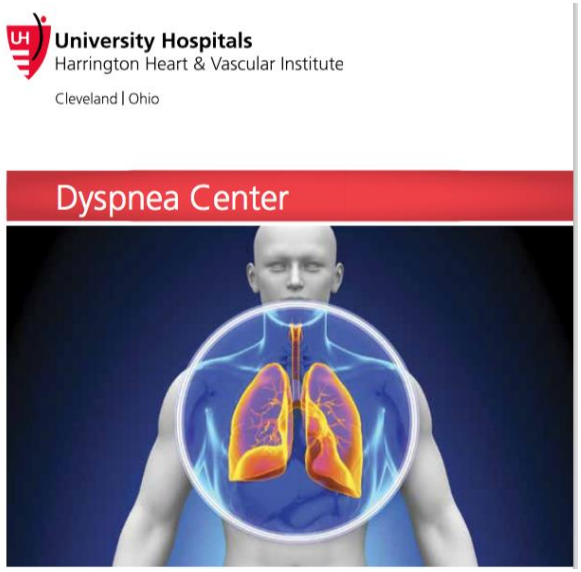
”I’m Short of Breath”
Systematic Evaluation, Workup and Lessons Borrowed from Advanced Dyspnea Clinics



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Conflict of Interest Statement

– No conflicts relevant to this talk

Objectives

- At the end of this lecture, participants should be able to:
  - Review standard evaluation of the dyspneic patient
  - Identify common causes of chronic dyspnea
  - List current causes of "difficult to diagnose" chronic dyspnea
  - Discuss advanced imaging, exercise and cardiopulmonary testing available for difficult to diagnose chronic dyspnea.

Introduction, Definitions, Background

Variable Definitions Of Dyspnea

- Unpleasant or uncomfortable respiratory sensations
- Difficult, labored, uncomfortable breathing
- Awareness of respiratory distress
- The sensation of feeling breathless or air hunger
- An uncomfortable sensation of breathing

- ATS guidelines: subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity

ATS. AJRCCM, 1999.

Dyspnea Symptom Prevalence

- Epidemiology of the problem:
  - 9-13% community residing adults have mild-moderate dyspnea
  - Age 40 or over: 15 – 18%
  - Age 70 or over: 25 – 37%

- Responsible for 3 – 4 million yearly ED visits

Parshall, AJRCCM 2012:185;435

Mechanisms Of Dyspnea: Respiratory Center Output

- Chemoreceptors
  - Peripheral: carotid bodies, aortic arch
    - Sense changes in PO_2, acidosis, hypercapnea
  - Central: medulla
    - pH and PCO_2 changes
- Hypercapnea
  - Potent stimulus of dyspnea
- Hypoxia
  - Less potent stimulus than hypercapnea

Manning. NEJM, 1995.

Mechanisms Of Dyspnea: Stimulation Of Mechanoreceptors

- Mechanoreceptors
  - Upper airway
  - Pulmonary receptors
    - Limitations of movement exacerbate dyspnea
    - The sensation of dyspnea varies with activation
  - Chest wall receptors
    - Restricted motion exacerbates dyspnea
    - Redundant to pulmonary receptors

Nausherwan. Chest, 2010.

Neuropsychological Components of Dyspnea

Pain and Dyspnea in the **Anterior Insula.** One of the key brain regions activated in both dyspnea and pain is the anterior insula. The “P” symbols show the locations of pain activations of the insula in a transverse slice at Z=+8. Pain data from various studies summarized by a meta analysis (Peyron et al. 2000). The larger circle labeled “D” shows the area activated by dyspnea (Banzett et al. 2000).

Lansing, Respir Physiol Neurobiol. 2009:167(1);53-60

Case

- 60 y/o with 2-3 years of increasing dyspnea manifest as insidious onset chest tightness/breathlessness chronic and present consistently at ascending 1 flight of stairs or equivalent.
- (-) Chest pain
- (-) cough or wheeze
- Intermittent trace edema (resolves)
- All other ROS (-)

