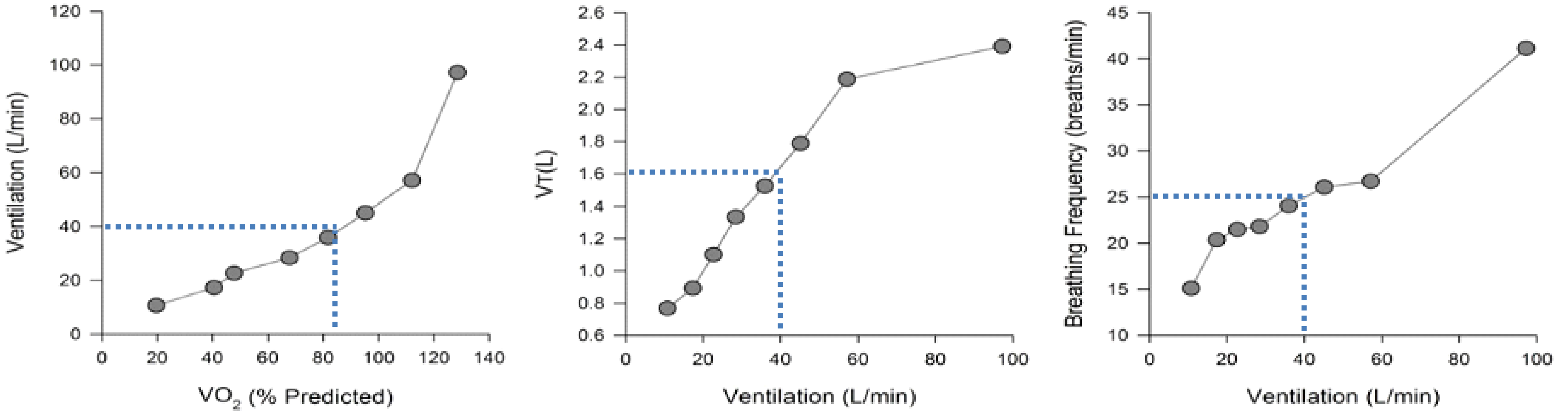
Optimal compromise
Frequency / Volume

V_T at peak exercise = 60-70% (55 ± 10%) Vital Capacity



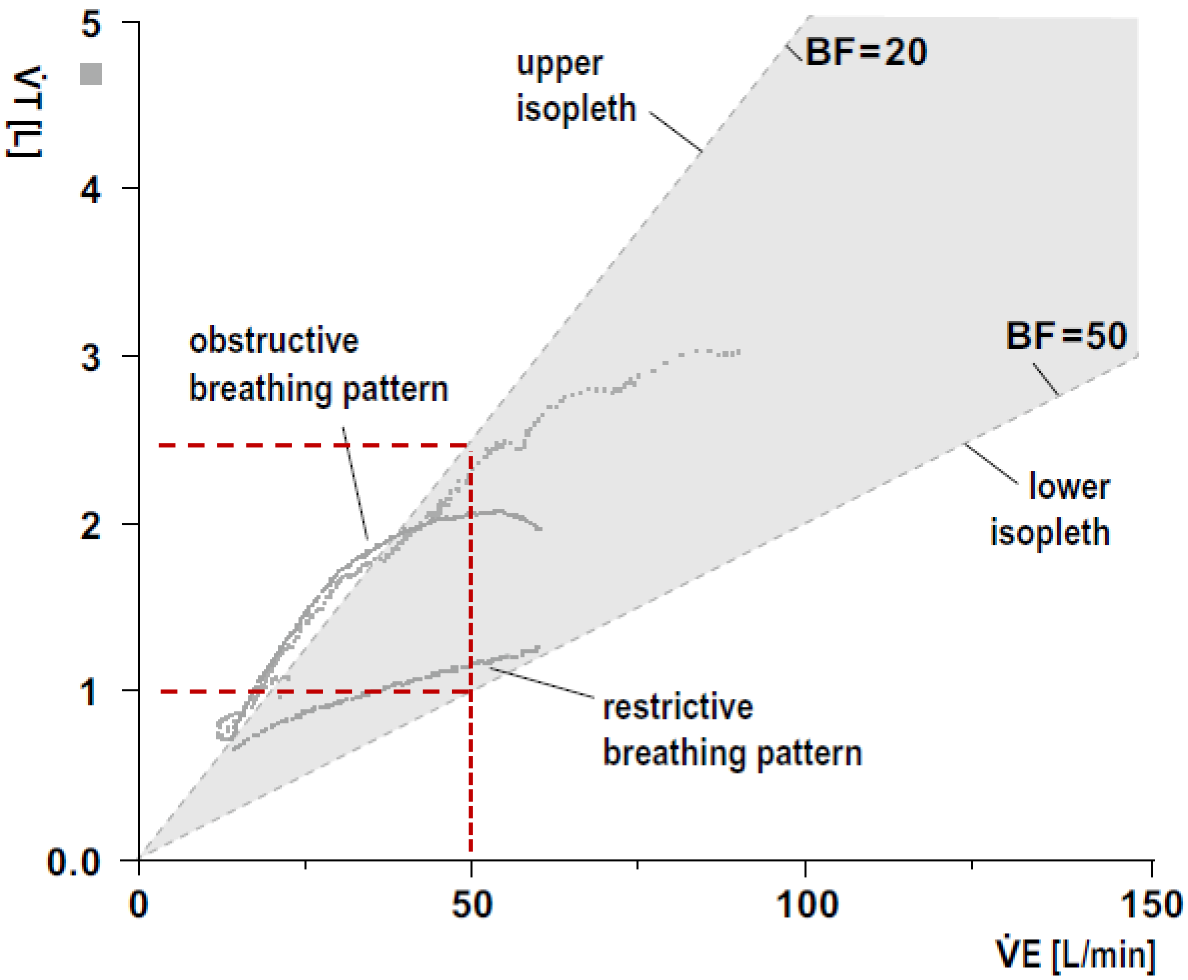


Normal Breathing Pattern

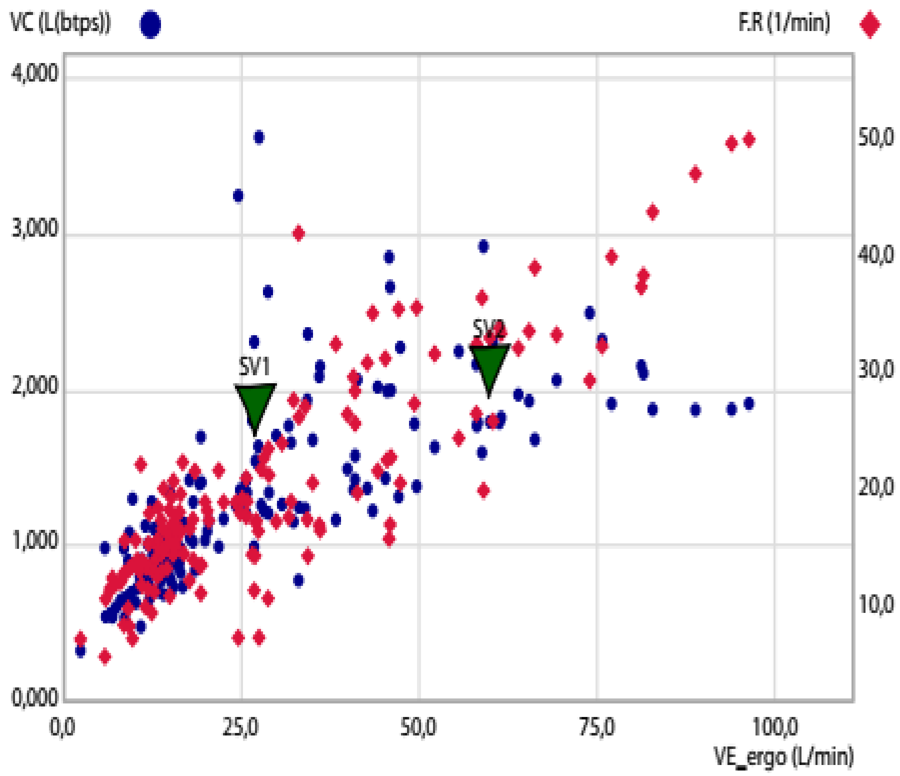


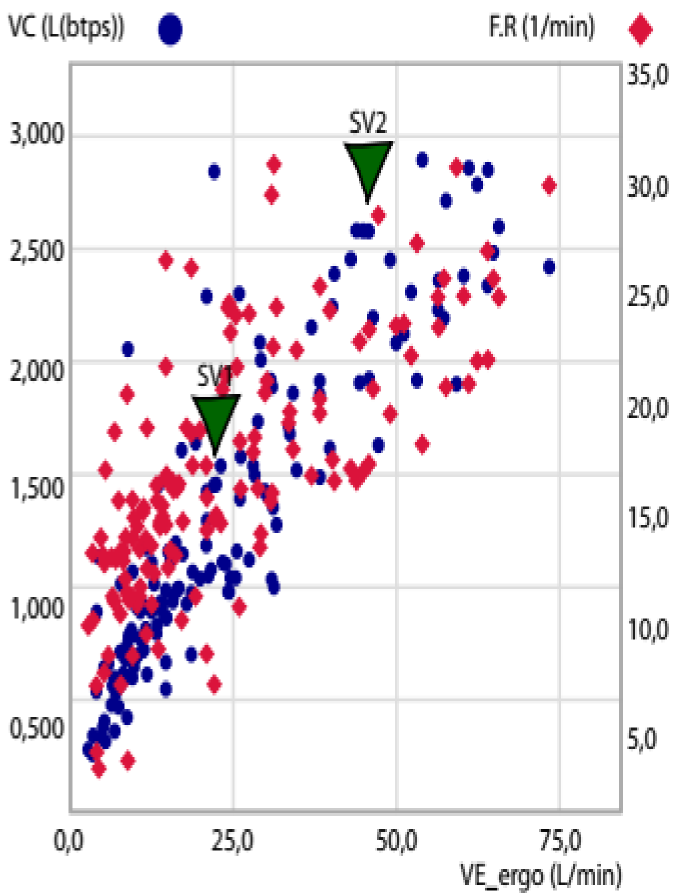
Power output (watts)	Rest	50 watts	100 watts	150 watts	200 watts	250 watts
$V'O_2$ ($L\ min^{-1}$)	0.300	1.18	1.69	2.22	2.92	3.64
V'_E ($L\ min^{-1}$)	6.8	26.6	38.6	51.4	76.7	103.9
V_T (L)	0.450	1.42	1.82	2.09	2.42	2.65
RR (breaths min^{-1})	15	19.2	21.8	25.1	32.2	40.1
T_I (s)	1.6	1.35	1.24	1.14	0.91	0.78
T_E (s)	2.4	1.86	1.57	1.35	1.03	0.80
T_I / T_{TOT}	0.4	0.42	0.44	0.46	0.47	0.49

Gallagher and Younes, 1989

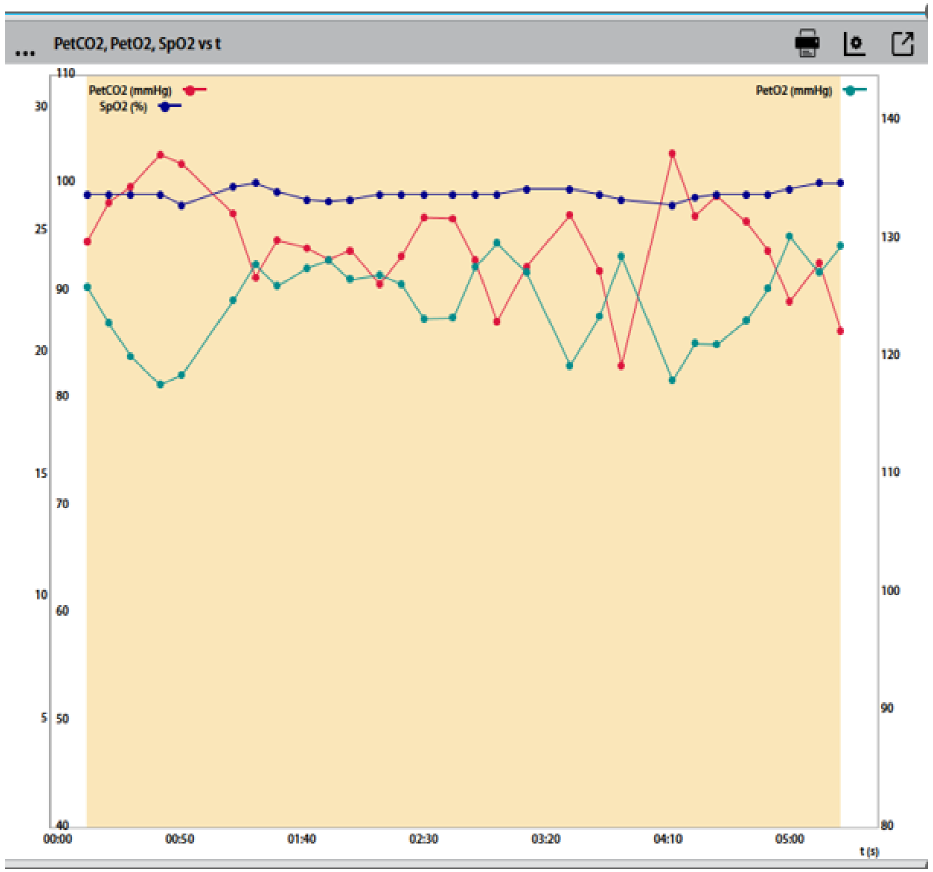


V̇T [L]
5
4
3
2
1
0.0
0
50
100
150
V̇E [L/min]
upper
isopleth
BF=20
BF=50
lower
isopleth
obstructive
breathing pattern
restrictive
breathing pattern

