Cardiopulmonary Exercise Testing: its principles, interpretation & application

DM Seminar

Harshith

Outline

- Physiology of exercise
- Introduction
- Equipment and working
- **Principles**
- **Interpretation and variables**
- Indications and contraindications
- **Clinical application**
- Recent advances

References

- ATS/ACCP statement on CPET.
  Am J Respir Crit Care Med.2003; 167:211-277

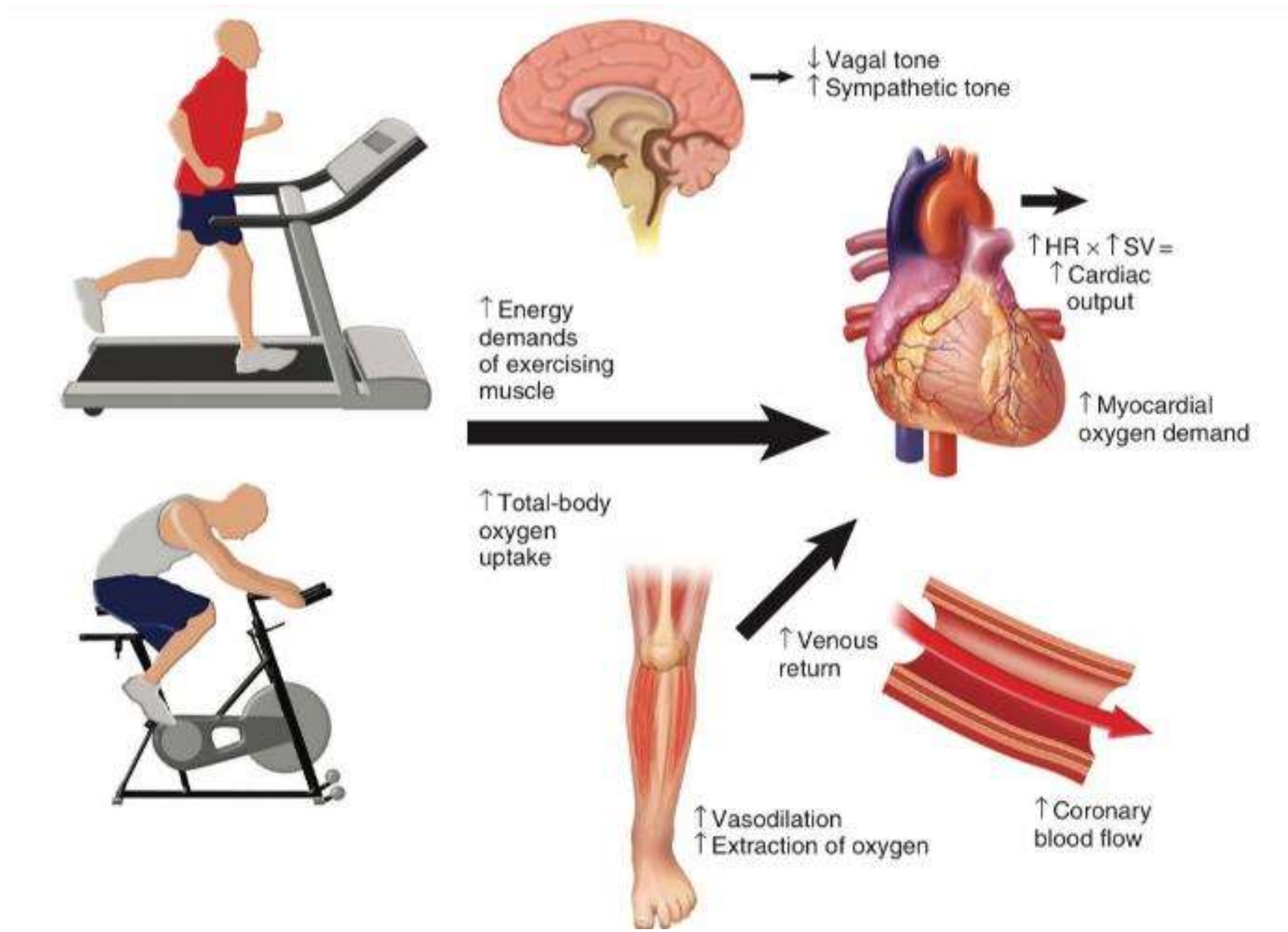
- AHA Clinician's guide to CPET in adults
  Circulation. 2010;122:191-225

- Fishman's pulmonary diseases and disorders
- Braunwalds heart disease

Exercise

- 2 types
  - Endurance
  - Resistance

Physiologic response to exercise



Introduction

- Non invasive
- Dynamic testing, evaluation of submaximal and peak exercise response
- Integrated analysis of multiple systems
  - Respiratory
  - Cardiac
  - Metabolic
  - Hematological
  - Musculoskeletal

Equipment

- Cycle ergometer/ treadmill
- Airflow or volume transducers
- Gas analysers
- Electrocardiograph
- NIBP
- Pulse oximetry
- Intra arterial BP monitoring and ABG (if invasive, optional)

medisoft®
CARDIO-RESPIRATORY INSTRUMENTATION

Ergocard Clinical & Professional models

Cardiopulmonary exercise testing

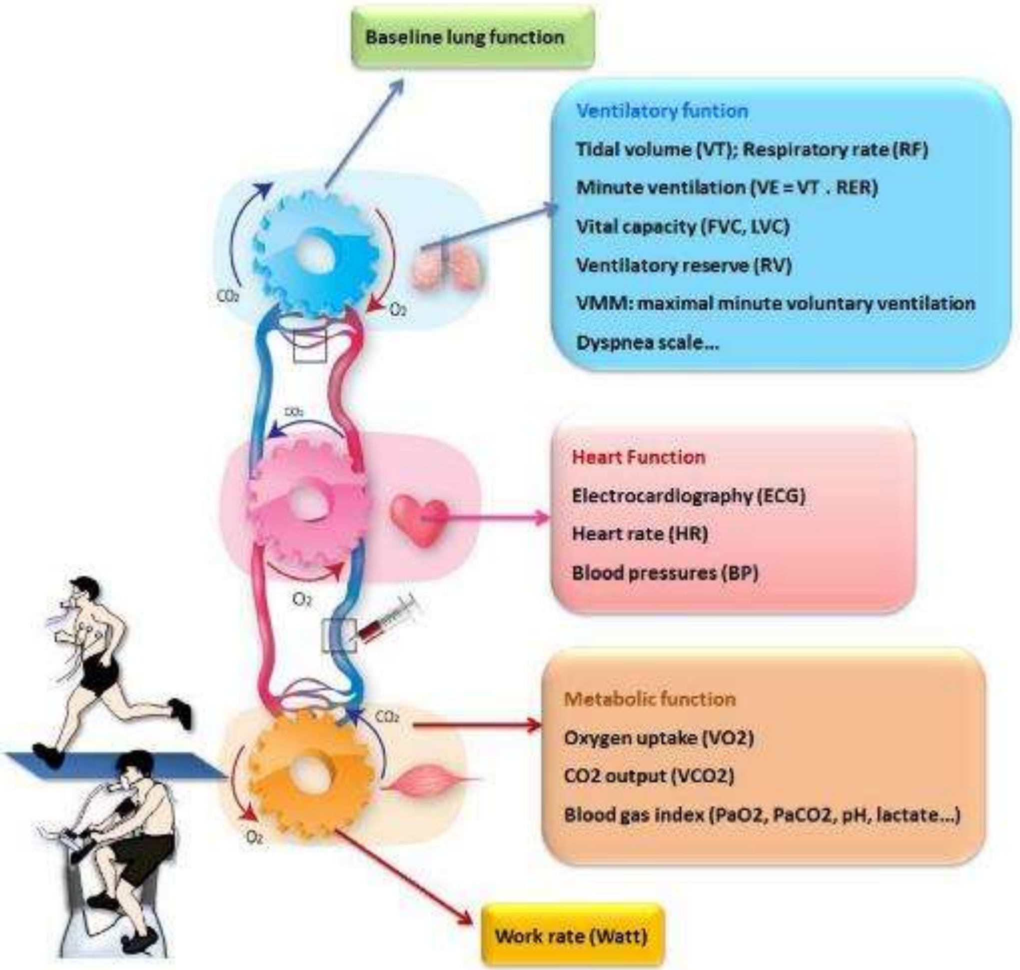
Options available for both models, **Clinical** and **Professional** :

