Physiological Insights of Exercise Hyperventilation in Pulmonary Hypertension

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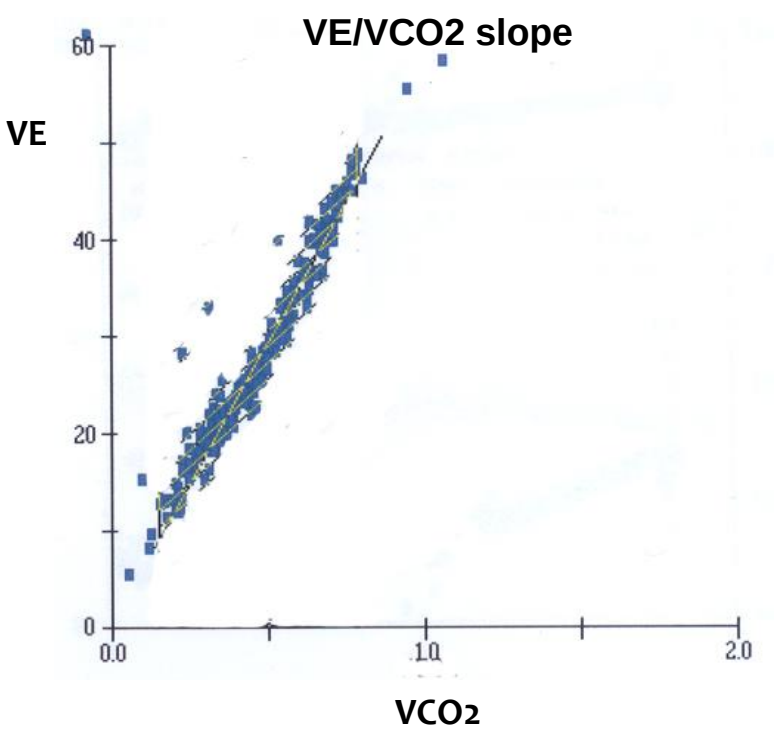
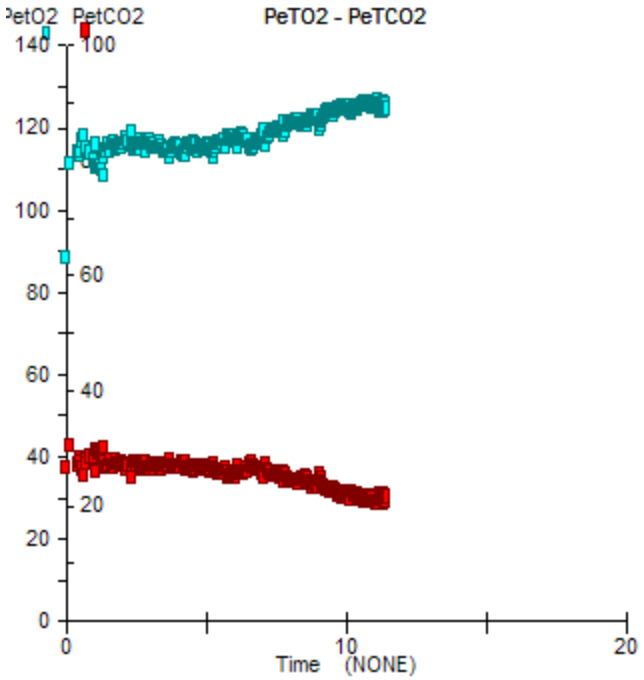
Pulmonary hypertension patients show a pronounced hyperventilation, meaning an excessive increase in pulmonary ventilation compared to carbon dioxide output that leads to high VE/VCO2 slope and low values of PetCO2.

VE/VCO2 slope and PetCO2 are important parameters for severity grading and prognosis: the higher the slope and the lower the PetCO2, the worse are both disease severity and prognosis.





There are several possible causes of hyperventilation in PAH patients including:

- Hypoxemia
- elevated dead space ventilation
- Ventilation/perfusion mismatch
- enhanced peripheral or central chemoreceptor activity.

The aim of our study was to evaluate the possible role of these causes in exercise hyperventilation in PAH patients.