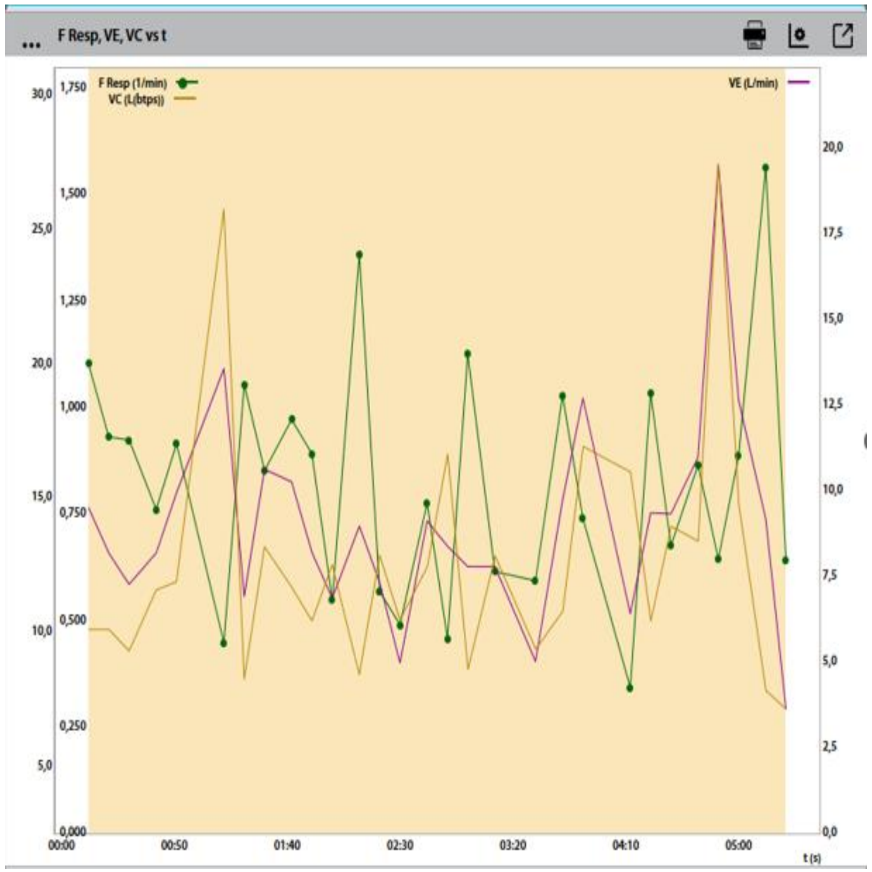




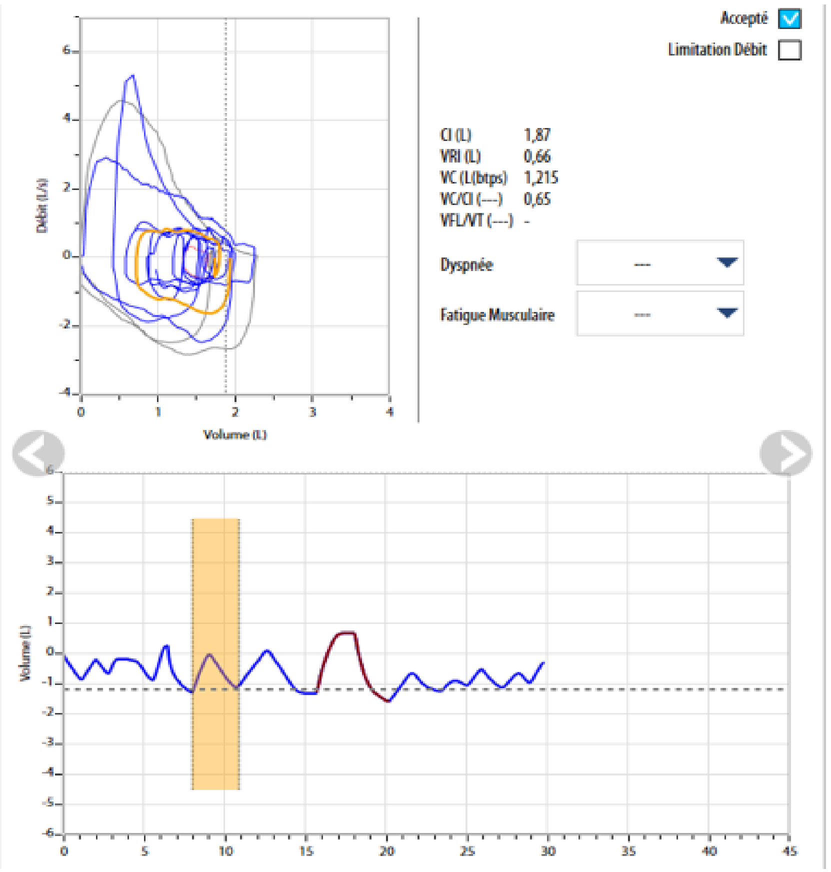
Laveneziana P, personal unpublished data

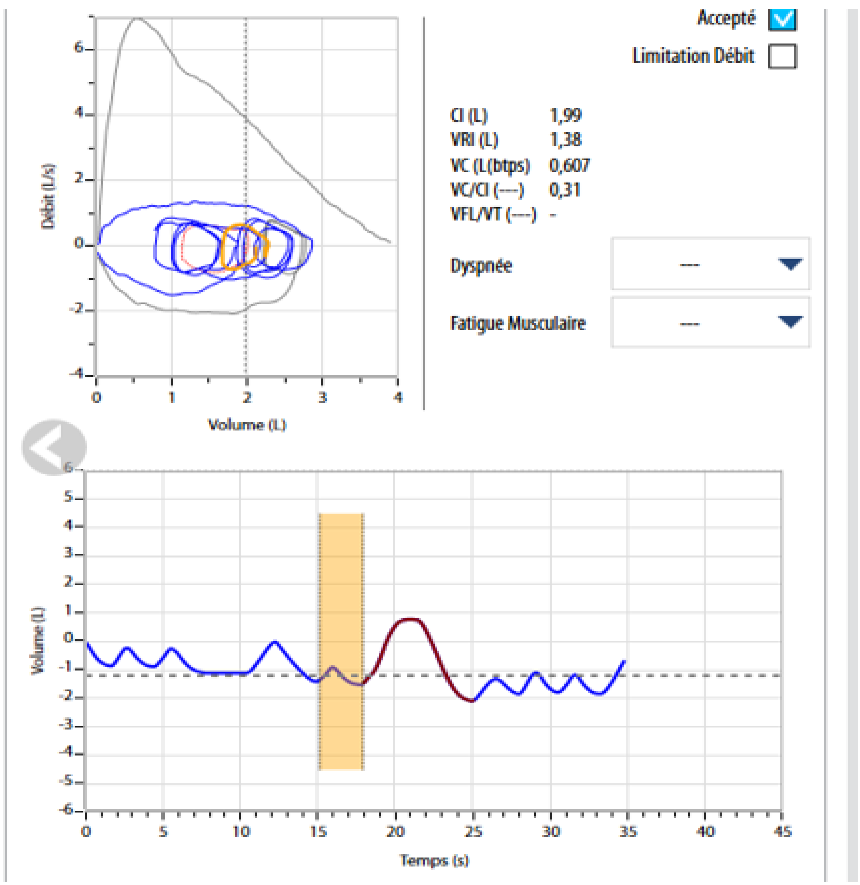


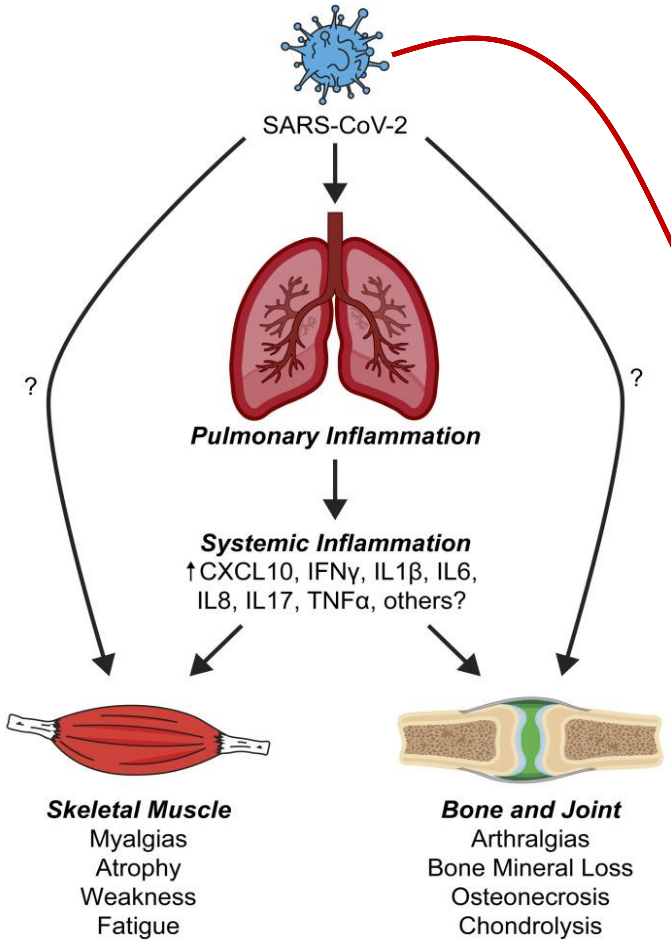
PetCO2, PetO2, SpO2 vs t
PetCO2 (mmHg)
SpO2 (%)
PetO2 (mmHg)
t (s)

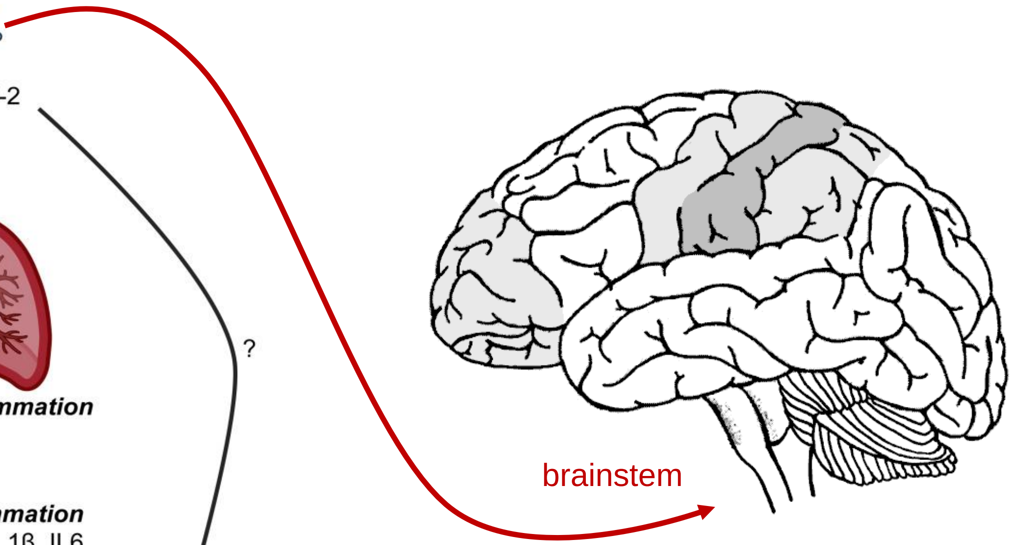


F Resp, VE, VC vs t
F Resp (1/min)
VC (L(btps))
VE (L/min)
t (s)


Accepté
Limitation Débit
CI (L) 1,87
VRI (L) 0,66
VC (L(btps) 1,215
VC/CI (---) 0,65
VFL/VT (---) -
Dyspnée
Fatigue Musculaire
Débit (L/s)
Volume (L)


