

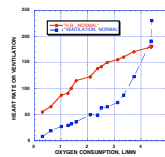
What I've Learned about Evaluating the Dyspneic Patient

- I can only help patients whose dyspnea is exacerbated by exercise, because exercise testing is what I do
- Almost every patient can be coached to give a reproducible maximal exercise effort with a progressive work exercise protocol
- A progressive work exercise test is the best clinical tool to identify the exercise-limiting organ system
- Checking TSH and hematocrit first saves unnecessary exercise tests
- Most physicians have not been taught anything about normal and abnormal responses to exercise

This Talk: The Plan

- A very brief review of the normal response to a maximal progressive work exercise test (PWET)
- Why maximal oxygen uptake is almost always a valid marker of maximal cardiac output
- Why maximal cardiac output is usually the limiting factor in PWET performance
- Cardiac limitation in symptomatic patients who have a normal resting cardiac echo and/or exercise stress echo
- Exercise-associated hypoxemia: Does desaturation always mean there is something wrong with the lung?

Normal ventilation and heart rate response in a PWET



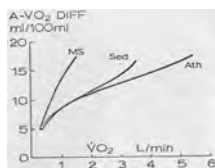
- Oxygen consumption increases 8 to 20 fold
- Stroke volume increases by ~50% from upright rest
- Heart rate increases 2 to 4 fold
- Arterio-venous O₂ extraction increases 3 fold

Fick equation

$$VO_2 = \frac{(\text{heart rate}) * (\text{stroke volume})}{(\text{arterial-venous } O_2 \text{ content difference})}$$

$$\text{Cardiac output} = \frac{VO_2}{(a-v O_2 \text{ difference})}$$

Peripheral Oxygen Extraction During a PWET



Rowell, LB *Human Circulation: Regulation During Physical Stress* Oxford, 1985

- Both healthy normal subjects and patients with cardiac disease are capable of extracting 80% of the arterial O₂ content with a maximal aerobic effort.

Sending the Patient Back to the Cardiologist: Part 1

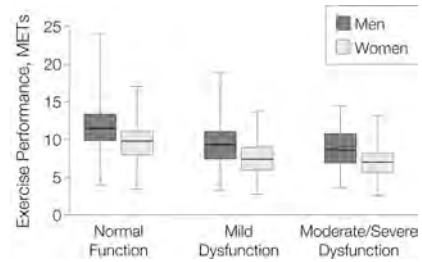
- Patient with exertional dyspnea and normal exercise echo
- PWET shows a low VO₂ max consistent with clinical history and an anaerobic threshold 2/3 of the way through the test
- Normal chronotropic response
- No evidence for ventilatory abnormalities or hypoxemia
- Probable diastolic dysfunction

Isolated Diastolic Dysfunction and Exercise Capacity

- 2867 patients with normal ejection fractions and no evidence for exercise-induced ischemia performed Bruce treadmill protocol
- Cardiac echos reviewed for six different parameters seeking evidence for diastolic dysfunction
- Diastolic dysfunction graded as normal, mild, or moderate/severe based on L atrial size and mitral diastolic flow measurements
- Maximal exercise capacity significantly reduced by diastolic dysfunction even after correction for age, sex, and hypertension

Grewal et al JAMA 2009; 301: 286-294

Association of Diastolic Function Grade With Exercise Capacity by Sex



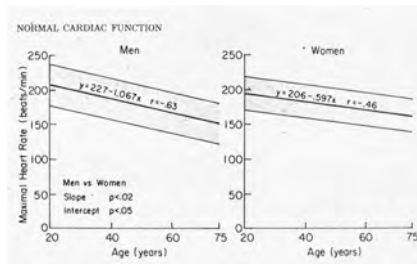
Grewal, J. et al. JAMA 2009;301:286-294.

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Sending the Patient Back to the Cardiologist: Part 2

- Patient with exertional dyspnea and normal exercise echo
- PWET shows a low VO₂ max consistent with clinical history and an anaerobic threshold 2/3 of the way through the test
- Limited chronotropic response
- The role of beta blockade
- How far below (220-age) is abnormal?