Study protocol

Day 1

Familiarization CPET

Day 2

Spirometry, DLCO, CPET with arterial blood gas sampling

Day 3

Peripheral and central chemoreceptor sensitivity

18 PAH patients in stable hemodynamic status

Demographics	
N	18
Sex Male (%)	7 (39)
Age (years)	56±15
BMI (kg/m^2)	24.9±3.39
LVEF (%)	61.5±4.4
Systolic Blood Pressure (mmHg)	117±14
Diastolic Blood Pressure (mmHg)	70±8
Heart Rate (beats/min)	70±10
NYHA Class II (%)	17 (94%)
NYHA Class III (%)	1 (5 %)
Atrial fibrillation (%)	2 (11%)
PH group 1 (%)	16 (89%)
PH group 4 (%)	2 (11%)
Connective tissue disease (%)	4 (22%)
Hemodynamic parameters	
PAPm (mmHg)	39±11
PAWP (mmHg)	10±3
CO (l/min)	4.76 ± 0.97
PVR (WU)	5.99±3.60
Therapy	
Ambrisentan5 mg/die (%)	4 (22.2)
Bosentan 250 mg/die (%)	4 (22.2)
Macitentan 10 mg/die (%)	8 (44.4)
Tadalafil 40 mg/die (%)	4 (22.2)
Sildenafil 60 mg/die (%)	9 (50)
Inhaled Iloprost 30 mcg/die (%)	1 (5.5)
Riociguat 7.5 mg/die (%)	1 (5.5)

Spirometry and CPET parameters	
FVC (L)	2.92±0.92
FVC %	87±22
FEV1 (L)	2.27±0.67
FEV1 (% predicted value)	82±20
FVC/FEV1 (% predicted value)	77.2±8.52
DLCO (% predicted value)	60 ±16
VE/VCO_2 slope	39.1±9.0
VE_{DS}/VCO_2 slope	13.5±7.1
VE_{ALV}/VCO_2 slope	26.9±5.2
peak VO_2 (l/min)	1.06±0.24
peak VO_2/Kg (ml/Kg/min)	13.3±3.58
VO_2 (l/min) at AT	0.66±0.16
rest $PetCO_2$	28.3±3.9
AT $PetCO_2$	29.4±4.3
peak $PetCO_2$	27.3±5.0
peak RQ	1.08±0.08
Watt	65±24
Peak HR (bpm)	136 ± 27

Group 1 PAH patients were mainly idiopathic in NYHA II.

VDS calculation

VDS was calculated rearranging the VE equation:

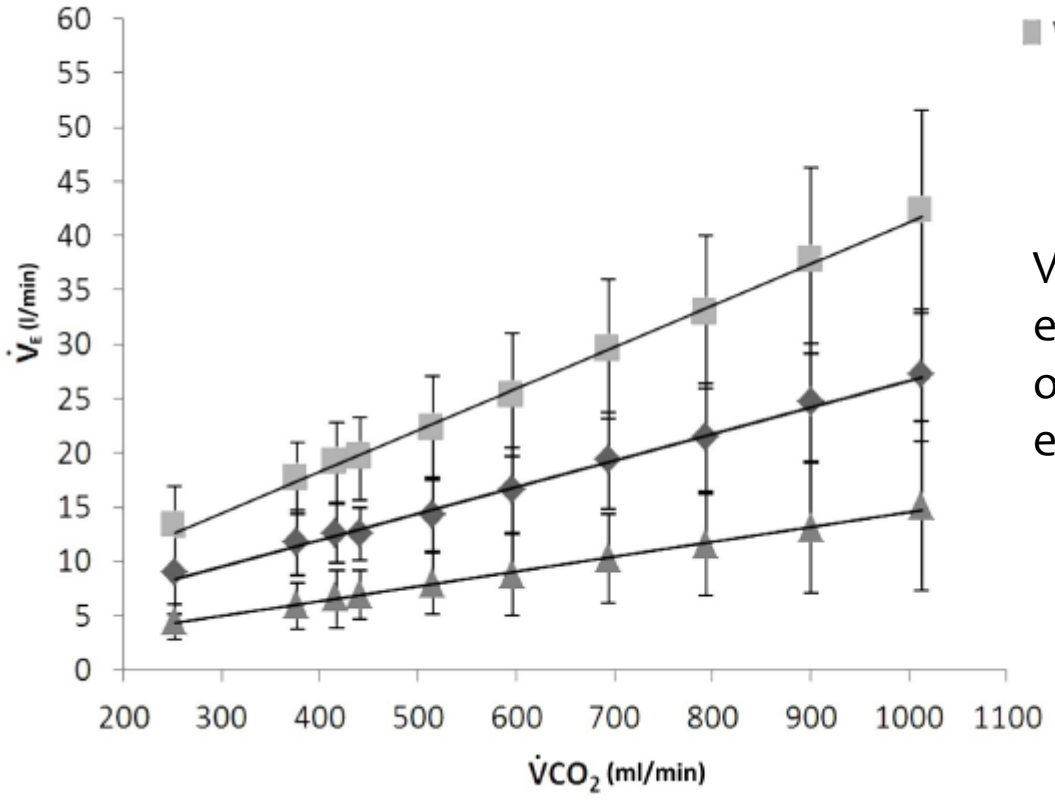
$VD/VT = (PaCO_2 - PECO_2 / PaCO_2$ and $PECO_2 = 863 * VCO_2)/VE$