Accepté
Limitation Débit
CI (L) 1,99
VRI (L) 1,38
VC (L(btps) 0,607
VC/CI (---) 0,31
VFL/VT (---) -
Dyspnée
Fatigue Musculaire
Débit (L/s)
Volume (L)
Temps (s)



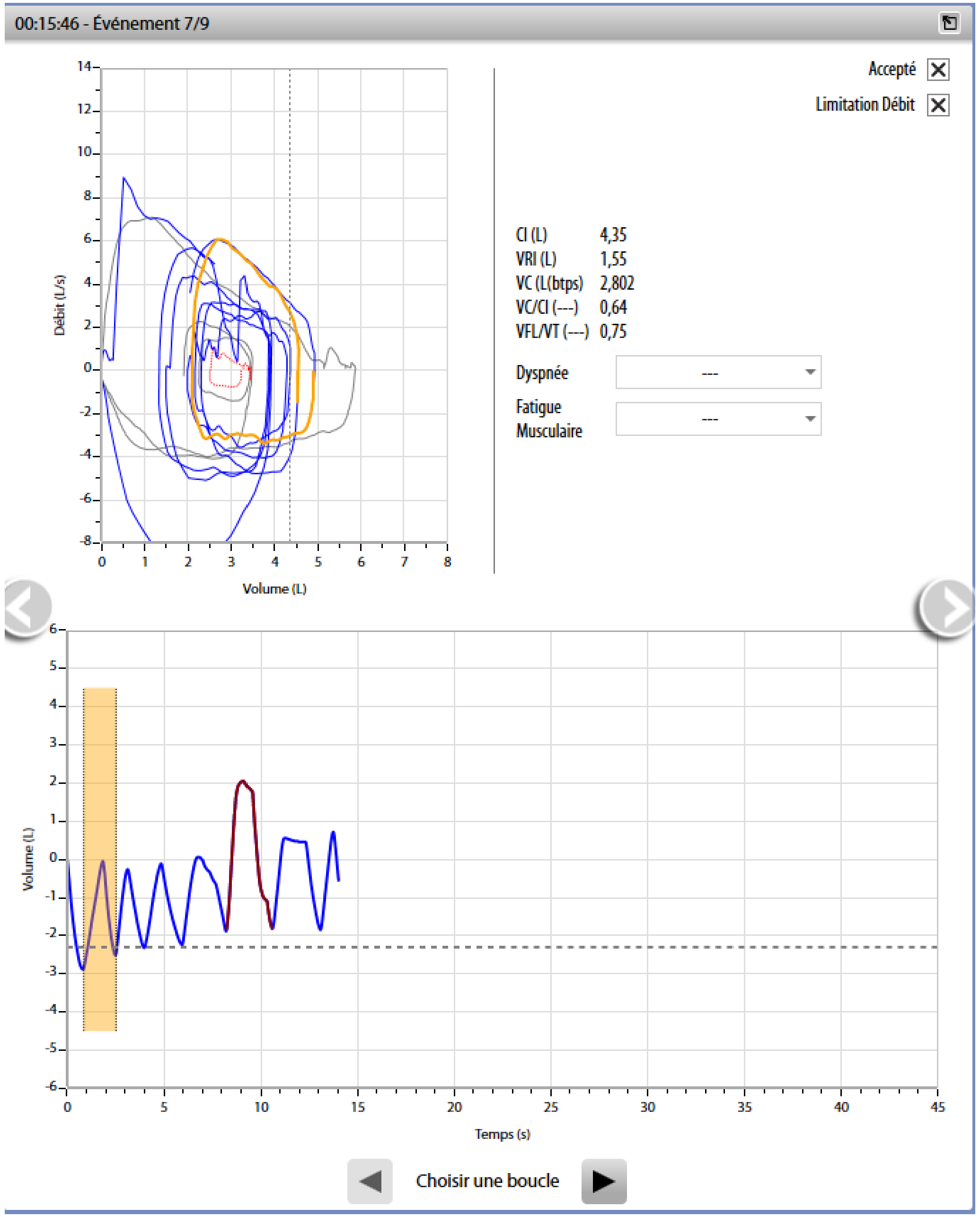


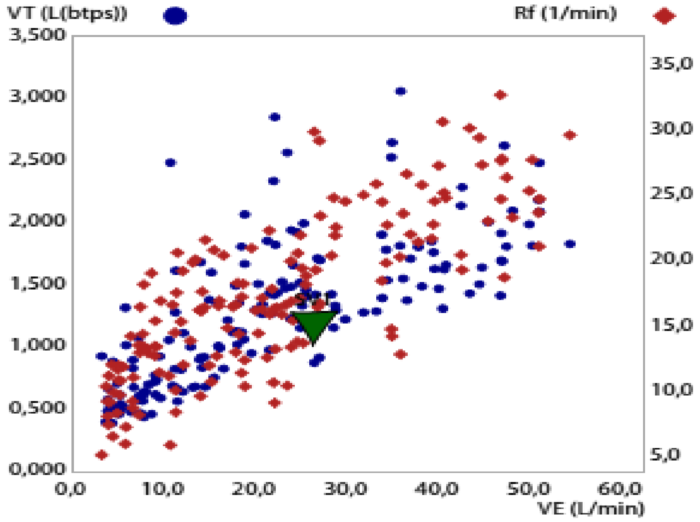
Why is the response not appropriate?

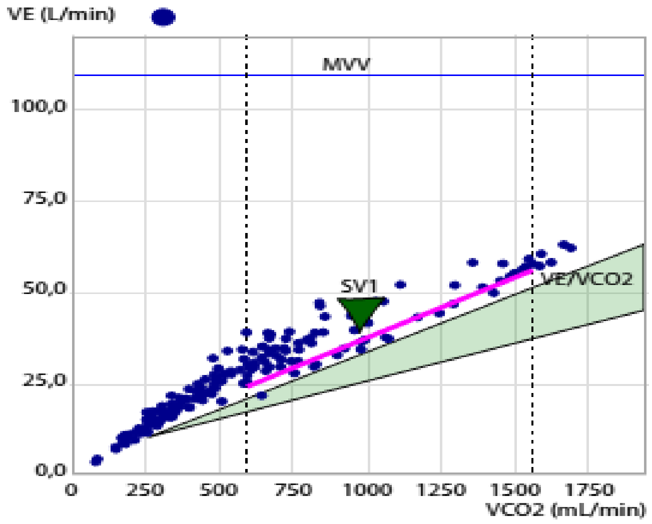
- **Won't respond appropriately →** ***"central" ("could, but won't")***

Laveneziana P, Morelot C et al. Eur Respir J. 2025 to be soon submitted

Dysfunctional Breathing







One ore more features of Dysfunctional Breathing identified on CPET:

- **high V_E/VCO_2 (> 35 at 40 Watts)**
- **low $P_{ET}CO_2$ (< 30mmHg ou < 4 kPa at rest and during CPET)**
- **erratic V_T and/or Bf response to workload**

Laveneziana P et al. ERR 2021

Diagnosis of dysfunctional breathing in severe asthma.

Soumagne T, Garcia G, Frija J, Chenivesse C, Perez T, Plantier L, Humbert M, **Laveneziana P**, Beurnier A, Taillé C, Degano B.

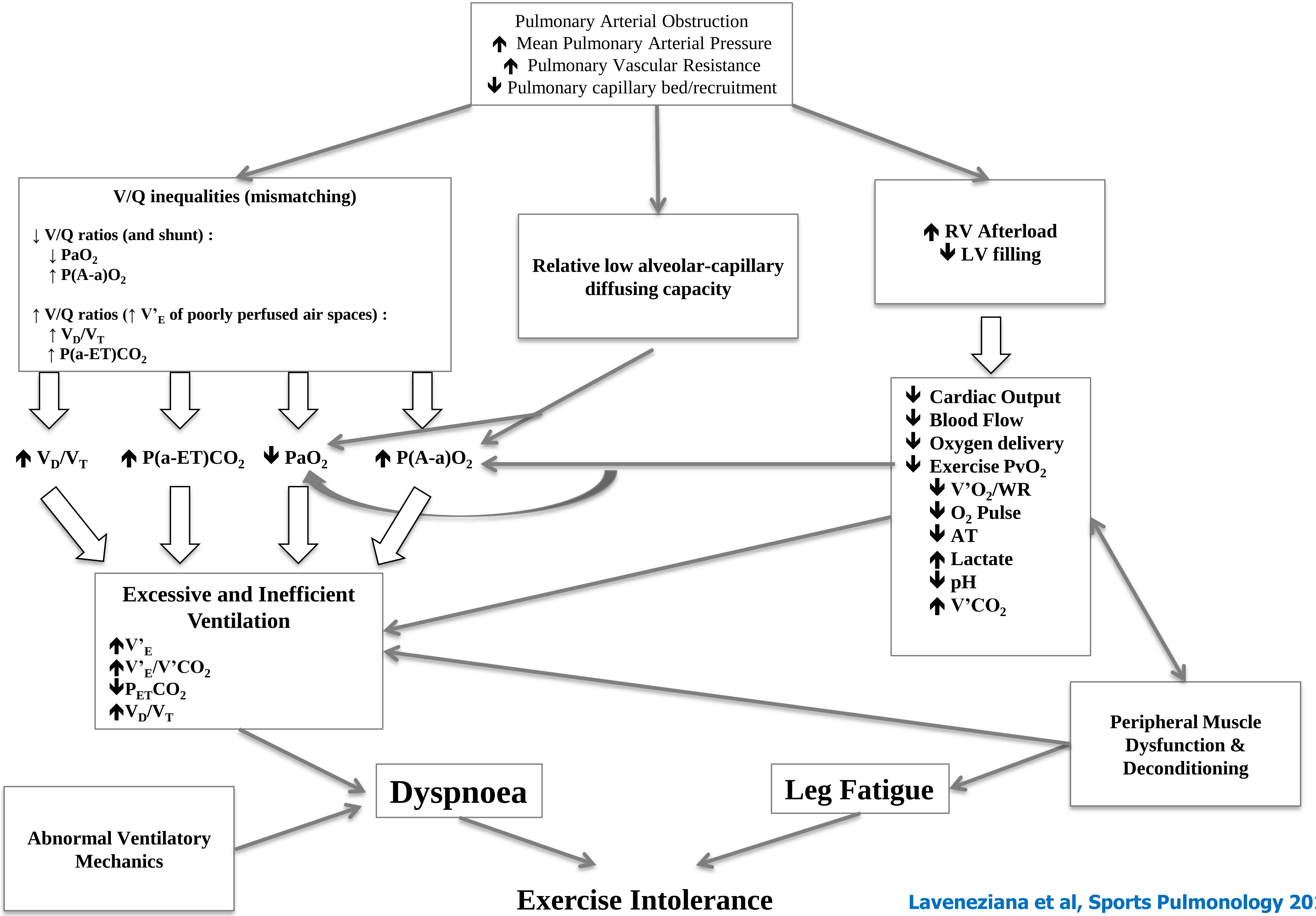
J Allergy Clin Immunol Pract. 2025 Apr 29:S2213-2198(25)00391-5. doi: 10.1016/j.jaip.2025.04.033. Online ahead of print.

Comparing methods to measure the dispersion of breathing parameters during exercise testing: A simulation study based on real-life parameters from patients with dysfunctional breathing.

Genecand L, Jaksic C, Desponds R, Simian G, Guerreiro I, Thorens S, Altarelli M, Frésard I, Cantero C, Bringard A, Beurnier A, **Laveneziana P**, Montani D, Bergeron A, Lador F, Bridevaux PO.