- Exercise flow-volume loop with flow-limitation evaluation.
- Interface and control of most Bike Ergometers and Treadmills.
- Heart rate chest belt.
- Advanced integrated 12 leads ECG module, for resting and exercise applications, one touch operation with complete ECG analysis, arrhythmia detection and analysis, real time printing.
- SpO2.
- Automated Blood pressure external Tango™ option, with exercise artifact rejection.

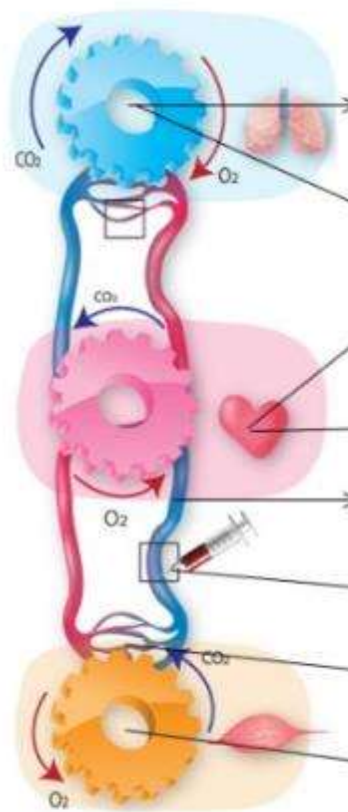
Can be combined with the following devices:

ECG, FeNO+, FOT Resmon Pro, BodyBox, HypAir, Micro 5000, Micro 6000, SpiroAir.