Maximal Exercise Heart Rate

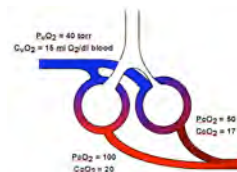


Hossack KF, Bruce RA: J Appl Physiol 53:799-804, 1982

Isolated Chronotropic Abnormalities and Exercise Capacity

- Wide range of normal maximal exercise heart rates
- Almost all cardiac diseases are associated with some level of reduction in maximal exercise heart rate
- Beta blockade a nearly universal treatment for cardiomyopathy
- Diagnosis helped most by documentation of progressive loss of maximal exercise heart rate and progressive resting bradycardia over time
- Motion-actuated pacemakers help some patients with chronotropic limitation

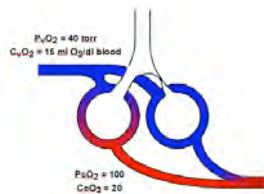
Hypoxemia with Exercise



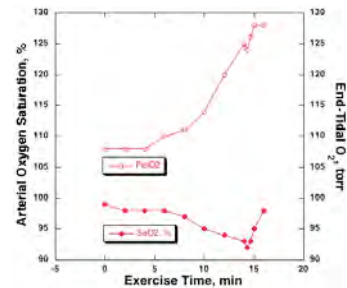
- Shunt
- V_A/Q Heterogeneity
- Hypoventilation
- Diffusion limitation
- Transient effects

Exercise Hypoxemia from Shunt

- Mixed venous O_2 content drops with exercise
- Extent of desaturation determined by shunt fraction
- Extent of desaturation determined by relative level of exertion
- Anemia decreases mixed venous saturation at any given exercise level



Exercise-Associated Desaturation, Pulmonary Hypertension with PFO



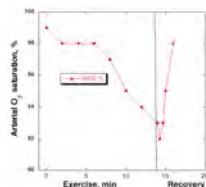
Hypoxemia During a PWET: Shunts

- Most consistent and predictable cause of exercise associated hypoxemia
- Subjects frequently drop to saturation levels not tolerated by other patients
- Identifying the anaerobic threshold difficult, since hypoxemia itself increases ventilation
- Arterial lactate measurements needed to identify an anaerobic threshold in these patients

Hypoxemia During a PWET: Oximeter Issues

- Oximeter HR must faithfully reflect the EKG HR
- True arterial desaturation during a PWET protocol decreases progressively and reaches a minimum in the initial minute of the recovery phase. Motion artifact interferes with pulse detection.
- Other artifacts: Methemoglobinemia and severe hyperlipidemia both produce low SpO_2 readings that do not decrease as power output increases

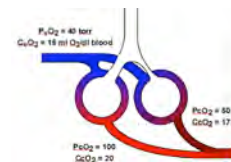
Pattern of Exercise-Associated Desaturation



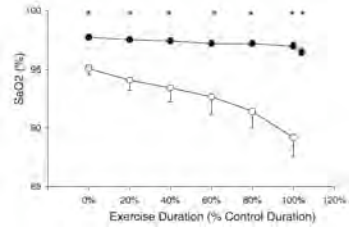
- Expect progressive decrease in saturation as effort increases
- Expect lowest saturation measurements in the first minute of recovery

Exercise Hypoxemia from V_A/Q Heterogeneity

- Hypoxemia due to low V_A/Q units
- Ventilation may improve with larger tidal volumes
- Significant desaturation with supplemental O_2 suggests concurrent shunt



Exercise Desaturation in CF



McKone et al. J Appl Physiol 99:1012-18, 2005.

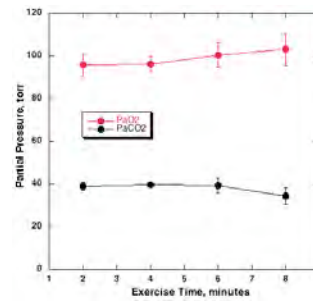
Hypoxemia During a PWET: Effects of V_A/Q heterogeneity

- Patients with mild and moderate COPD may improve resting hypoxemia with exercise
- Patients with severe airflow obstruction demonstrate progressive desaturation with exercise
- Patients with airflow obstruction alone do not have clinically significant desaturation during exercise with 30% supplemental oxygen (LVRS trial)
- Consider PFO or other diagnosis for COPD patients with significant exercise desaturation while breathing oxygen

Arterial Oxygenation in Normal Exercising Subjects

- Oxygen saturation normally unchanged with a maximal exercise effort in a PWET
- Arterial blood gases show an unchanged PaO_2 during maximal effort
- Maximal effort also associated with a metabolic acidosis and a compensatory respiratory alkalosis
- Hence the $A-aDO_2$ increases with maximal exercise

Arterial Blood Gases During a PWET (8 subjects, ages 28-63)