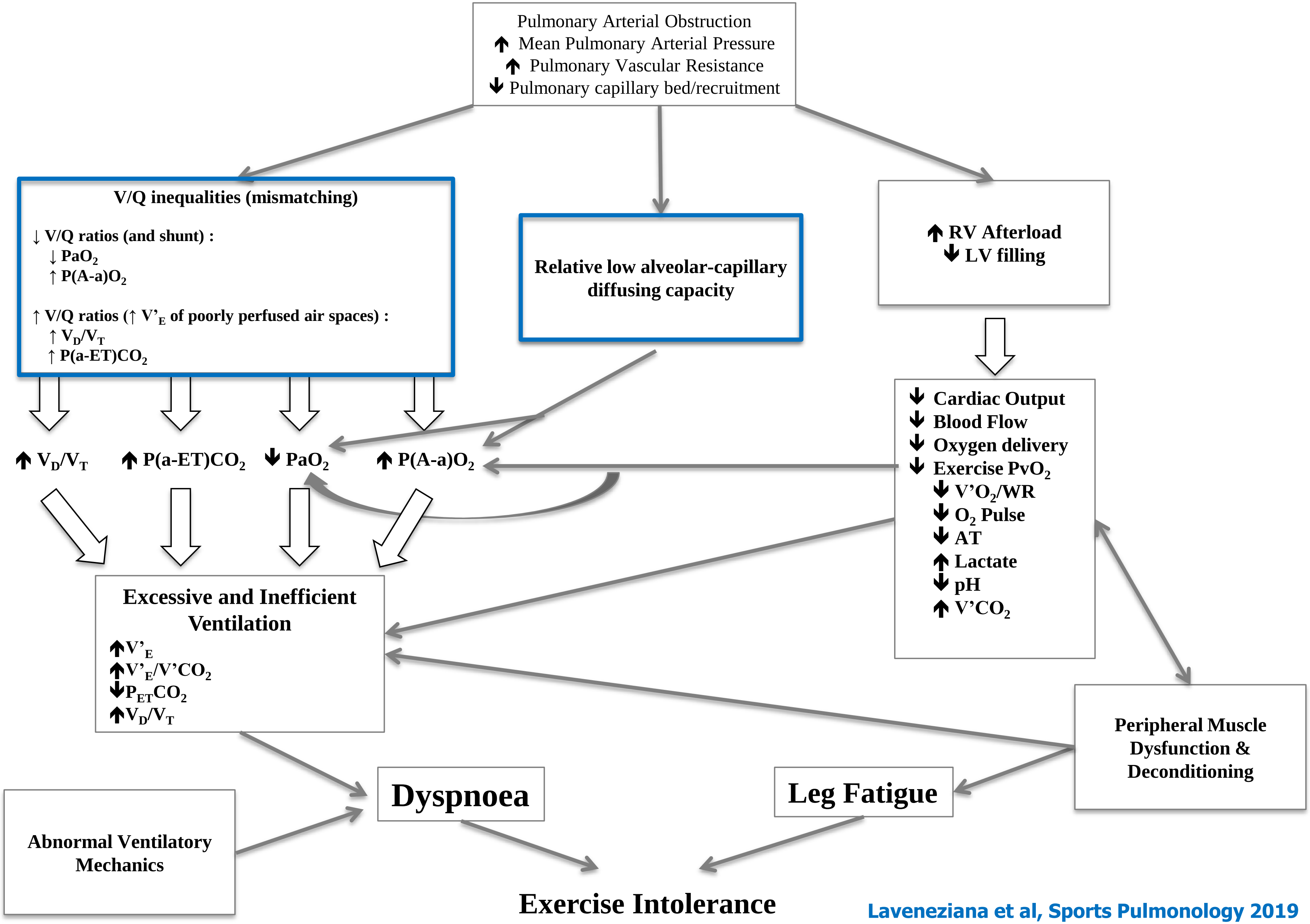
Physiol Rep. 2025 Mar;13(5):e70233. doi: 10.14814/phy2.70233.

Exercise intolerance in Pulmonary Vascular Diseases



Laveneziana et al, Sports Pulmonology 2019 and ERR 2021

Exercise intolerance in Pulmonary Vascular Diseases



Laveneziana et al, Sports Pulmonology 2019

V/Q inequalities (mismatching)

- ↓ V/Q ratios (and shunt) :
  - ↓ PaO_2
  - ↑ $P(A\text{-}a)O_2$

- ↑ V/Q ratios (↑ V'_E of poorly perfused air spaces) :
  - ↑ V_D/V_T
  - ↑ $P(a\text{-}ET)CO_2$

Enlargement of Exercise $P(A-a)O_2$

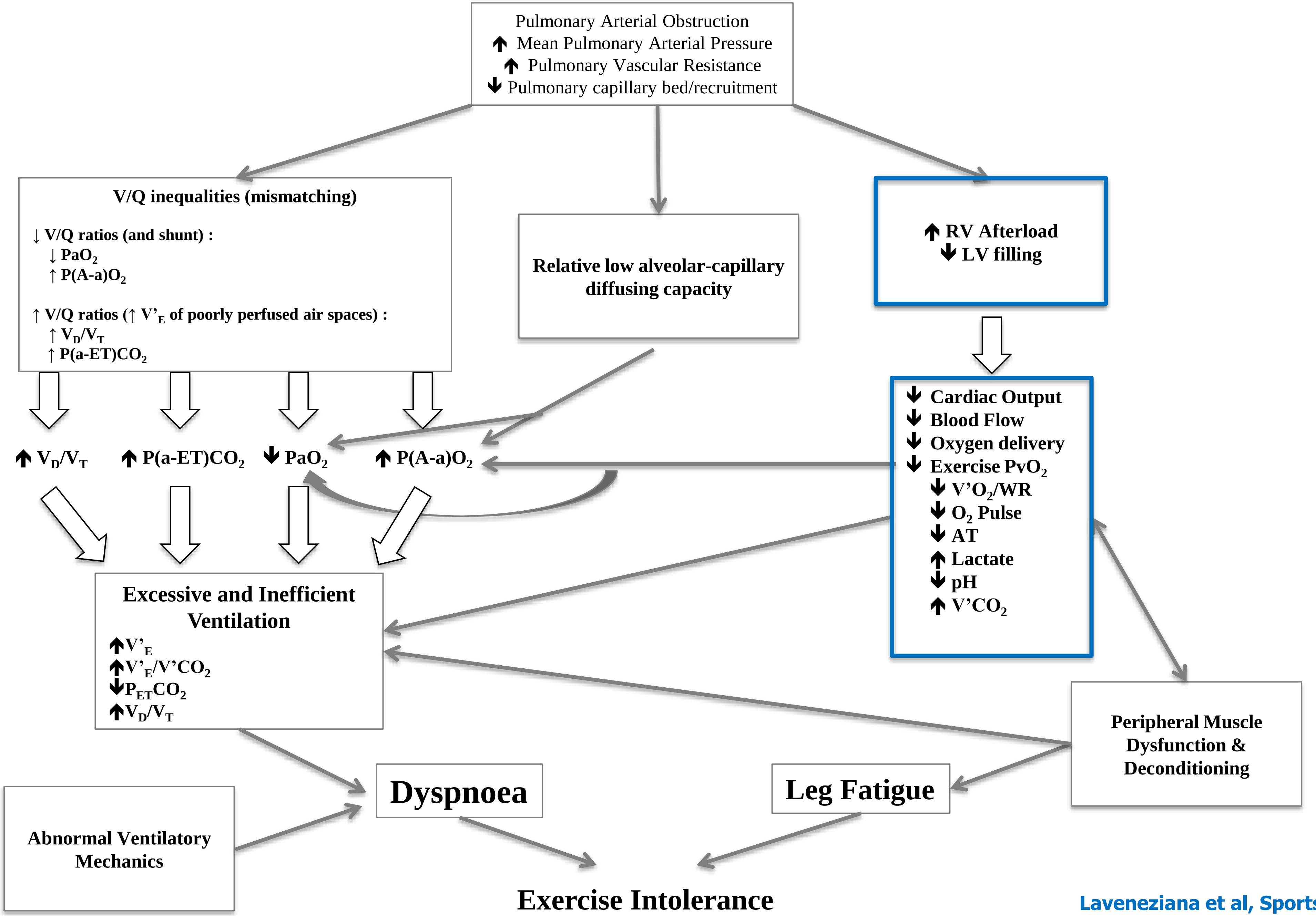
- Low V_A/Q
- Right to Left Shunt
- Relative low diffusing capacity
- Influence of low exercise PvO2

V/Q inequalities (mismatching)

- ↓ V/Q ratios (and shunt) :
  - ↓ PaO_2
  - ↑ $P(A\text{-}a)O_2$

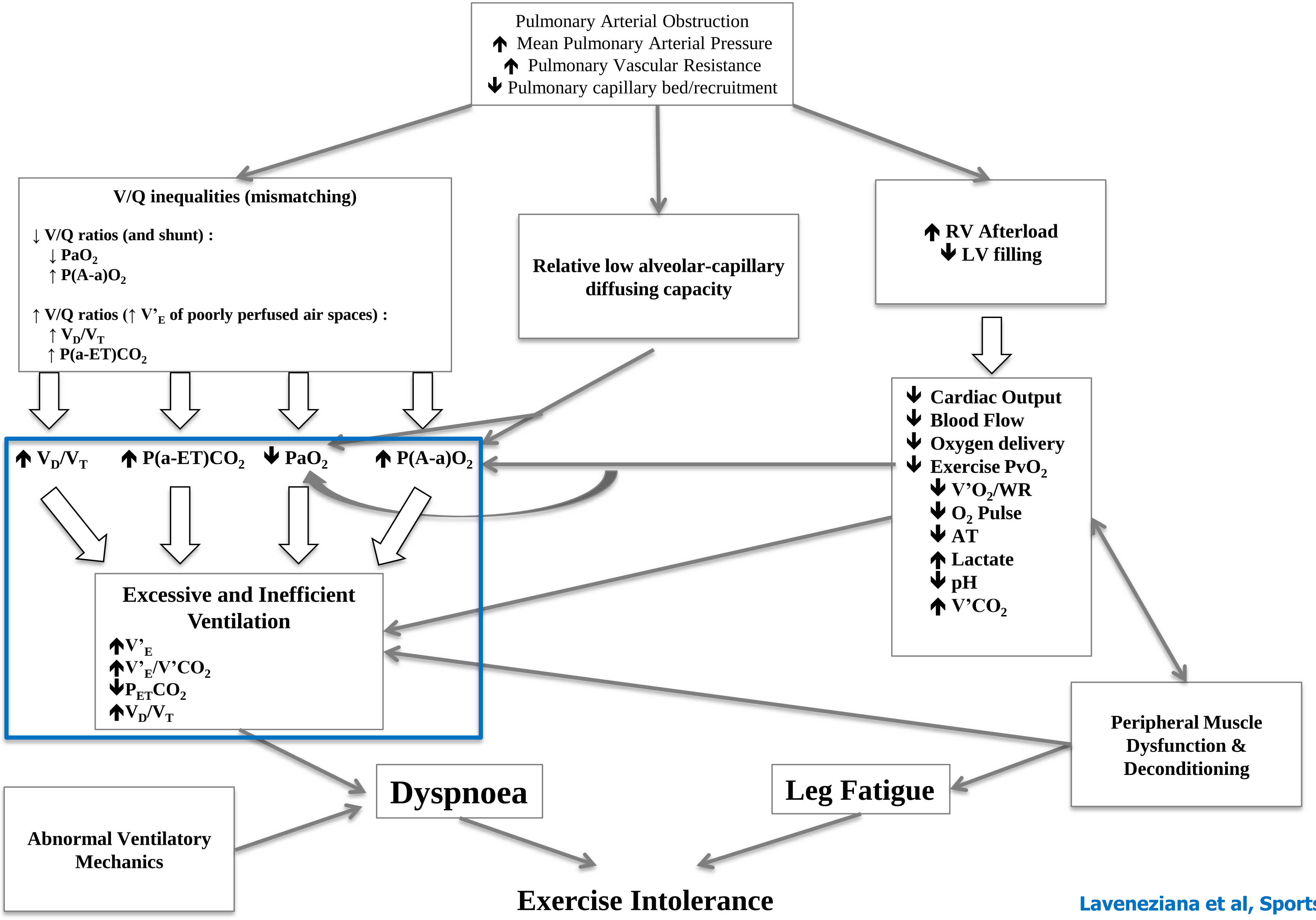
- **↑ V/Q ratios (↑ V'_E of poorly perfused air spaces) :**
  - **↑ V_D/V_T**
  - **↑ $P(a\text{-}ET)CO_2$**