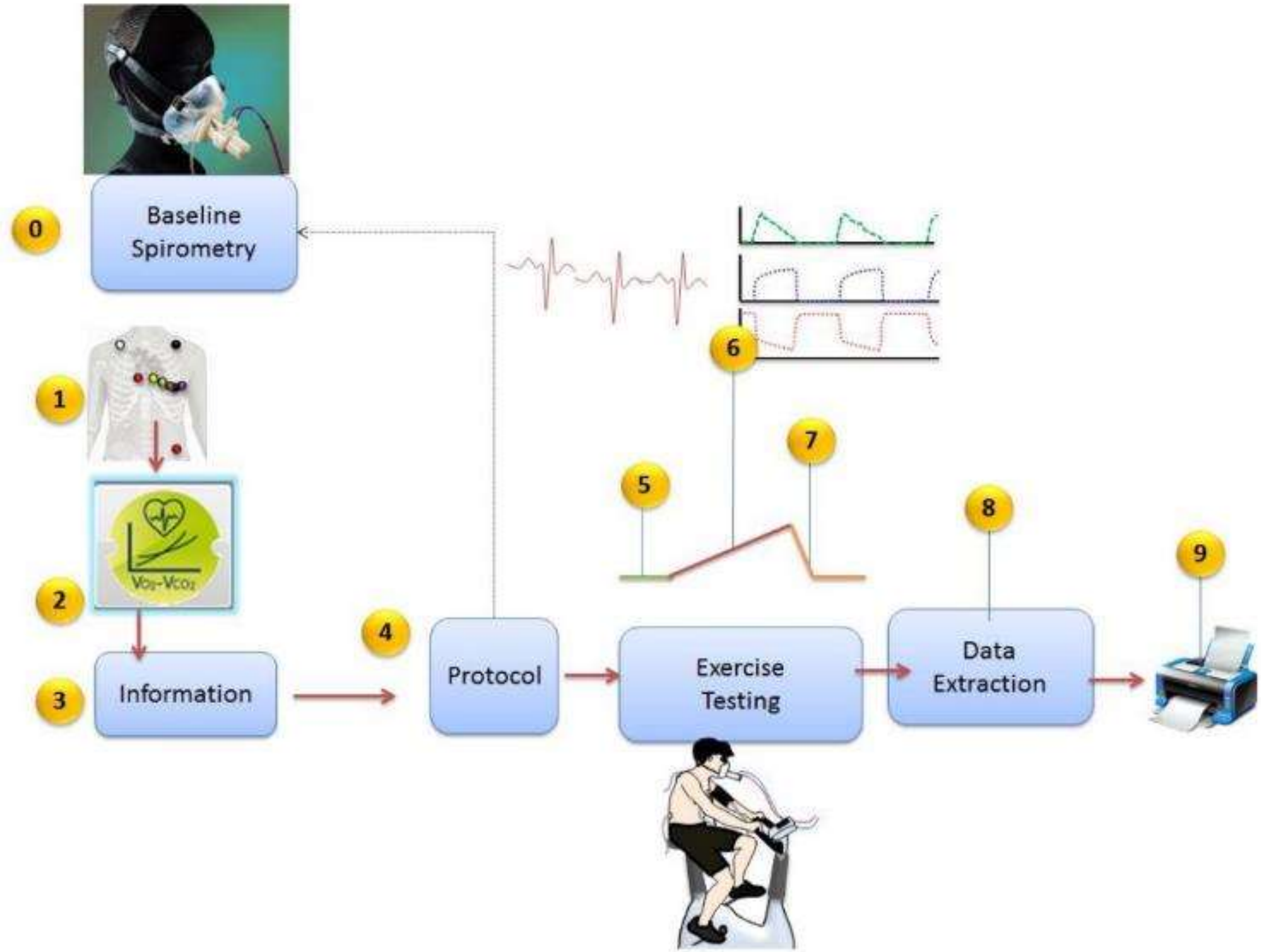
Parameters monitered



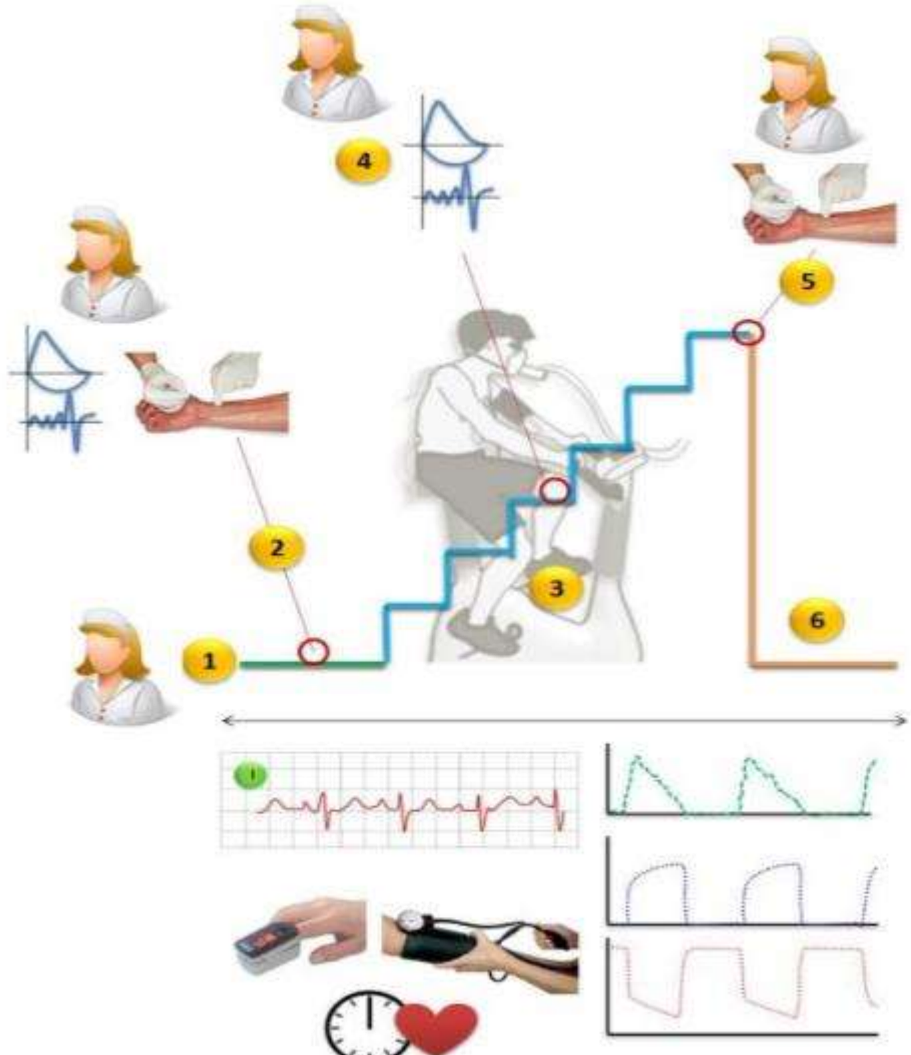
Comparing the test modes



	a (PFT)	b (VO_2-VCO_2)	c (VO_2-VCO_2)	d (ECG)	e (ECG)	f (ECG)
Spirometry	✓	✓	✓	✗	✗	✗
VO2, VCO2	✗	✓	✓	✗	✗	✗
ECG	✗	✗	✓	✓	✓	✓
Heart rate	✗	✓	✓	✓	✓	✓
Blood pressure	✗	✓	✓	✓	✓	✓
Blood gas	✗	✓	✓	✗	✓	✗
Pulse oxymetry	✗	✓	✓	✗	✓	✗
+Stress	✗	✓	✓	✗	✓	✗


0
Baseline
Spirometry
1
2
3
Information
4
Protocol
Exercise
Testing
5
6
7
8
Data
Extraction
9

Exercise testing stages



How do we do it? Protocols

- Based on work rate applied
  - Continuous ramp
  - **Multistage (modified Bruce)**
  - Constant work rate (modified Balke)
  - Discontinuous

Cycle ergometry vs treadmill

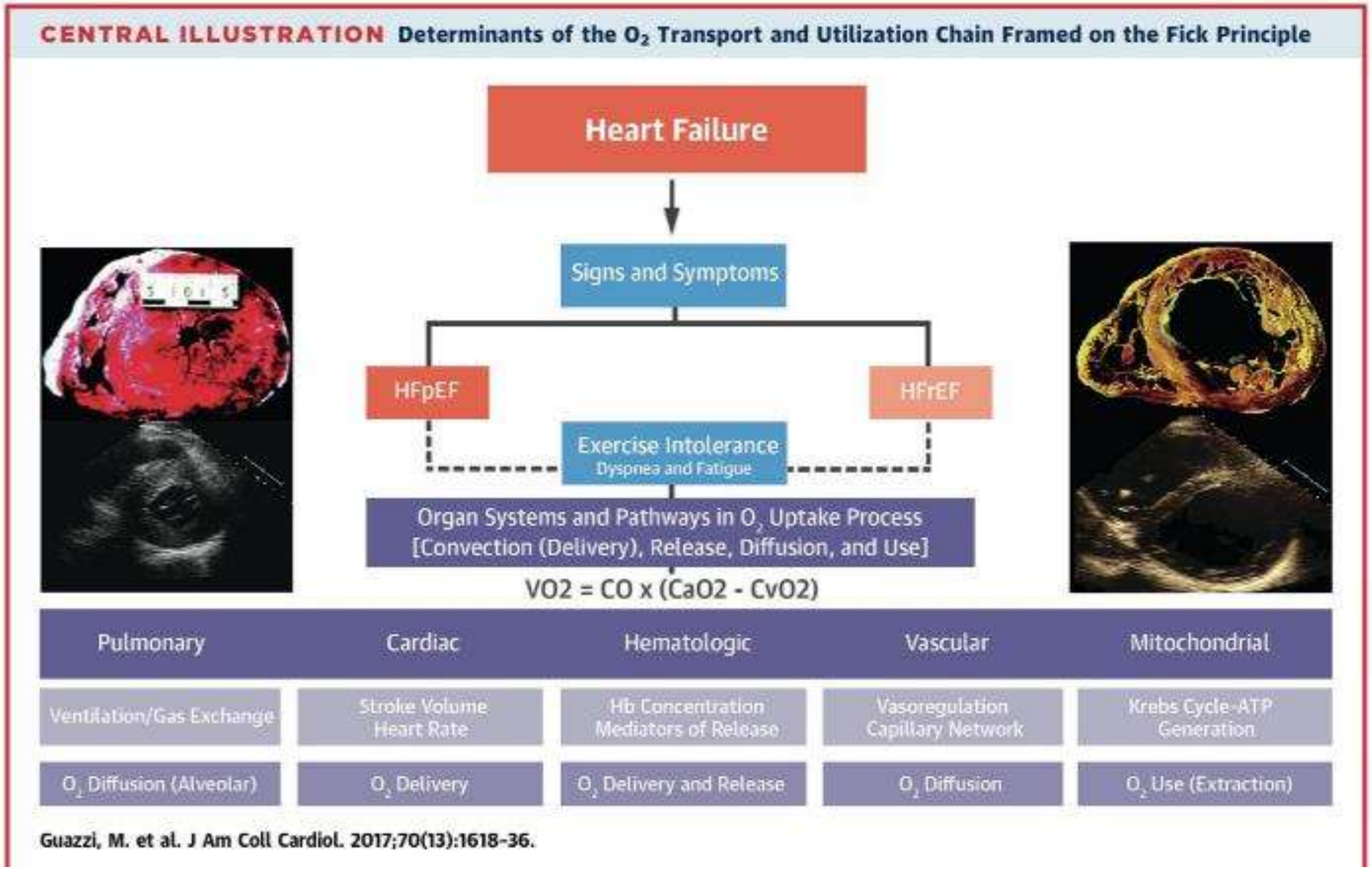
Variable	Cycle	Treadmill
Peak oxygen content (PVO_2)	Lower	Higher
Work rate measurement	Yes	No
Blood gas collection	Easier	More difficult
Noise and artefacts	Less	More
Safety	Safer	Less safe?
Weight bearing in obese subjects	Less	More
Degree of leg muscle training	Less	More
More appropriate for	Patients	Active normal subjects