Alveolar gas equation

$$VCO_2 = V_A \cdot (P_A CO_2 / P_B)$$

$$VO_2 = V_A \cdot (P_I O_2 / P_B) - V_A \cdot (P_A O_2 / P_B)$$

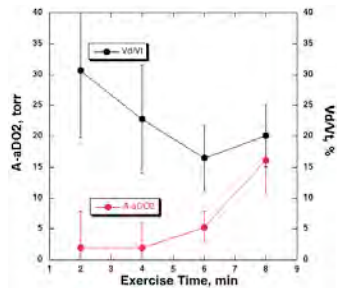
$$R = P_A CO_2 / (P_I O_2 - P_A O_2)$$

$$P_A O_2 = P_I O_2 - P_A CO_2 / R$$

R.Q. and the Respiratory R

- Both terms reflect the measured ratio of VCO_2/VO_2
- R. Q. is measured over sustained time during complete rest
- R.Q. reflects the mix of nutrients being metabolized, ranging from ~.78 (fat) to 1.0 (carbohydrate)
- R represents that same ratio measured over short times, and can have different values within different lung regions, determined by the local V_A/Q ratio
- R has a much larger range with transient changes of ventilation and/or exercise (from ~0.5 to ~1.5)
- The alveolar gas equation uses R, not R.Q.

Gas Exchange During a PWET (8 subjects)

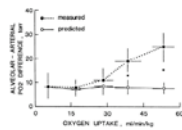


Hypoxemia During a PWET: Normal Subjects

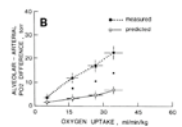
- Progressive increase in A-aO₂ difference seen in every normal subject giving a maximal effort
- MIGET studies of normal subjects reveal modest broadening of V_A/Q distribution that explains the increased A-aO₂ difference during heavy exercise
- MIGET studies of some elite athletes show more hypoxemia than predicted from V_A/Q heterogeneity alone
- Diffusion limitation contributes to arterial hypoxemia with very high cardiac output athletes or during exercise with normals in hypoxic environments

Diffusion Limitation Increases A-aDO₂ During Heavy Exercise or Hypoxia

Exercise at sea level



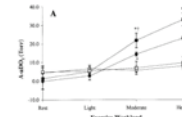
Exercise at P_B 430 torr



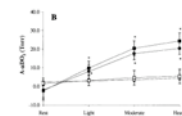
Wagner PD et al, J Appl Physiol 61: 260-270, 1986

A-aDO₂ in Elite Cyclists

Normoxia



Hypoxia

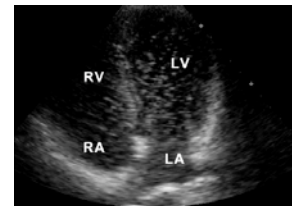


Rice et al J Appl Physiol 87:1802-1812, 1999

Hypoxemia During a PWET: The Air Contrast Controversy

- Cardiac echo following air contrast injection shows delayed appearance of bubbles in left ventricle for intrapulmonary shunts
- During high-level exercise with cardiac echo, delayed transmission of injected air contrast into LV observed in all subjects
- Finding suggests that intrapulmonary shunts develop in everyone during heavy exercise
- Postulated as the mechanism for the normal increase in A-aO₂ difference at high-level exercise

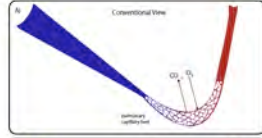
Exercise-Associated Bubble Shunt



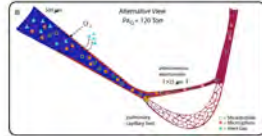
Lovering et al, J Appl Physiol 104:1418-1425, 2008

Postulated Development of Intrapulmonary Shunts with Exercise

Pathway for blood at rest



Pathway for blood during high-level exercise

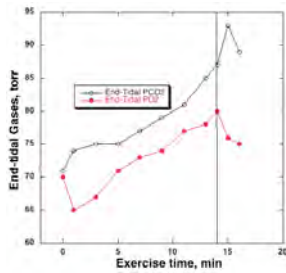


Lovering et al, J Appl Physiol, epub 2008

Chronic Respiratory Acidosis with Normal Lungs

- Primary ventilatory muscle failure with normal lungs
- Thoracic cage restriction with (relatively) normal lungs
- Progressive exercise still associated with an increase in R value
- Significant effect only noted with baseline hypercarbia

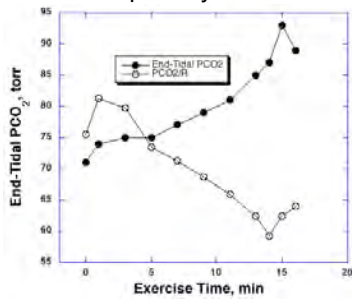
Chronic Neuromuscular Respiratory Failure



Exercise in Chronic Respiratory Acidosis

- Respiratory R (VCO_2/VO_2)
- $P_AO_2 = 150 - PaCO_2 / R$
- With severe hypercarbia, exercise-associated changes in R have a large effect on alveolar PO_2