Exercise intolerance in Pulmonary Vascular Diseases



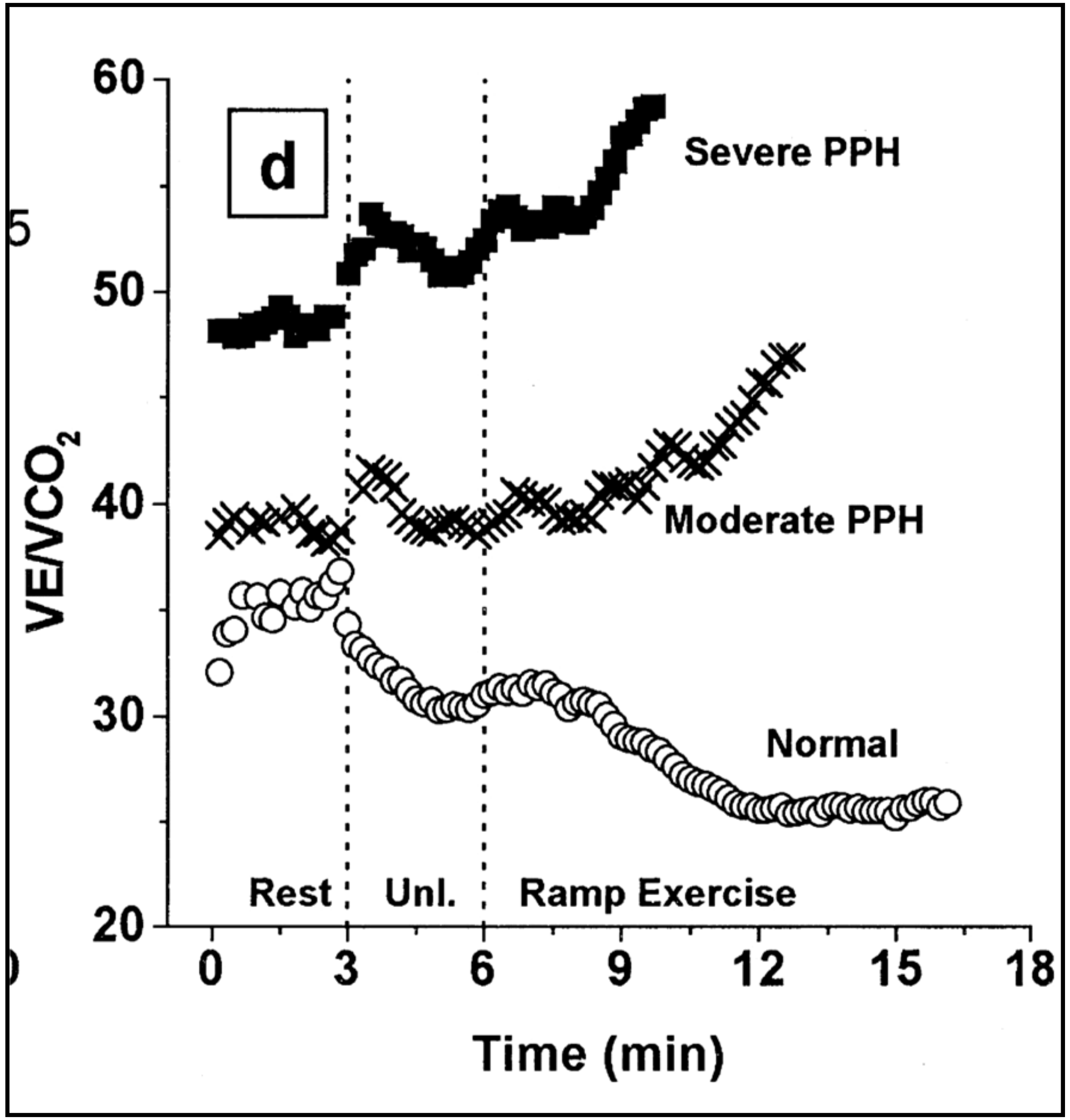
Laveneziana et al, Sports Pulmonology 2019

Exercise intolerance in Pulmonary Vascular Diseases



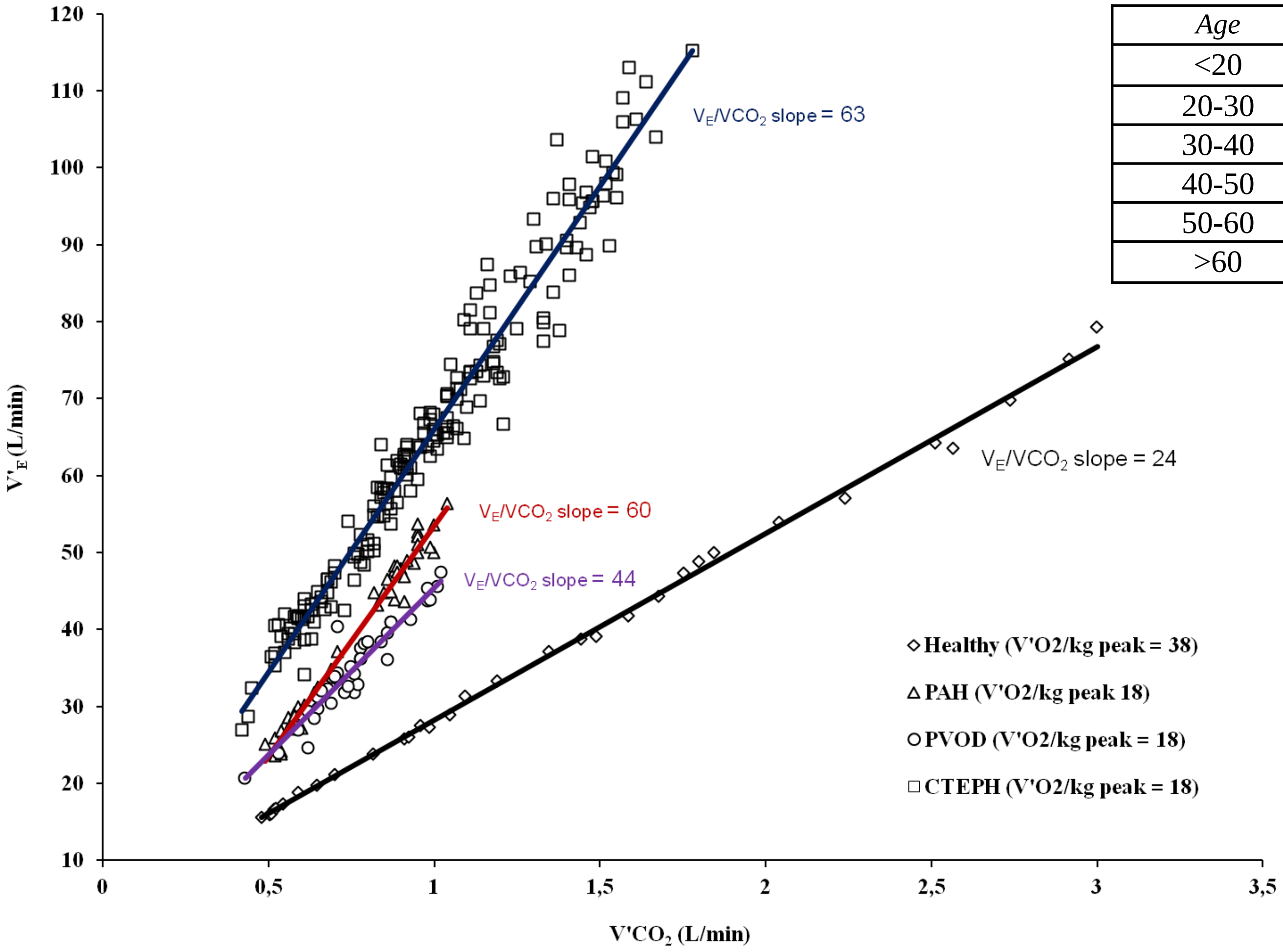
Laveneziana et al, Sports Pulmonology 2019

Ventilatory response



Sun X-G, et al. Circulation 2001

Ventilatory Efficiency



Age	*V_E/VCO2*
<20	**23** ± **2**
20-30	**24** ± **2**
30-40	**25** ± **2**
40-50	**26** ± **2**
50-60	**28** ± **2**
>60	**29.5** ± **2**

Laveneziana and Weatherald, Frontiers in Physiology 2020
Laveneziana P, Eur Respir J 2013
Laveneziana P, Montani D, et al Eur Respir J 2014

idiopathic PAH

M, 20yrs;
177 cm, 59 kg

		Rest	AT	Peak	Pred	% Pred
Travail						
Temps	min	02:41	08:41	12:56		
Charge	watts	0	70	134	249	54%
Met		2,3	5,8	8,4		
Aptit. aérobie						
VO2 sp	ml / kg	8	20	29	50	59%
VO2	L/min	0,471	1,197	1,731	3,409	51%
VCO2	L/min	0,392	1,203	2,020		
Q.R.		0,83	1,01	1,17		
Lactate	mMole/L	1,80		8,30		

		Rest	AT	Peak	Pred	% Pred
Ventilation						
V.E.	L/min	16,1	42,8	91,1	152,3	60%
Vt	L	1,19	2,16	2,65		
F.R.	#/min	12,6	18,4	32,0		
Eq O2		34	36	53		
Eq CO2		41	36	45		
Vd/Vt		0,21		0,11		
Vd/Vt réel	mm Hg	0,40		0,42		
Rés Ven	%	89	72	40		
Hématose						
PaO2	mm Hg	90,5		69,7		
PaCO2	mm Hg	40,2		34,8		
pH		7,4		7,3		
SaO2	%					
PAO2	mm Hg	97,6		116,1		
P(A-a)O2	mm Hg	7,1		46,4		
P(a-ET)CO2	mm Hg	10,0		10,6		
PetCO2	mm Hg	30	32	24		

Unpublished data from authors' lab

$V'_E/V'O_2$ at its nadir (AT) and $V'_E/V'CO_2$ at its nadir (RC)

$V'_E/V'O_2$	$V'_E/V'CO_2$
22-27	**26-30**

$V'_E/V'O_2$ and $V'_E/V'CO_2$ at AT (for sedentary, middle-aged men)

$V'_E/V'O_2$	$V'_E/V'CO_2$
26.5±4.4	**29.1±4.3**

Mean values for women and men over 60 should be slightly higher (1-2); for men under 30, slightly lower (1-2).

NB: normal values of $V'E/V'O_2$ and $V'E/V'CO_2$ at AT with a $PETCO_2$ of approximately 40 mmHg suggest a normal V_D/V_T and uniform matching of alveolar ventilation (V_A) to pulmonary perfusion (Q) (V_A/Q).

- **high $V'_E/V'CO_2$ at AT (≥ 34–35) and**
- **low $P_{ET}CO_2$ at AT (≤ 30 mmHg)**
- **without an alternative explanation in patients presenting with unexplained dyspnoea and exercise limitation**
- **should prompt further diagnostic testing to exclude PAH or CTEPH**
- **particularly in those patients with risk factors, such as prior venous thromboembolism, systemic sclerosis or a family history of PAH**
- **these gas exchange anomalies are usually not found in patients with pulmonary venous hypertension secondary to cardiac diseases**

Laveneziana and Weatherald, Frontiers in Physiology 2020

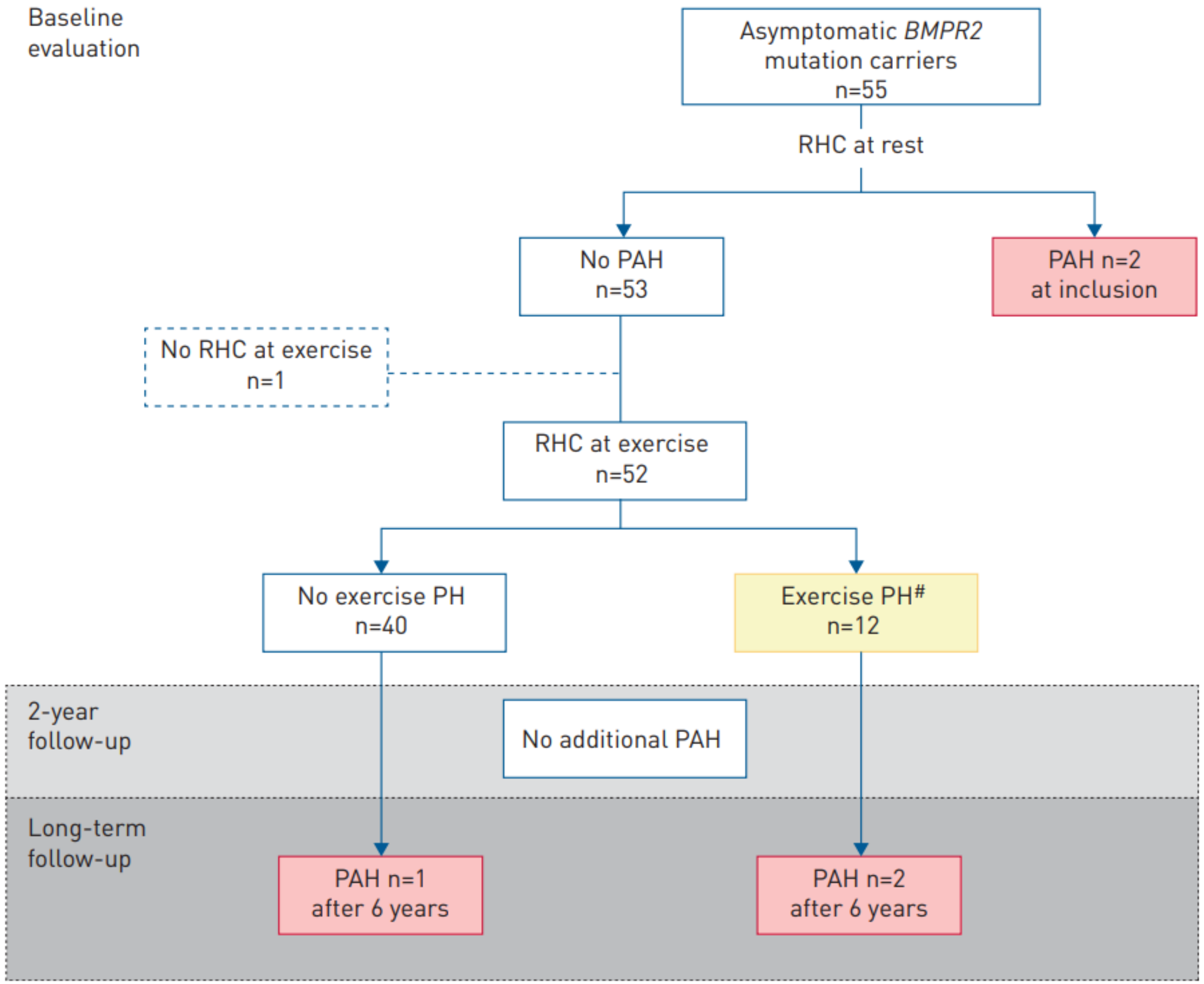
EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
D. MONTANI ET AL.

Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation

David Montani[1,2,3,14], Barbara Girerd[1,2,3,14], Xavier Jaïs[1,2,3], Pierantonio Laveneziana[4,5], Edmund M.T. Lau[6], Amir Bouchachi[3,7], Sébastien Hascoët[3,8], Sven Günther[9], Laurent Godinas[1,2,3], Florence Parent[1,2,3], Christophe Guignabert[1,3], Antoine Beurnier[3,10], Denis Chemla[3,10], Philippe Hervé[3,11], Mélanie Eyries[12,13], Florent Soubrier[12,13], Gérald Simonneau[1,2,3], Olivier Sitbon[1,2,3], Laurent Savale[1,2,3] and Marc Humbert[1,2,3]

[1]School of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [2]Service de Pneumologie et Soins Intensifs Respiratoires, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [3]INSERM UMRS 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [4]INSERM UMRS 1158, Neurophysiologie Respiratoire Expérimentale et Clinique, Sorbonne Université, Paris, France. [5]Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée, Département Médico-Universitaire "APPROCHES", Hôpitaux Universitaires Pitié-Salpêtrière, Tenon et Saint-Antoine, AP-HP, Sorbonne Université, Paris, France. [6]Dept of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, Australia. [7]Service de Cardiologie, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [8]Pôle de Cardiologie Pédiatrique et Congénitale, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [9]Service de Physiologie, AP-HP, Georges Pompidou European Hospital, Paris, France. [10]Service de Physiologie, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [11]Service de Chirurgie Thoracique, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [12]Département de Génétique, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France. [13]INSERM UMRS 1166, Sorbonne Université and Institute for Cardiometabolism and Nutrition (ICAN), Paris, France. [14]These two authors contributed equally to this work.

Cite this article as: Montani D, Girerd B, Jaïs X, *et al.* Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. *Eur Respir J* 2021; 58: 2004229 [DOI: 10.1183/13993003.04229-2020].



Supplemental Table S1. Investigational cardiopulmonary exercise testing probability score of pulmonary hypertension

Variables	Values	Score
$P_{(a\text{-}ET)}CO_2$ at peak	Negative value	0
	Positive value	2
$P_{(A\text{-}a)}O_2$ at peak	≤29 mmHg	0
	≥30 mmHg	2
V'_E/VCO_2 at AT	≤29	0
	30-34	1
	≥35	2
$P_{ET}CO_2$ at AT	≥36 mmHg	0
	35-31 mmHg	1
	≤30 mmHg	2
V_D/V_T at peak	decreases from baseline	0
	stable or decreases slightly from baseline	1
	Increases from baseline	2

TABLE 2 Baseline results of investigational cardiopulmonary exercise testing probability score of pulmonary hypertension

Total score	Likelihood	Subjects	No pulmonary hypertension	Exercise pulmonary hypertension	PAH
0–2	Unlikely	31	28 (90.3)	3 (9.7)	0
3–5	Possible	21	11 (52.4)	9 (42.9)	1 (4.8)
6–8	Likely	1	1 (100)	0	0
9–10	Very likely	1	0	0	1 (100)

Data are presented as n or n (%). PAH: pulmonary arterial hypertension.

TABLE 4 Diagnosis of pulmonary arterial hypertension (PAH) and exercise pulmonary hypertension according to ECG, cardiopulmonary exercise testing (CPET) probability score and diffusing lung capacity for carbon monoxide (D_{LCO}) in asymptomatic relatives at inclusion in DELPHI-2

	All subjects	No pulmonary hypertension	Exercise pulmonary hypertension	PAH
Subjects	54	40	12	2
Number of criteria[#]				
0	21	18 (85.7)	3 (14.3)	0
1	20	16 (80.0)	4 (20.0)	0
2	10	6 (60.0)	4 (40.0)	0
3	3	0	1 (33.3)	2 (66.7)

Data are presented as n or n (%). [#]: the three criteria included 1) ECG with signs that could be suggestive of pulmonary hypertension, 2) CPET probability score "possible, likely or very likely" for PAH and 3) D_{LCO} <70% predicted.

Long-term follow-up (after 6 years)

Three additional PAH cases were diagnosed 6 years after the initial visit in

- two females (aged 50 and 73 years)
- and a 47-year-old male

Three patients had signs of pulmonary hypertension on ECG, two had "very likely" pulmonary hypertension based on the CPET probability score and the other had a 22% decrease of V′O2 at peak (CPET probability score not evaluable because of the absence of arterial blood gases at exercise), and two of them had DLCO <70% predicted

Cite this article as: Montani D, Girerd B, Jaïs X, *et al.* Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. *Eur Respir J* 2021; 58: 2004229 [DOI: 10.1183/13993003.04229-2020].

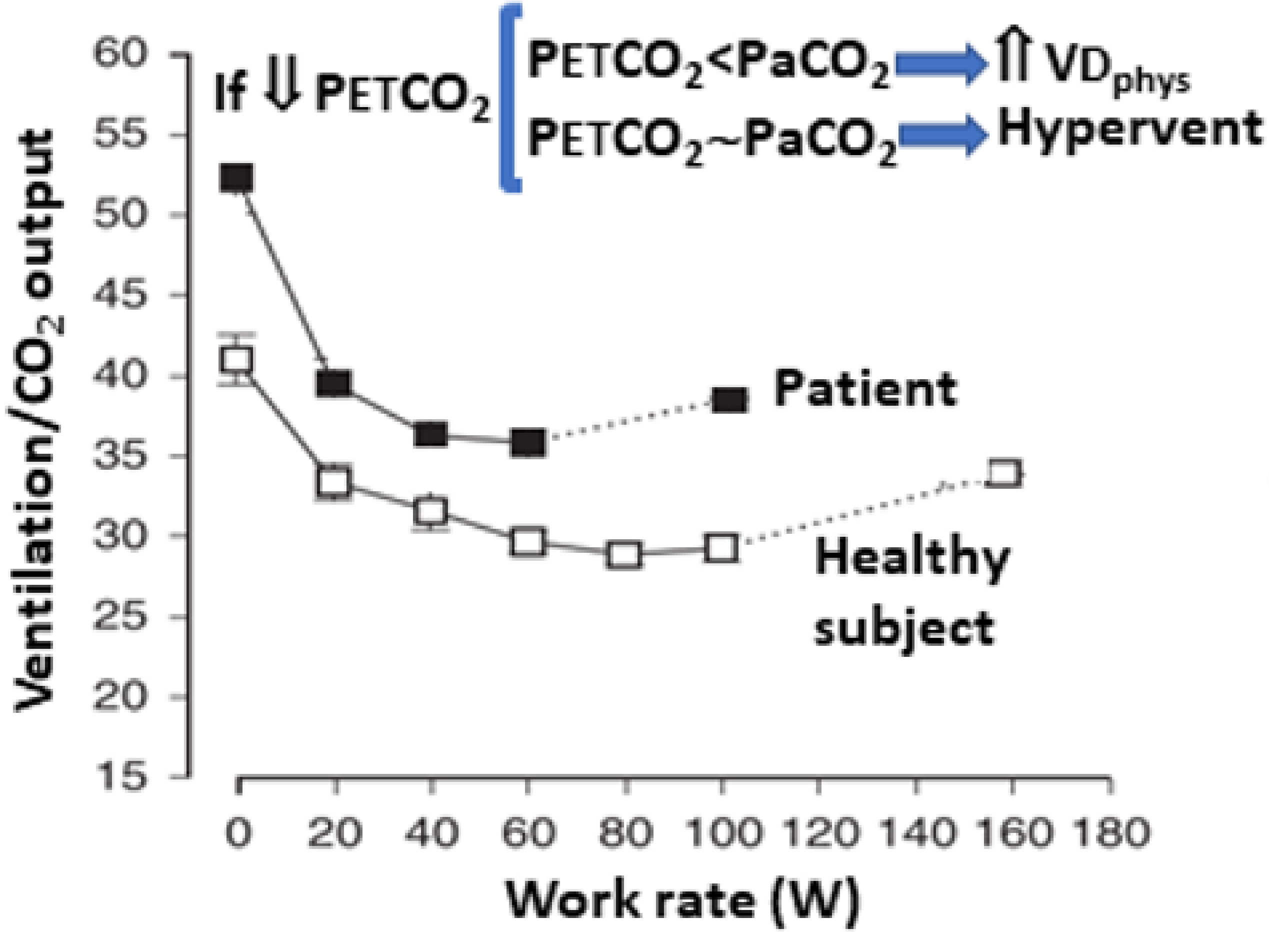
Pulmonary vascular limitation to exercise is not easy to define and may rely on evidence of:

- increased V'_E/V'_{CO_2} slope and ratio at AT
- other typical features of pulmonary vascular disease are:
  - low levels of P_{ETCO_2} at AT
  - a V_D/V_T which remains stable or increases or fails to decrease from baseline
  - a $P_{(a-ET)CO_2}$ which fails to became negative during exercise and, sometimes
  - $P_{(A–a)O_2}$ which widens on exertion
- Associated low levels of haemoglobin will enhance oxygen flow deficiency
- Electrocardiographic or blood pressure anomalies during CPET

Pulmonary gas exchange limitation to exercise is not straightforward either, and may rely on evidence of:

- inefficient CO_2 exchange
  - which can be signalled by high V_D/V_T
  - and often by high exercise V'_E/V'_{CO_2}
- or (alone or in combination with) inadequate O_2 exchange
  - signalled by low P_{aO_2}
  - or, less directly, by desaturation at pulse oximetry
  - and a reduced V'_{O_2}peak

⇑ V̇E-V̇CO_2

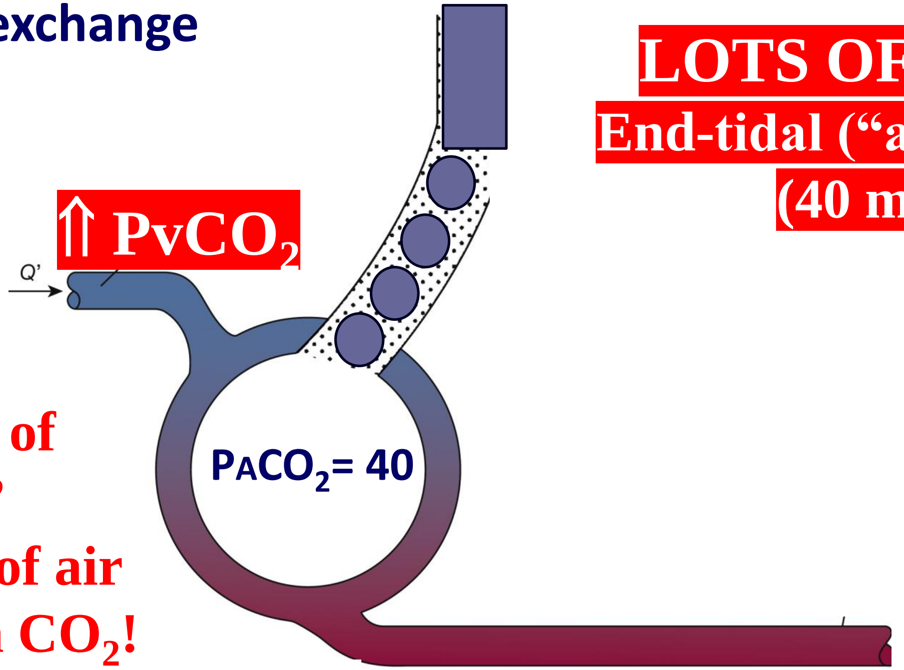


The larger the $PaCO_2$ underestimation by $P_{ET}CO_2$, the larger the physiological dead space (i.e., more positive $P(a\text{-}ET)CO_2$)