Adapted from ATS/ACCP Statement on Cardiopulmonary Exercise Testing.[1]

Ficks principle

- VO_2= cardiac output x (CaO_2-CvO_2)

- Pulmonary – ventilation, gas exchange
- O_2 carrying capacity of blood – Hb, Hb-O_2 dissociation
- Cardiac function – Heart rate, Stroke volume
- Tissue extraction – Capillary, mitochondrial density, tissue perfusion


CENTRAL ILLUSTRATION Determinants of the O2 Transport and Utilization Chain Framed on the Fick Principle
Heart Failure
Signs and Symptoms
HFpEF
HFrEF
Exercise Intolerance
Dyspnea and Fatigue
Organ Systems and Pathways in O2 Uptake Process
[Convection (Delivery), Release, Diffusion, and Use]
VO2 = CO x (CaO2 - CvO2)
Pulmonary
Cardiac
Hematologic
Vascular
Mitochondrial
Ventilation/Gas Exchange
Stroke Volume
Heart Rate
Hb Concentration
Mediators of Release
Vasoregulation
Capillary Network
Krebs Cycle-ATP
Generation
O2 Diffusion (Alveolar)
O2 Delivery
O2 Delivery and Release
O2 Diffusion
O2 Use (Extraction)
Guazzi, M. et al. J Am Coll Cardiol. 2017;70(13):1618-36.

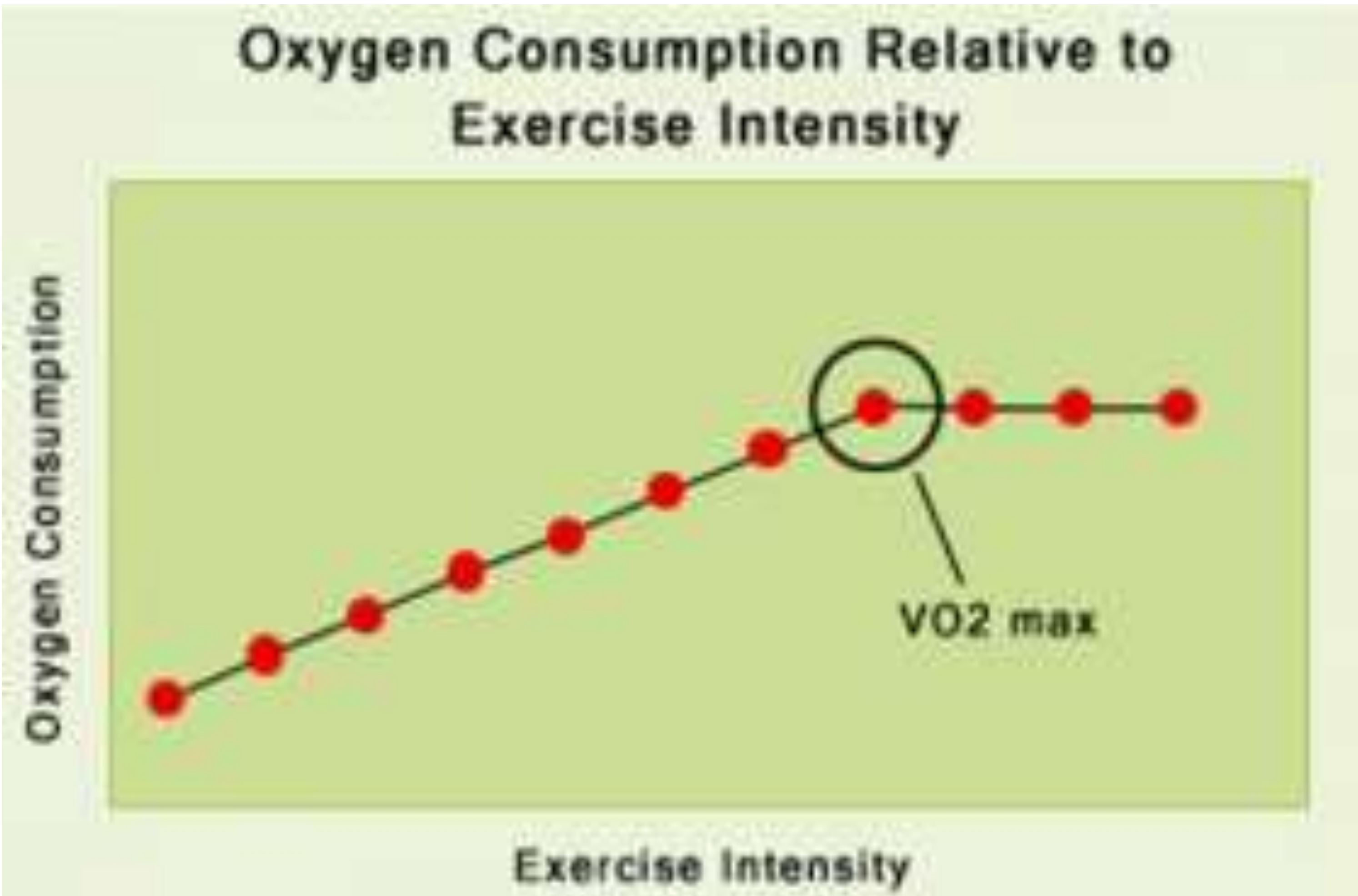
Variables for interpretation

Measurements	Noninvasive	Invasive
External work	WR	
Metabolic gas exchange	VO_2, VCO_2, RER, AT	Lactate/ bicarbonate
Cardiovascular	HR, ECG, BP, Oxygen pulse	
Ventilatory	Ve, Vt, fR	
Pulmonary gas exchange	SpO_2, Ve/VCO_2, Ve/VO_2, Pet O_2, Pet CO_2	pH, pCO_2, pO_2, SaO_2, P(A-a) O_2, Vd/Vt
Symptoms	Dyspnea, fatigue, chest pain	

Oxygen uptake (Vo2)