Case

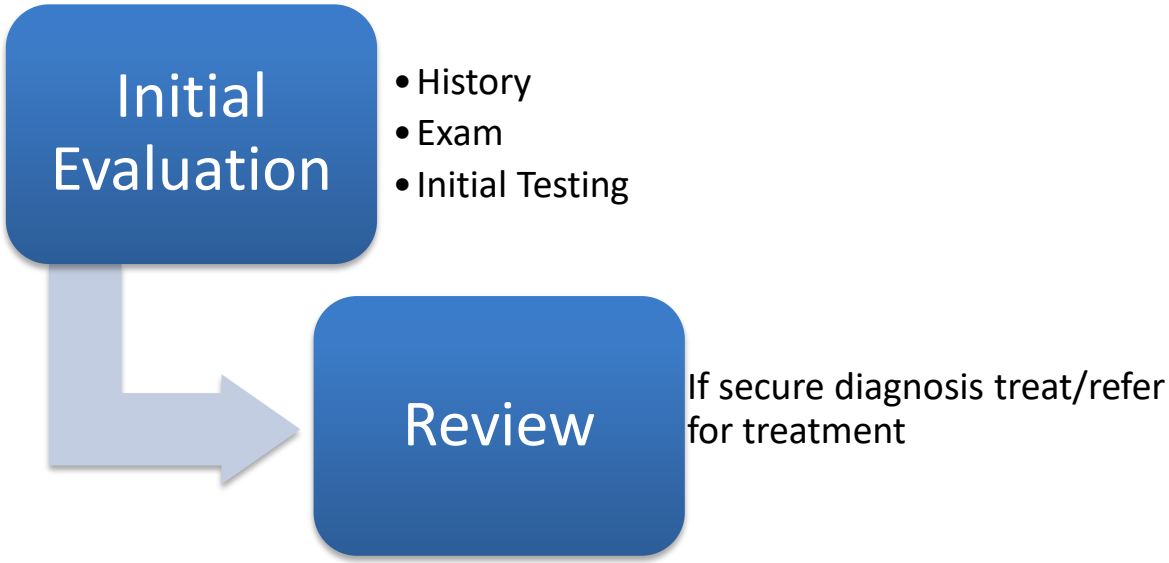
- Controlled essential hypertension, Treated and compliant OSA, dyslipidemia, Type II DM with no complications, hypothyroidism on replacement
- Social history non-smoker, no exposures, no hobby exposures, retired floor nurse
- Family history CV disease
- Exam: BMI =33, SpO2 = 98%
- Labs: Normal

What next?

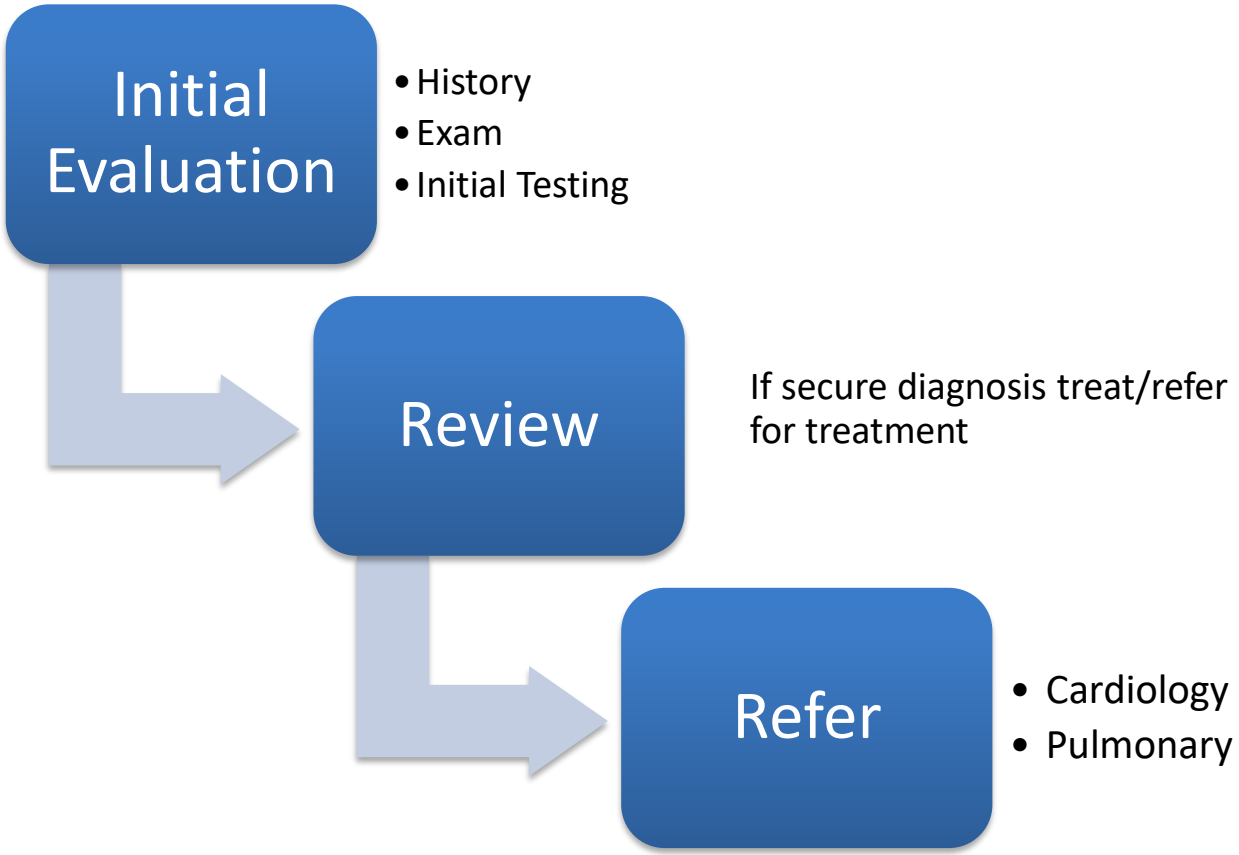
A) Spirometry
B) Echo
C) CXR
D) Stress Testing
E) CT Chest
F) 6 Minute Walk Testing
G) None of the above
H) All A-F