Laveneziana P, Eur Respir Monograph 2018

Preserved gas exchange efficiency

LOTS OF EXPIRED CO_2
End-tidal (“alveolar) CO_2 ($P_{ET}CO_2$)
(40 mmHg or higher)

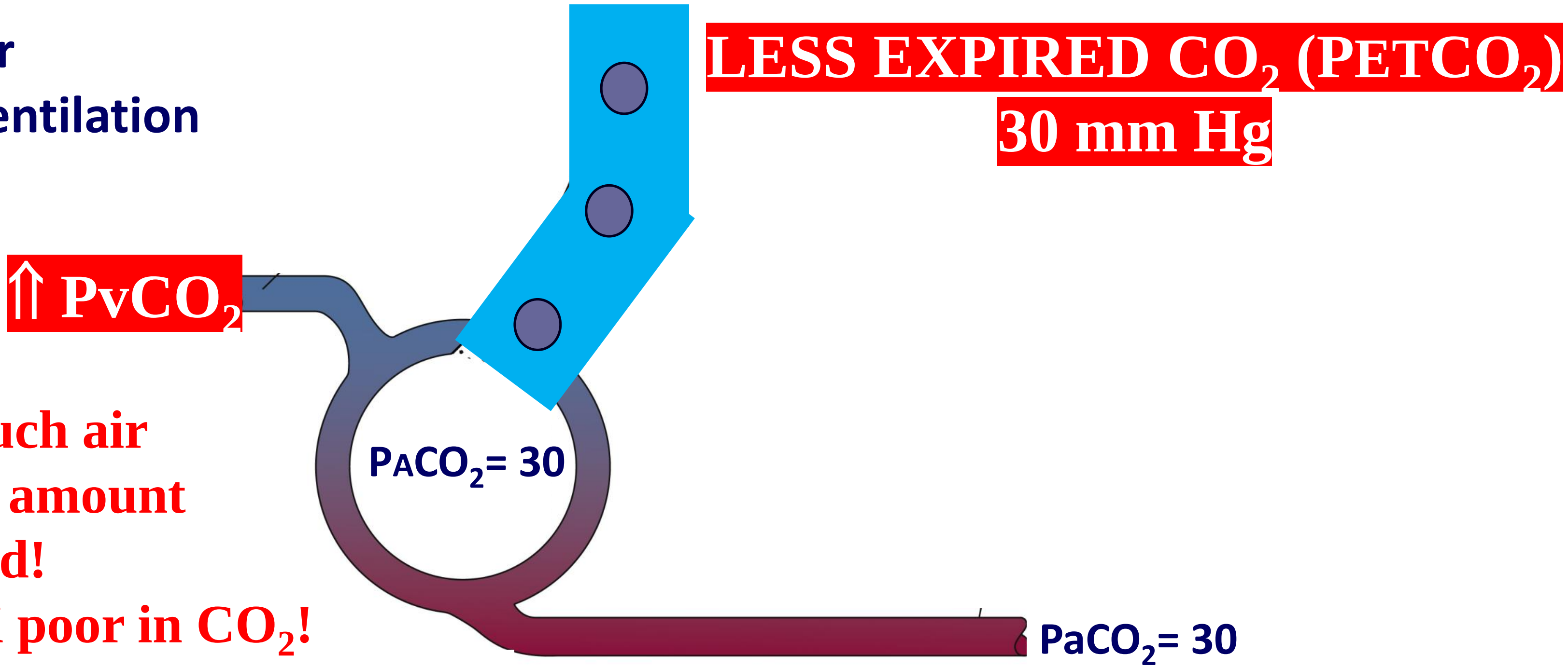


Right amount of blood “meets” right amount of air
Alveoli rich in CO_2!

Matched V/Q= $P_{ET}CO_2$ equal or even higher than $PaCO_2$

Laveneziana P, Eur Respir Monograph 2018

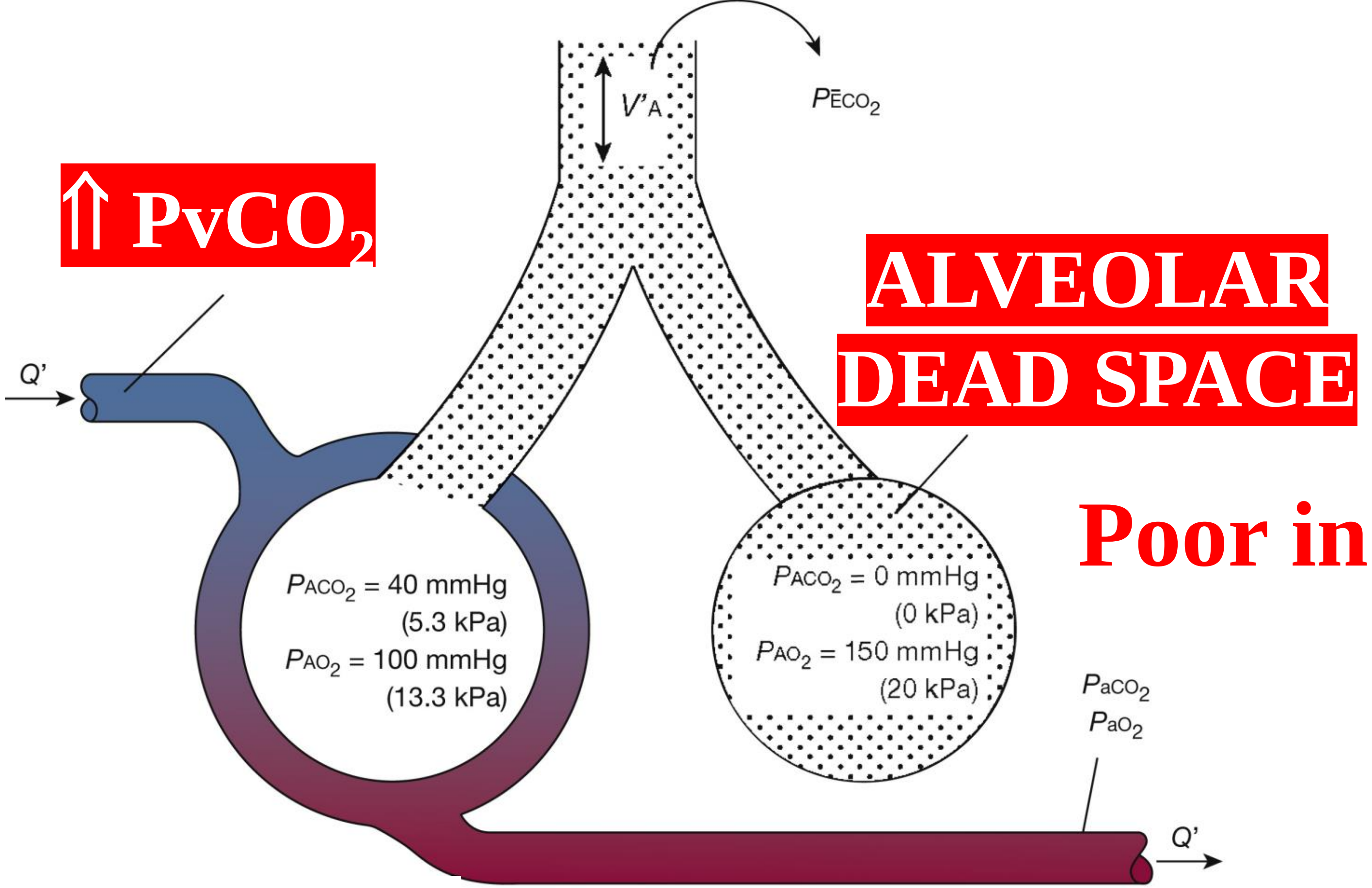
Alveolar
hyperventilation



Too much air
for the amount
of blood!
Alveoli poor in CO_2!

High V relative to preserved Q= low $P_{ET}CO_2$ equal to low $PaCO_2$

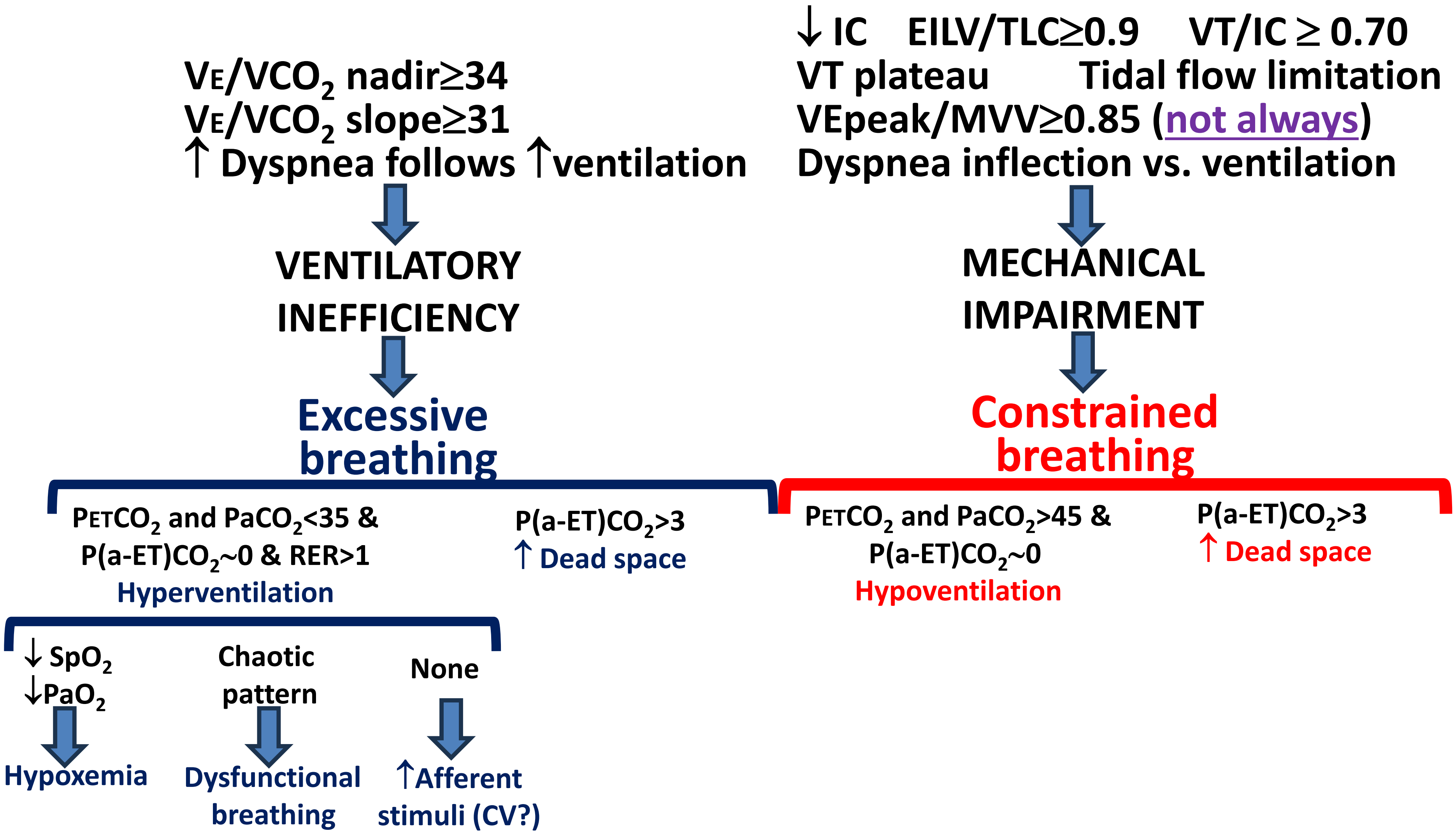
Laveneziana P, Eur Respir Monograph 2018