- Key measurement in exercise testing
- 250ml/min or 30-50ml/kg/min(MET)
- Age, sex, body wt, conditioning of muscles
- Indicators of exercise capacity
- 2 types
  - Maximum Vo2
  - Peak Vo2

Oxygen uptake (Vo2)



Vo2 max vs Vo2 peak

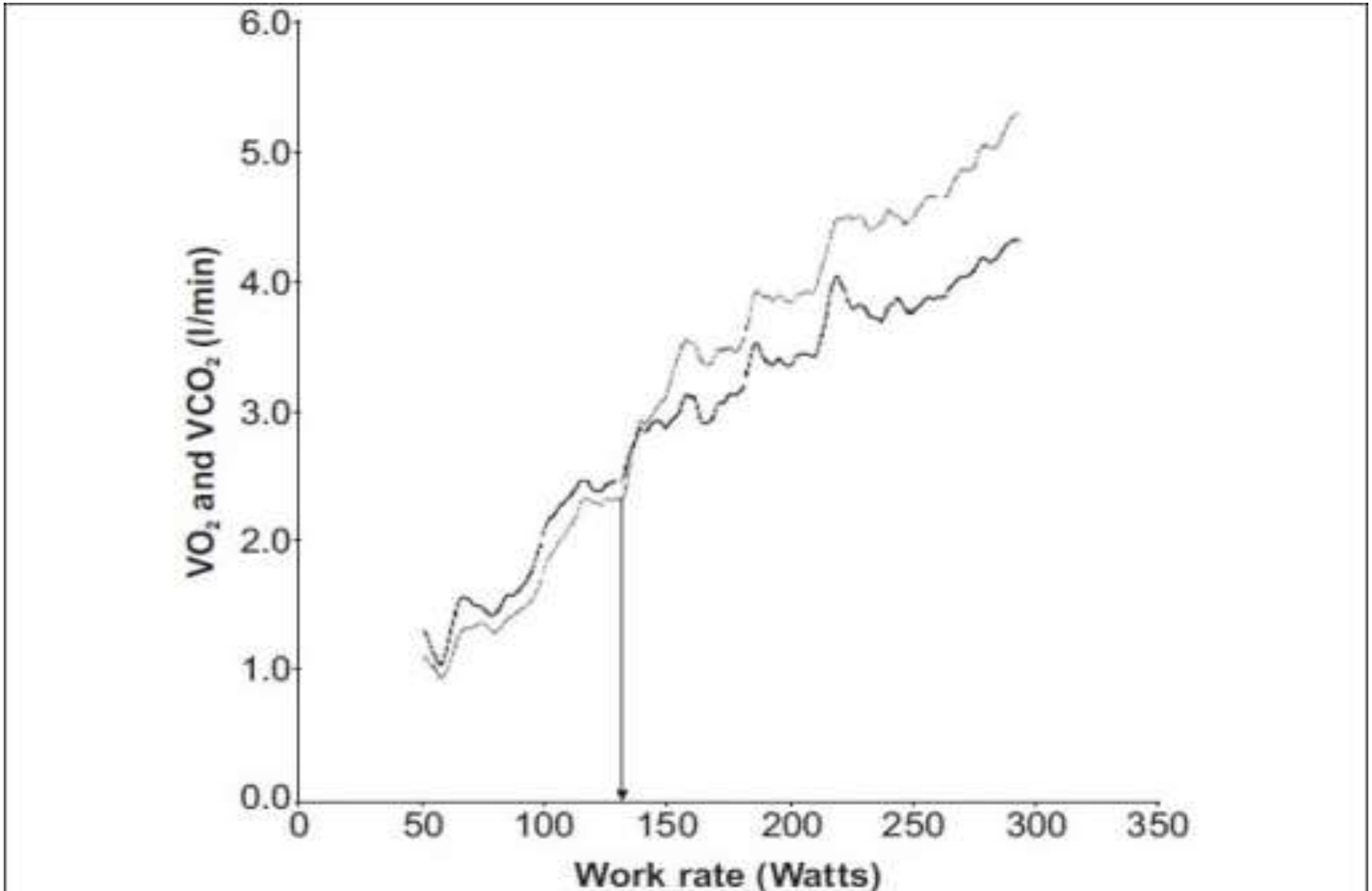
- Maximal achievable level of oxidative metabolism
- Gold std for assessing cardio-respiratory fitness
- Best index of aerobic capacity
- Plateau achieved with max exercise

- In Patients : clear plateau not reached
- Practical purposes
- Rough estimate of max o2 uptake

Recommendation

- Vo_2max/Vo_2 peak should be obtained from the maximal Vo_2 value measured during an incremental exercise protocol taken to symptom limitation even if a plateau in Vo_2 is not seen. Noteworthy symptoms should be appropriately recorded

VCO2 :CO2 production



Respiratory exchange ratio

- Ratio of VCO2/VO2
- Measure of respiratory quotient at tissue level
- In steady state, RER=RQ
- RER >1 indicates lactic acidosis, hyperventilation

Ventilatory/Anaerobic threshold

- Estimator of onset of metabolic acidosis due to rise in arterial lactate during exercise
- Expressed as % of VO2max
- Normally, 50-60% of predicted VO2max