Importance of R in Exercise with Chronic Respiratory Failure

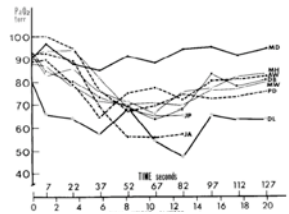


Hypoxemia While Stair Climbing

- Young and Woolcock study 1978
- 9 subjects with arterial lines
- Stair climbing @ 3 floors/min
- Arterial blood draws @ 15 second intervals
- Minute ventilation measured during climb

Young & Woolcock J Appl Physiol 44:93-96, 1978

Arterial blood gases, stair climbing

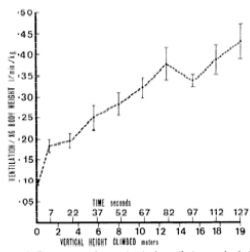


Young & Woolcock J Appl Physiol 44:93-96, 1978

Blood Gas Findings

- All subjects but one showed hypoxemia, maximal at 60 seconds
- Hypoxemia improved during second minute of stair climbing
- All subjects maintained stable PaCO₂
- Hypoxemia reproduced in one subject over three days

Increase in V_E with continued stair climbing



Potential explanations for Findings

- Hypoventilation relative to metabolic demands
- However, PaCO₂ remains normal
- Transient dissociation between components of the respiratory R
- Requires data on unsteady state changes in venous gases

Changes in PvO₂ and PvCO₂ at Start of Exercise

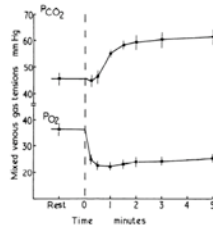
- Edwards et al applied their rebreathing method used for C.O. measurement
- Subject exhales and rebreathes N₂/CO₂ mix
- Gas fluctuations watched with a mass spec
- Proper gas mixes enable identification of a plateau for O₂ and CO₂

Experimental Protocol

- Subjects seated on cycle ergometer and immediately began exercise at 150 watts (~60-70% VO₂ max)
- Rebreathing trials done at 15 second intervals over several different increments, up to three minutes

Venous Blood Gases, Sudden Onset Exercise

- Sudden start at 150 Watts on ergometer
- Rebreathing technique for mixed venous gas measurements
- Slower CO₂ response
- Hence, transient low R value within first minute



Edwards et al J Appl Physiol
32:165-169, 1972

Sudden Onset Venous Changes

- PvO₂ almost immediately drops from 38 to 25 torr, about 5 volumes %
- PvCO₂ rises by about 2-3 torr, ~ 2.5 volumes %, catches up by 2 minutes
- This corresponds to a mixed venous R of 0.5 at 15 seconds

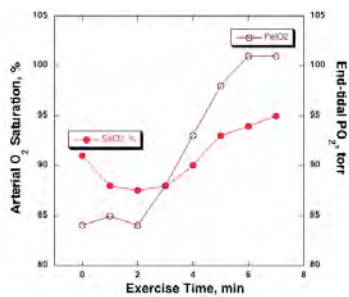
Alveolar Gas Equation, Exercise Onset

- Using the (transient) mixed venous gas contents
- $P_{A}O_2 = 150 - 40/0.5$
- $P_{A}O_2 = 70$ torr

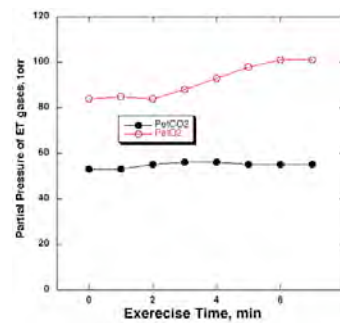
Hypoxemia at Exercise Onset with Normal Lungs

- Effect requires sudden onset high-level of exertion
- Hypoxic transient more augmented in subjects with blunted hypoxic response
- Hypoxemia is due to the transient decrease in the R value
- A-aO₂ difference remains normal if the appropriate R value is used

Early Desaturation During Treadmill Test, BMI 42



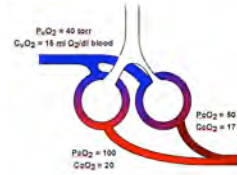
End-tidal Gases in PWET for BMI 42



Role of R in Transient Desaturation During Heavy Exercise

- Sudden onset heavy exercise causes immediate venous hypoxia but delayed venous hypercarbia, hence R at the lung is low (more O₂ uptake relative to CO₂ elimination)
- Transient low R means a decreased alveolar PO₂
- Exercise with the very obese- unloaded pedaling or slow walking require a high energy expenditure
- 6-minute walks in the very obese- transient desaturation a common finding that does not reflect pulmonary abnormalities
- Stair climbing with an oximeter - transient modest desaturation is a normal finding

Hypoxemia with Exercise



- Shunt
- V_A/Q Heterogeneity
- Hypoventilation
- Diffusion limitation
- Transient effects