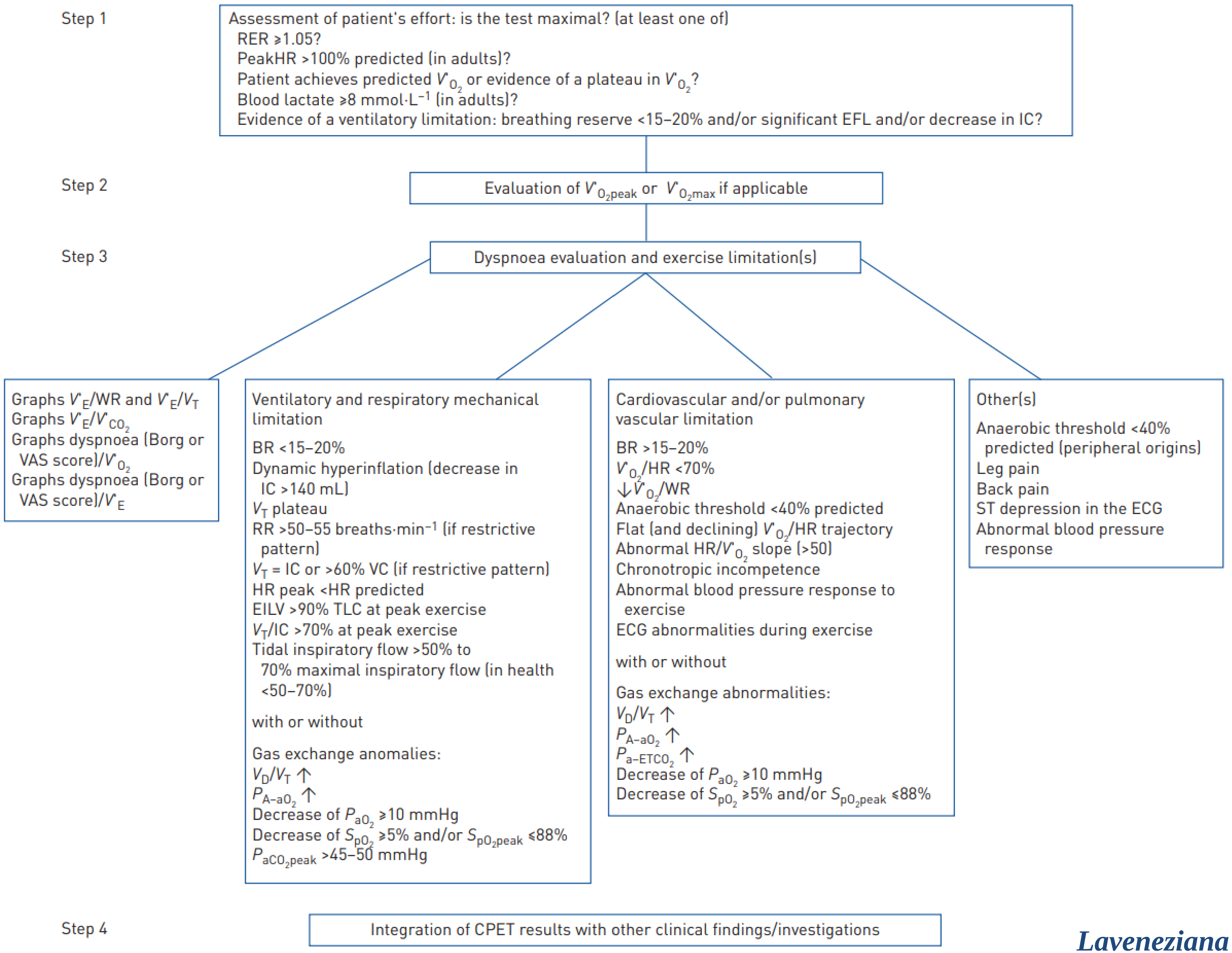
Poor in CO_2!

↑P(a-ET)CO2

The larger the dead space, the lower the expired CO_2!
So, please do NOT use end-tidal CO_2 ($P_{ET}CO_2$) as equal to $PaCO_2$!
Do NOT use the automatic estimation of dead space based on $P_{ET}CO_2$ in patients – the higher the dead space, the lower the value!
Low $P_{ET}CO_2$ can be WASTED VENTILATION and/or HYPERVENTILATION!

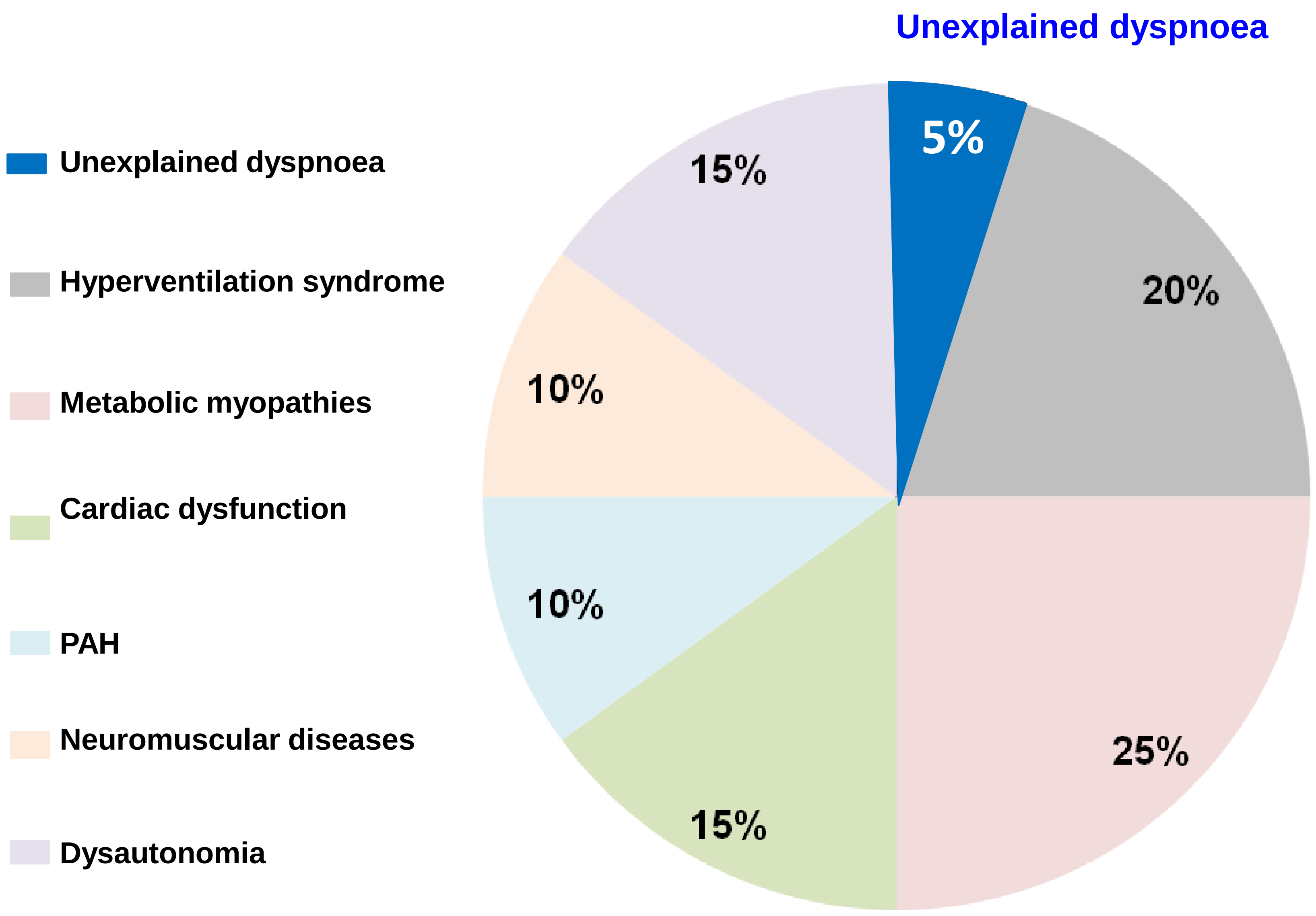


Laveneziana P, Eur Respir Monograph 2018



Laveneziana P et al, Eur Respir Rev 2021; 30: 200187

Diagnostic performance in the context of unexplained dyspnoea



- Graphical representations of CPET variables are crucial
- Peak $V'O_2$ in an incremental CPET has well-defined normal values
- The anaerobic threshold has the advantage of being an effort-independent measure of exercise tolerance
- The entirety of exercise response should be displayed, not only peak values
- It should be highlighted here that an interval average of 30 s may be excessive, as it may underestimate peak values or overestimate AT values

Laveneziana P et al, Eur Respir Rev 2021

- This data display is important for discriminating what is normal from what appears to be abnormal in the exercise response:

  - patterns of ventilatory and gas exchange responses to CPET can be discerned that define specific pathophysiological entities

  - it can be determined whether exercise is limited by cardiovascular, muscle-metabolic, gas exchange or ventilatory limitation (or a combination of these)

  - additional manoeuvres can be added to the test to clarify pathophysiology, e.g. IC manoeuvres to assess dynamic hyperinflation

  - some assessments require arterial blood sampling to allow normality or abnormality of V_D/V_T to be predicted with confidence

- Last, but not least, the use of appropriate normal reference values for the CPET variables is crucial

Laveneziana P et al, Eur Respir Rev 2021

“Discriminating a magnitude or pattern of deviation from the normal response (of the age-, gender- and activity-matched standard subject) and matching the magnitude or pattern of abnormality with that characteristic of particular impairments of physiological system function”

Laveneziana P et al, Eur Respir Rev 2021

Clinical Utility of CardioPulmonary Exercise Testing (CPET)

Exercise testing

- to determine peak oxygen consumption ($V'O_2$) and level of disability
- to identify factors contributing to dyspnoea and exercise limitation
- to objectively evaluate the impact of therapeutic interventions:
  - ✓ Oxygen
  - ✓ Bronchodilators
  - ✓ Vasodilators
  - ✓ Exercise training
- to assist in planning individualized exercise training
- to generate prognostic information:
  - ✓ surgical risk
  - ✓ survival
  - ✓ time to clinical worsening
  - ✓ exacerbations
- to screen for coexistent ischemic heart disease, peripheral vascular disease, arterial hypoxemia

Laveneziana P et al, Eur Respir Rev 2021

CrossMark

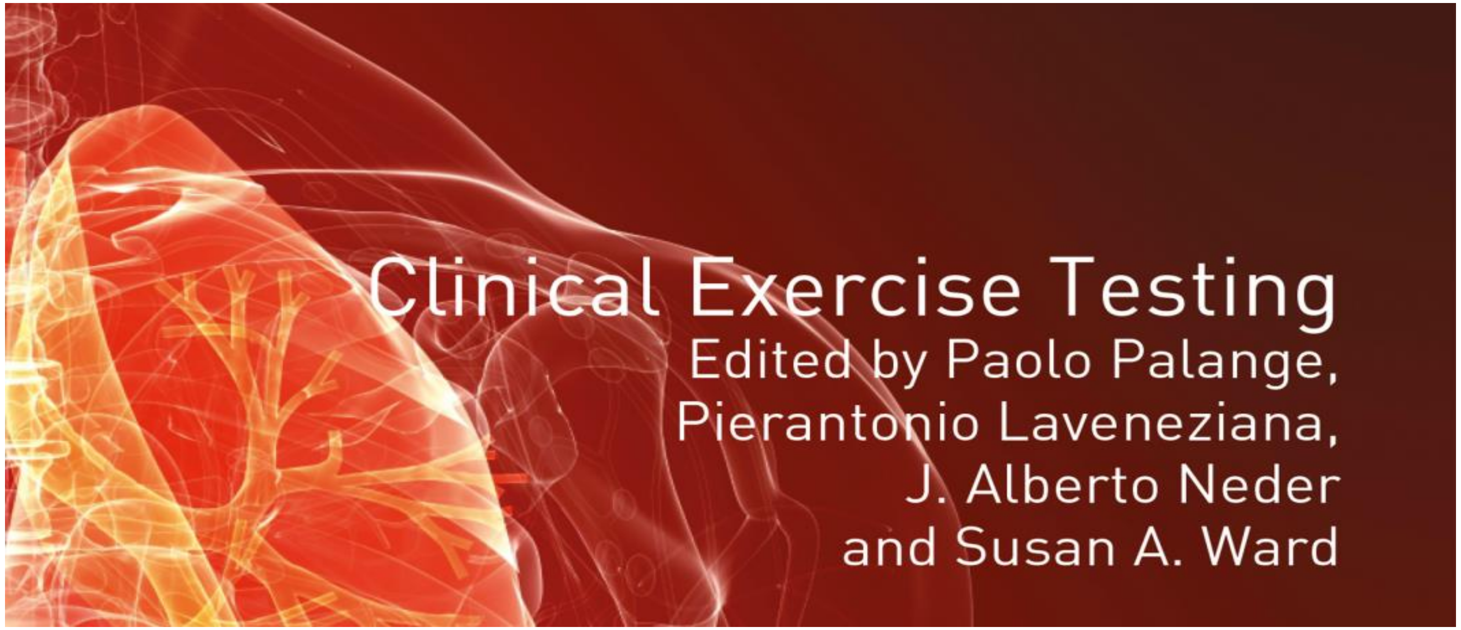
The clinical value of cardiopulmonary exercise testing in the modern era

Pierantonio Laveneziana[1,2], Marcello Di Paolo[3] and Paolo Palange[3]

Number 1 in the Series "Ventilatory efficiency and its clinical prognostic value in cardiorespiratory disorders"
Edited by Pierantonio Laveneziana and Paolo Palange

Eur Respir Rev 2021; 30: 200187 [https://doi.org/10.1183/16000617.0187-2020]

Eur Respir Monograph 2018



THANKS !