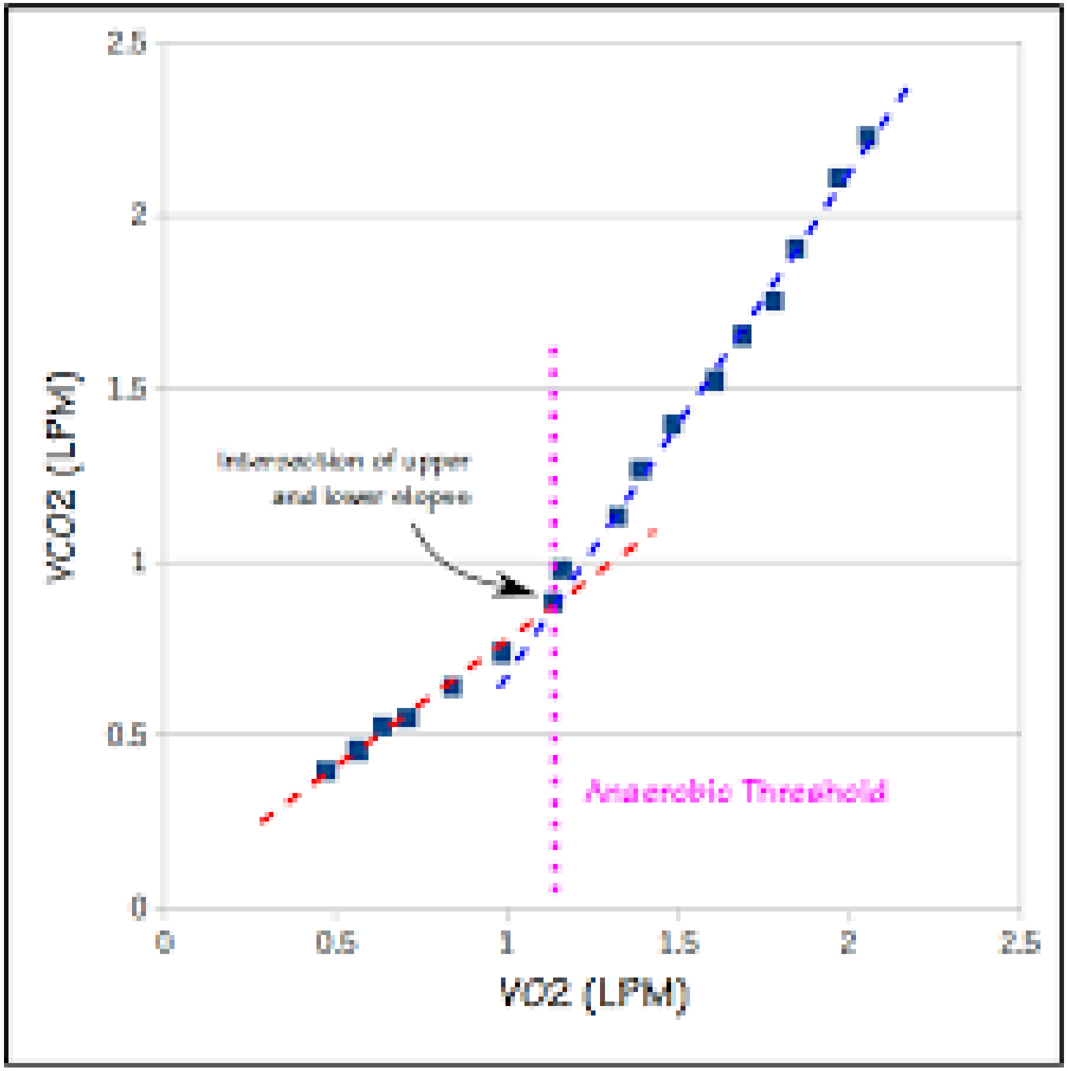
AT clinical significance

- Signifies the upper limit of exercise intensities which can be done aerobically
- Exercise prescription
- Limited discriminatory ability in distinguishing clinical conditions

How to determine AT?

- Invasive
  - Lactate
  - bicarbonate
- Noninvasive
  - Ventilatory equivalents
    - VE/VO2
    - VE/VCO2
  - V slope method

V slope method



Cardiac Output

- Best index of cardiac function
- Linear function of Vo2
- Early exercise by increase in HR and Stroke volume
- Mod to severe exercise by increase in HR only
- Routinely not measured in clinical exercise testing

Heart Rate

- Linear relationship with VO2
- Initially by decreased parasympathetic activity and later almost exclusively by increased sympathetic tone
- Compared with age predicted maximal HR (220-age)
- Heart rate reserve

Significance

- Peak heart rate = maximal patient effort
- HR VO2 slope indicates stroke volume

Oxygen pulse

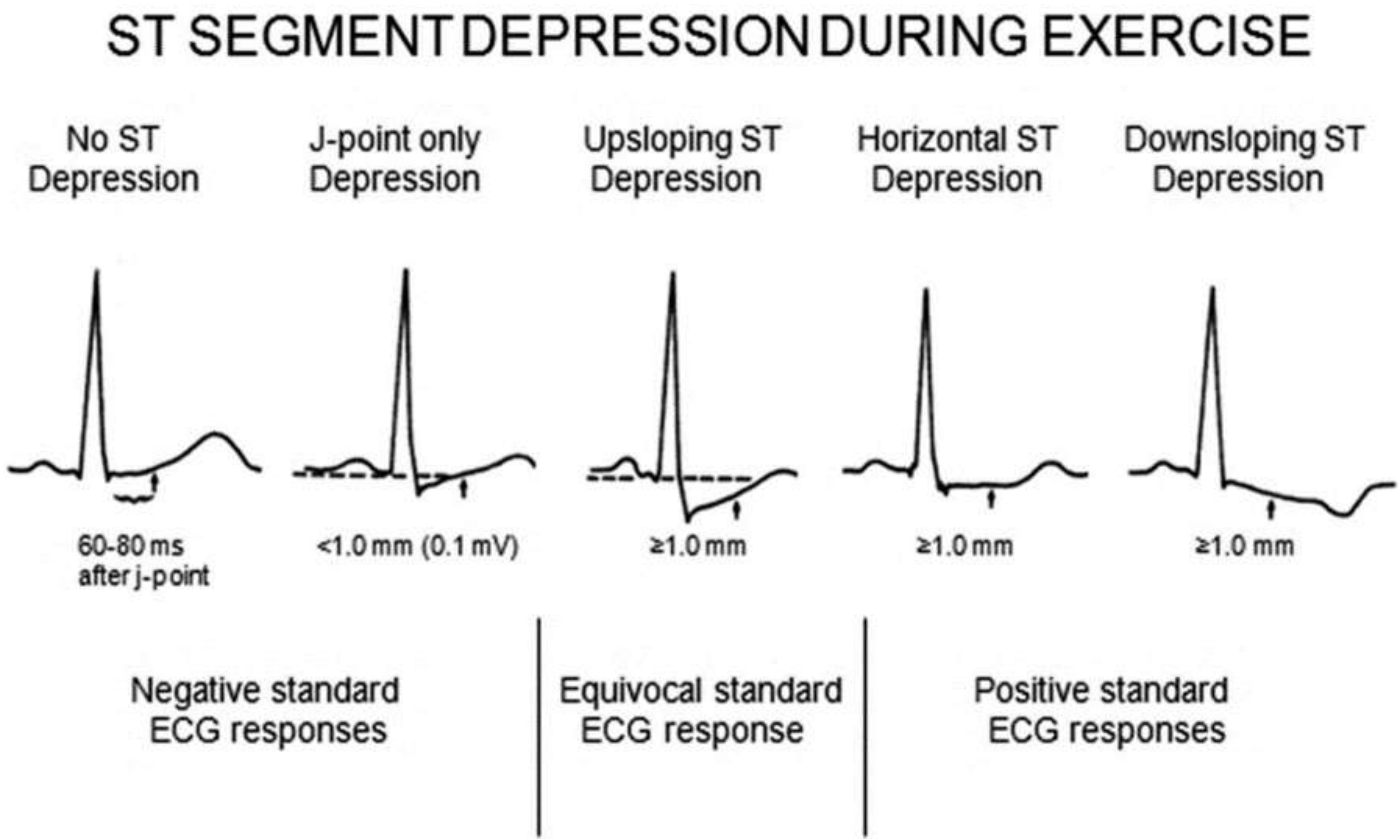
- Ratio of VO_2/HR
- Reflects amount of O_2 extracted per heart beat
- Estimates stroke volume during exercise

Blood pressure

- Normally systolic BP increases and diastolic BP may remain constant or decline slightly with increasing Vo2

- Excessive rise: abnormal BP control
- Declining BP/ fails to rise: cardiac limitation, abnormal sympathetic control

ECG-Ischemia



Ventilation

- Assessment
  - Minute ventilation (VE)
  - Breathing pattern
    - Tidal volume (VT)
    - Respiratory rate (f)