VT = tidal volume, $PaCO_2$ is the arterial partial pressure of CO_2, $PECO_2$ is the average expiratory partial pressure of CO_2 and 863 is a constant.

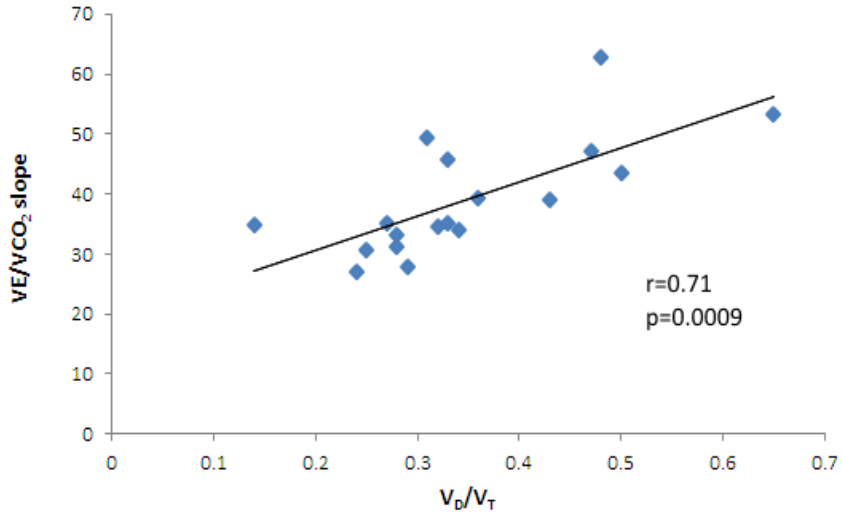
VA was then calculated as VE – VDS

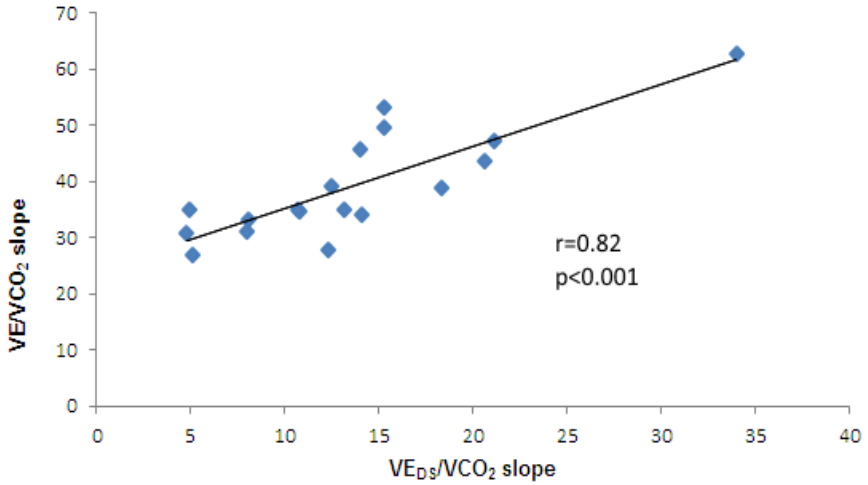
VDS during exercise

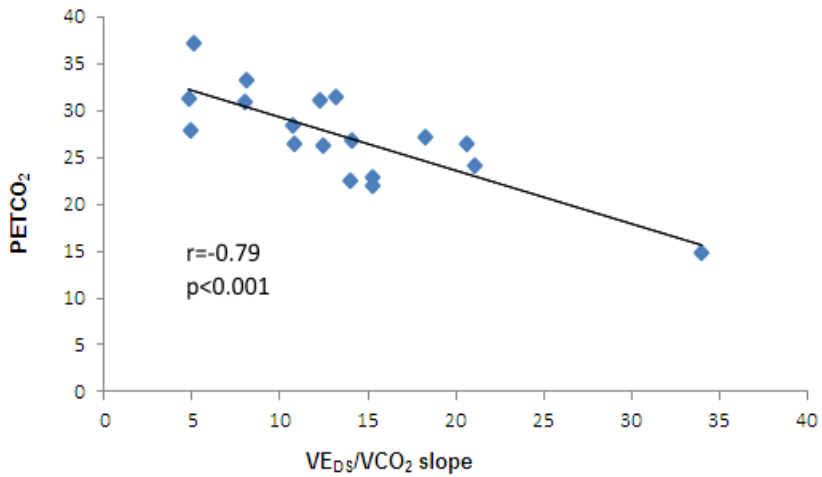
Average total ventilation (VE), alveolar ventilation (VA) and dead space ventilation (VDS) vs. carbon dioxide output (VCO2) calculated every minute