Breathing pattern

- Mild exercise: VT
- Moderate exercise: both VT and f
- Severe exercise: mostly f

- Decrease in TE and TI both (TE>TI)

Ventilatory reserve

- Percentage of MVV achieved at peak exercise
- Or difference between MVV and VE at peak exercise
- MVV = FEV1 x (35-40)

- Decreased in pulmonary diseases, old age and low fitness

VE VCO2 relationship

- Represents ventilatory response in relation to rise in CO_2

- Increased in cardiac and pulmonary disorders
- Discriminates cardiopulmonary disorders from obesity and deconditioning

Respiratory muscle evaluation

- Inspiratory pressures at FRC or at RV
- Expiratory pressures at TLC

- Indices for assessment of respiratory muscle weakness

Hypoxemia

- $SpO_2 < 88\%$
- $PaO_2 < 55 mmHg$
- $\Delta SpO_2 > 4\%$

- Decreased in ILD, PVD
- Differentiates between cardiac and pulmonary disease

P(A-a)O2

- Normally less than 10 mmHg at rest
- May increase to >20mmHg during exercise

- >35mmHg indicates possible gas exchange abnormalities
- >50mmHg likely indicates pulmonary abnormality

VD/VT

- Ratio of physiological dead space to tidal volume
- Indicates the fraction of breath that is wasted and inefficiency of ventilation

- Dependent on the breathing pattern
- VD/VT = (PaCO2-PECO2)/PaCO2
- PECO2 is mixed expired value of alveolar and dead space gas

VD/VT and exercise

- Normally 0.3
- Generally falls with increasing intensity of exercise

- Higher values are seen in pulmonary disease & Requires increased minute ventilation

Symptom assessment

- Perceptual response
- Report dyspnea, leg discomfort, chest pain

- Quantification
  - Visual analogue scale (VAS)
  - Category ratio (CR) 10 Scale

Normal exercise limitation

- No single exercise limiting factor
- Predominant factors limiting exercise in health
  - Cardiac output (gas transport abnormality)
  - Tissue oxygen extraction (metabolic)

Exercise limitation in disease

- Predominantly by **symptom perception**
- Cardiovascular
  - Reduced oxygen delivery
- Respiratory
  - Decreased ventilation
  - Decreased gas exchange
  - Respiratory muscle dysfuntion
- Peripheral
  - Muscular
  - metabolic

Indications

- Evaluation of exercise tolerance
  - Functional impairment or capacity
  - Exercise limiting factors
- Evaluation of undiagnosed exercise tolerance
  - Contribution of cardiac and pulmonary etiology in coexisting disease
  - Unexplained dyspnea

- Cardiovascular disease
  - Functional assessment and prognosis of heart failure
  - Cardiac transplantation
  - Exercise prescription and cardiac rehabilitation

- Respiratory diseases
  - COPD
    - Exercise limitation
    - Magnitude of hypoxemia, O2 prescription
  - ILD
    - Early detection of gas exchange abnormalities
    - Magnitude of hypoxemia, O2 prescription
    - Assessing therapeutic response
  - PVD
  - Cystic fibrosis
  - Exercise induced bronchospasm

- Specific clinical application
  - Preoperative evaluation
    - Lung resection surgery
    - Major abdominal surgeries
  - Pulmonary rehabilitation
  - Lung, lung heart transplantation

Contraindications

Cardiac

- Acute MI <5days
- Unstable angina
- Uncontrolled arrhythmias
- Syncope
- Active endocarditis
- Acute myocarditis
- Severe aortic stenosis
- Uncontrolled heart failure
- Dissecting aneurysm

Pulmonary

- Respiratory failure
- Acute PTE
- Uncontrolled asthma
- Pulmonary edema
- RA desaturation <85%

- Any disorder aggravated by exercise or which affects exercise performance

Risks to the patient

- Relatively safe procedure
- 2-5 deaths per 1,00,000 clinical exercise tests
- Risk is related to the underlying disease

Exercise termination

- Ischemic chest pain/ECG changes
- Complex ectopy/ 2nd 3rd degree heart block
- Fall in SBP > 20mmHg
- BP >220/120mmHg
- Severe desaturation <80% with symptoms
- Respiratory failure
- Pallor/ syncope
- Confusion/incordination

TABLE 18. USUAL CARDIOPULMONARY EXERCISE RESPONSE PATTERNS

Measurement	Heart Failure	COPD	ILD	Pulmonary Vascular Disease	Obesity	Deconditioned
$\dot{V}O_2max$ or $\dot{V}O_2peak$	Decreased	Decreased	Decreased	Decreased	Decreased for actual, normal for ideal weight	Decreased
Anaerobic threshold	Decreased	Normal/decreased/ indeterminate	Normal or decreased	Decreased	Normal	Normal or decreased
Peak HR	Variable, usually normal in mild	Decreased, normal in mild	Decreased	Normal/slightly decreased	Normal/slightly decreased	Normal/slightly decreased
O_2 pulse	Decreased	Normal or decreased	Normal or decreased	Decreased	Normal	Decreased
$(\dot{V}E/MVV) \times 100$	Normal or decreased	Increased	Normal or increased	Normal	Normal or increased	Normal
$\dot{V}E/\dot{V}CO_2$ (at AT)	Increased	Increased	Increased	Increased	Normal	Normal
V_D/V_T	Increased	Increased	Increased	Increased	Normal	Normal
Pa_{O_2}	Normal	Variable	Decreased	Decreased	Normal/may increase	Normal
$P(A–a)O_2$	Usually normal	Variable, usually increased	Increased	Increased	May decrease	Normal

CLINICAL APPLICATION AND RECENT ADVANCES OF CPET

Peak VO2 & survival

Table 2. Peak VO_2 and improved survival by disease.

Disease	Measurement/modality	Subjects (n)
Normal men	Estimated aerobic exercise capacity in METs (1 MET = 3.5 ml/kg/min)/treadmill	2534
Normal women	Estimated aerobic exercise capacity in METs (1 MET = 3.5 ml/kg/min)/treadmill	2994
Coronary artery disease	Estimated aerobic exercise capacity/ treadmill Measured VO_2/treadmill	3679 2812
Heart failure and cardiac transplantation	Measured VO_2/both treadmill and cycle	114 284
Chronic obstructive pulmonary disease	Measured VO_2/cycle ergometer Measured VO_2/cycle ergometer Measured VO_2/treadmill	150 365 195
Pulmonary hypertension	Measured VO_2/53 treadmill/17 cycle ergometer	70
Surgery – thoracic	Measured VO_2/cycle ergometer	22 80 204
Surgery – abdominal	Measured VO_2/cycle ergometer	187

William W Stringer (2010) Cardiopulmonary exercise testing: current applications, Expert Review of Respiratory Medicine, 4:2, 179-188

Severity of heart failure

Table 3. Use of the physiologic variables peak VO_2 and gas exchange lactic acid threshold to quantify the severity of heart failure.				
Severity	Class	Peak VO_2 (ml/kg/min)	Gas exchange anaerobic threshold (ml/kg/min)	Maximum cardiac index (l/min per m^2)
None to mild	A	>20	>14	>8
Mild-to-moderate	B	16–20	11–14	6–8
Moderate-to-severe	C	10–16	8–11	4–6
Severe	D	6–10	5–8	2–4
Very severe	E	<6	<4	<2

Data from [2,11].

Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic heart failure. *Am. J. Cardiol. 55, A22–A31*(1985).

Systolic vs diastolic Heart failure

- Farr *et al. comparing* CPET responses in SHF and DHF patients with similar NYHA symptom classes did not show any systematic clinical or statistical differences
- 185 patients with SHF (mean EF: 30%),
- 43 patients with DHF (mean EF: 56%)

- found that peak VO2 and VE/VCO2 ratios were very similar in the two groups

Farr MJ, Lang C, LaManca J *et al.* Cardiopulmonary exercise variables in diastolic versus systolic heart failure. *Am. J. Cardiol. 102, 203–206 (2008).*

VE/VCO2 slope and prognosis

- increasing VE/VCO2 slope resulted in decreasing event-free survival

Table 4. V_E/VCO_2 slope and survival in heart failure.

Ventilatory classification	V_E/VCO_2 slope	Event-free survival over 2 years (%)
VC I	≤29	97.2
VC II	30–35.9	85.2
VC III	36.0–44.9	72.3
VC IV	≥45	44.2

Arena R, Myers J, Abella J *et al.* Development of a ventilatory classification system in patients with heart failure. *Circulation 115, 2410–2417 (2007).*

Perioperative mortality

- Brunelli *et al. assessed preoperative CPET in 204* consecutive patients who were to undergo pulmonary lobectomy or pneumonectomy, the **peak VO2** was the best predictor of postoperative complications and mortality. Patients with a peak VO2 of greater than 20 ml/kg/min had dramatically fewer complications than those with a peak VO2 less than 12 ml/kg/min.
- For those with a VO2 of less than 12 ml/kg/min, pulmonary complications increased by eightfold, cardiac complications by fivefold and mortality by 13-fold

Brunelli A, Belardinelli R, Refai M *et al.* Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest 135, 1260–1267 (2009).*

Role in lung resection

- VO2 peak less than 50% of predicted is associated with higher morbidity and mortality after lung resection
- Beneficial in evaluation of borderline patients on spirometry

Brunelli A, Belardinelli R, Refai M *et al.* Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest 135, 1260–1267 (2009).*

CPET in exercise tolerance

- Subjective measures of a patient's quality of life shows a stronger corelation with exercise tolearnce than with either spirometry or oxygenation

Curtis JR et al. pulmonary rehabilitation in chronic respiratory insufficiency. Thorax 1994;49:162-170

Regenerative medicine

- Wisloff et al. demonstrated the use of CPET as an outcome variable in regenerative research in a study in rats
- Rats were selected across generations for either low or high aerobic capacity
- Over 11 generations, there was a dramatic difference in VO2max (43 vs 68 ml/kg/min);

Wisloff U, Najjar S, Ellingsen O *et al.* Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science 307, 418–420 (2005).*

Heart transplantation: AHA guidelines

- Peak VO2
  - <14ml/kg/min: relative indication
  - <10ml/kg/min: absolute indication

Costanzo MR et al. Selection and treatment of candidates for heart transplantation; A statement for health professionals from committee on heart failureand cardiac transplantation of the council on clinical cardiology, American heart association. Circulation 1995;92:3593-3612

Role in lung transplantation

- Useful in assessment of
  - Disease progression before Tx
  - Functional capacity
  - Causes of exercise limitation
  - Rehabilitation after lung Tx
- Presently, no consensus on how indices of exercise performance may impact the clinical decision for lung transplantation selection

Williams RJ et al. Role of cardiopulmonary exercise in lung and heart lung transplantation. Progress in respiratory research. 2002;32: 254-263

CPET in ILD

- Exercise tolerance corelates strongly with the prognosis of IPF patients

Veinshelboim B et al. Physical activity and exertional desaturation are associated with Mortality in IPF. J Clin Med 2016;5:E73

- Impairement in exercise capacity and abnormal ventilatory responses during CPET were confirmed to be associated with poorer survival in a study performed in 34 IPF patients who were followed for 40 months

Vainshelboim B et al. The prognostic role of ventilatory efficiency and exercise capacity in IPF. Respir Care 2016;61:1100-1109

- Currently, no data suggest a clinically significant minimal important difference(MID) identified on CPET in monitoring ILD patients
- Recent data suggest a role of 6MWD

Bohannon et al. Minimal clinically important difference for change in 6MWD of adults with pathology. J Eval Clin Pract 2016 (doi:10.1111/jep.12629)

CPET and PVD

- VO2 max corelates with severity and functional capacity
- CPET and 6MWT provide complimentary information in evaluation of PVD

Sun XG et al. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001;104:429-435

CPET and cystic fibrosis

- VO2 peak predicts prognosis
- CPET results and estimates of muscle size cross sectional area may provide an optimized exercise prescription for CF patients

Moser C et al. Muscle size and cardiorespiratory response to exercise in cystic fibrosis. Am J Respir Crit Care Med 2000;162:1823-1827

Role in asthma?

- May be used for increasing physical activity and for optimizing exercise prescription in asthmatic patients

Garfinkel SK et al. Physiologic and non physiologic determinants of aerobic fitness in mild to moderate asthma. Am Rev Respir Dis 1992;145:741-745

European respiratory society recommendations for CPET in practice

Detection of exercise-induced bronchoconstriction	A
Detection of exercise-induced arterial oxygen desaturation	B
Functional evaluation of subjects with unexplained exertional dyspnea and/or exercise intolerance and normal resting lung and heart function	D
To recognize specific disease exercise response patterns that may help in the differential diagnosis of ventilatory versus circulatory causes of exercise limitation	C
Functional and prognostic evaluation of patients with COPD	B, C
Functional and prognostic evaluation of patients with ILD	B, B
Functional and prognostic evaluation of patients with CF	C, C
Functional and prognostic evaluation of patients with PPH	B, B
Functional and prognostic evaluation of patients with CHF	B, B
Evaluation of interventions	
– Maximal incremental test	C
– High-intensity constant work-rate 'endurance' tests	B
Prescription of exercise training	B

The grade of recommendation is from A to D, with A = highest and D = lowest. Of note, grade A is relatively rare and grade B is usually considered the best achievable.
CF: Cystic fibrosis; CHF: Chronic heart failure; COPD: Chronic obstructive pulmonary disease; ILD: Interstitial lung disease; PPH: Primary pulmonary hypertension.
Reproduced from [5] with permission.

Take home message

- CPET is definitely an important armamentarium of practicing clinicians for evaluation of cardio respiratory disorders

- Provides thorough assessment of integrative multiorgan physiological response to exercise

- Huge scope for research in its clinical application

Future research

- Evidence based approach for CPET
- Sensitivity, specificity, PPV, NPV of individual variables in diagnosing and differentiating different diseases
- Classification of level of fitness based on CPET variables
- Relationship between perceptual and physiologic response during exercise
- Role of CPET in lung transplantation

THANK YOU