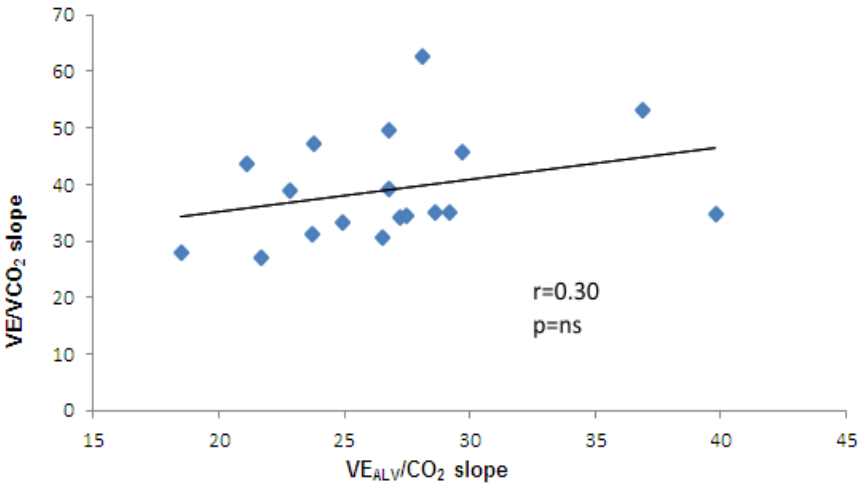


VDS increases during exercise represents ~30% of V̇E throughout the exercise

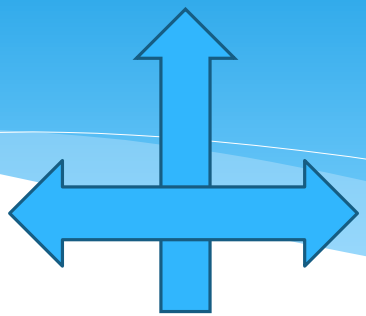

VE/VCO2 slope
VD/VT
r=0.71
p=0.0009


VE/VCO2 slope
VEDS/VCO2 slope
r=0.82
p<0.001


PETCO2
VEDS/VCO2 slope
r=-0.79
p<0.001

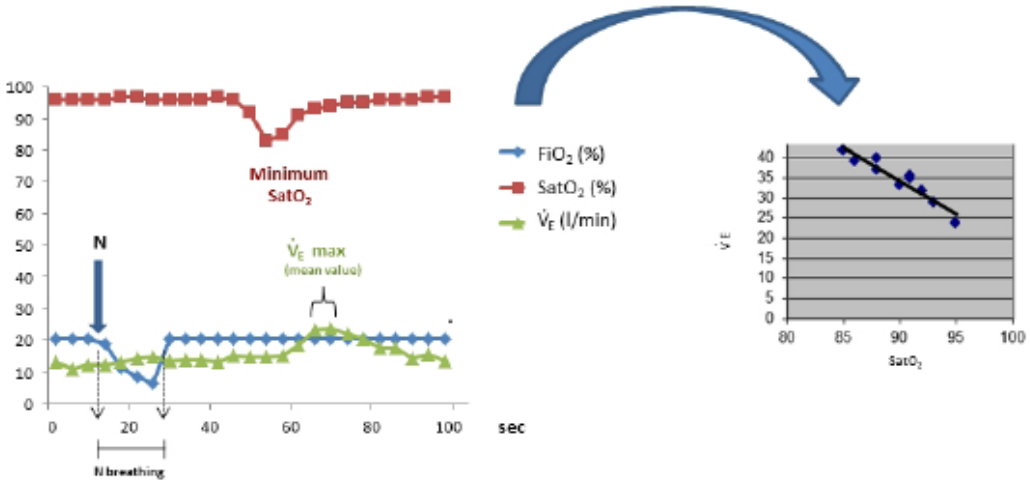

VE/VCO2 slope
VEALV/CO2 slope
r=0.30
p=ns

High VE/Q mistmatch

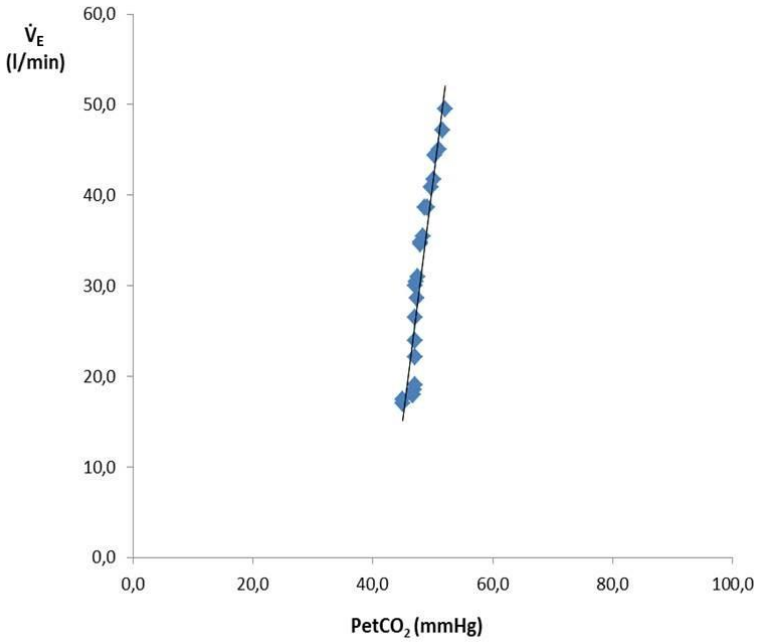


	rest	1'	2'	3'	4'	5'	6'	7'	8'	9'	Peak
$PaCO_2$ (mmHg)	30±5	31±5	33±5	33±4	34±3	34±4	34±5	34±5	35±4	34±5	33±5
PaO_2 (mmHg)	84±16	87±18	87±17	88±17	87±20	87±19	84±19	82±21	84±21	83±22	81±24
$PetCO_2$ (mmHg)	28±4	28±4	28±4	29±5	29±4	29±4	29±5	29±5	28±5	29±5	27±5
$PetO_2$ (mmHg)	112±6	112±5	112±5	112±5	112±5	113±5	114±5	110±25	117±6	118± 5	120±5
$P(a\text{-}et)CO_2$ (mmHg)	2.1±3.7	2.7±3.8	2.5±7.5	4.8±2.9	3.1±9.1	5.6±3.9	5.3±4.0	5.8±4.3	6.3±4.3	8.7±8.9	6.0±4.2
V_D/V_T	0.36±0.1	0.34±0.1	0.34±0.1	0.35±0.1	0.35±0.1	0.34±0.1	0.35±0.1	0.35±0.1	0.34±0.1	0.33±0.1	0.35±0.1
$V_E/VCO2$ ratio	55±13	48±9	47±10	45±9	43±7	43±8	43±8	42±7	42±8	39±6	43±8
PAO2 (mmHg)	111±7	110±6	110±11	107±5	109±11	106±6	105±5	105±5	106±5	107±6	109±6
$P(A\text{-}a)O_2$ (mmHg)	27±17	23±17	23±18	19±17	22±22	20±19	21±20	23±21	21±21	23±22	26±25

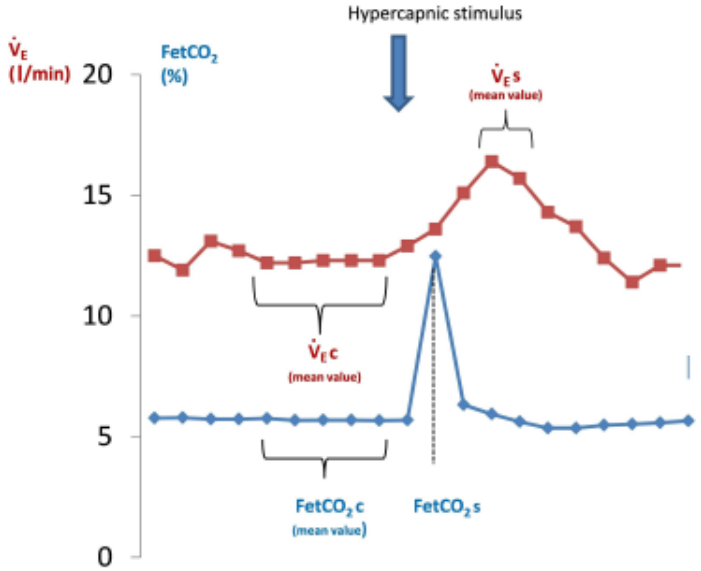
Peripheral response to hypoxia

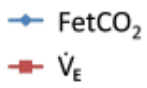


Central response to hypercapnia



Peripheral response to hypercapnia

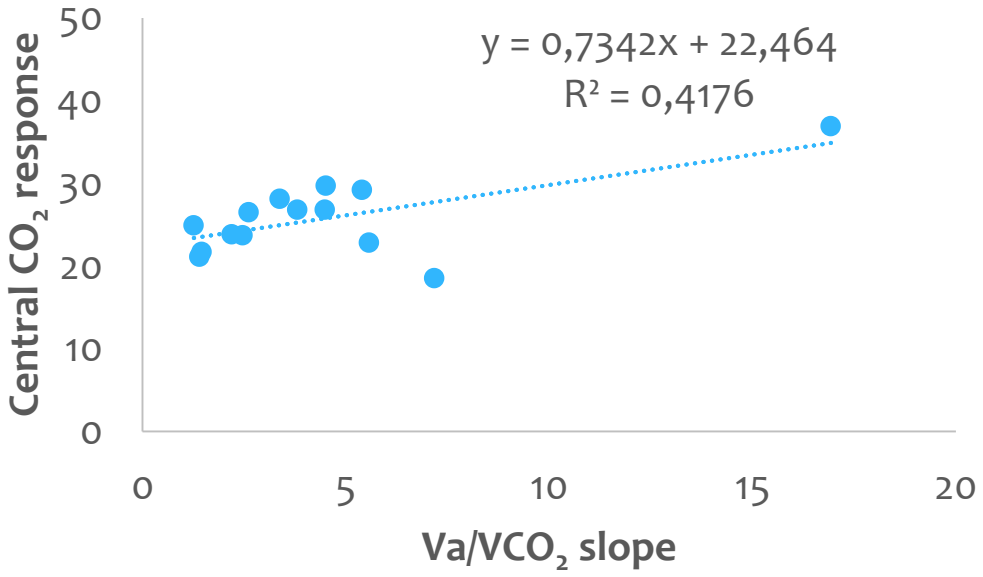




$$S = \frac{\dot{V}_E s - \dot{V}_E c}{(FetCO_2 s - FetCO_2 c)} \times (PB\text{-}47)$$

	PAH	control
Chemoreceptor response Hypoxia	0.416±0.402	0.285±0.221
Chemoreceptor response HyperCO2	0.076±0.047	0.066±0.043
Central hyperCO2 sensitivity	4.475±3.990	2.352±0.936

- Peripheral chemoreceptor responses were **unrelated with exercise.**
- positive correlation was found between central CO2 response and VA/VCO2 slope (r=0.65, p=0.013).



Conclusions

- ➔ V_E/VCO_2 slope correlates with peak exercise V_D/V_T
- ➔ V_{DS} increases during exercise, representing ~30% of V_E throughout the exercise
- ➔ Both V_E/VCO_2 slope and $PetCO_2$ at peak exercise significantly correlate with V_{DS}/VCO_2 slope
- ➔ Peripheral chemoreceptor activity unrelated to exercise hyperventilation
- ➔ Central CO_2 chemoreceptor activity correlates with V_A/VCO_2 slope, so that, the higher the central CO_2 chemoreceptor activity, the higher the V_A/VCO_2 slope during exercise.

Increased DS and VE/Q mismatch are among the main mechanisms involved in exercise hyperventilation in PH