Traditional Approach to the Patient with Chronic Dyspnea

Typical Stepwise Evaluation in Chronic Dyspnea

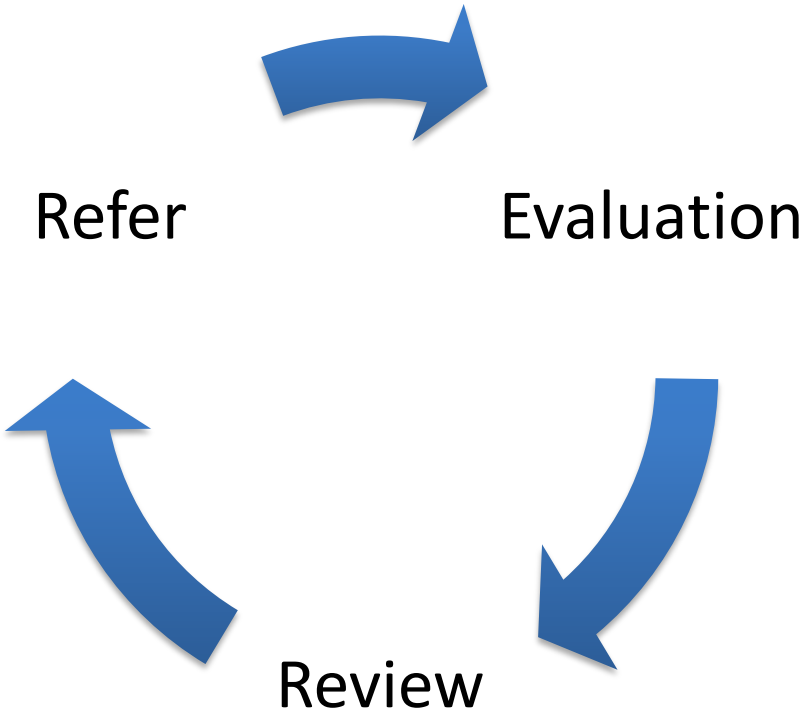


Typical Stepwise Evaluation in Dyspnea



Typical Argument Among Consultants: Is It The Heart or the Lungs?

Typical Outcome of the Process in Some (Many) Cases



Typical Outcome of the Process in Some (Many) Cases

Clues, Pearls and Protocols to Help Unravel Chronic Dyspnea

My Approach to Chronic Dyspnea

- Know what you are up against
- Play the Odds
- Protocolize the Workup
- Be aware of advanced specialty diagnostics (Dyspnea Center Techniques)

Know What You are up Against: Differential Diagnosis of Chronic Dyspnea

- Cardiac
  - Heart failure
  - Coronary artery disease
  - Arrhythmia
  - Pericardial disease
  - Valvular heart disease
- Pulmonary
  - Chronic obstructive pulmonary disease
  - Asthma
  - Interstitial lung disease
  - Pleural effusion
  - Pulmonary hypertension
  - Malignancy
  - Bronchiectasis
- Non-cardiac/Non-pulmonary
  - Thromboembolic disease
  - Psychogenic
  - Deconditioning
  - Obesity
  - Anemia
  - GERD
  - Metabolic conditions
  - Cirrhosis
  - Thyroid disease
  - Neuromuscular
  - Chest wall
  - Upper airway
  - Medications

Play the Odds:

1) Where are you?
2) What do you see?
3) When did it/does it happen?

Playing the odds: 1) Where are you?

Rescue service	Emergency room	General practice
Heart failure (15–16%)	COPD (16.5%)	Acute bronchitis (24.7%)
Pneumonia (10–18%)	Heart failure (16.1%)	Acute upper respiratory infection (9.7%)
COPD (13%)	Pneumonia (8.8%)	Other airway infection (6.5%)
Bronchial asthma (5–6%)	Myocard. infarction (5.3%)	Bronchial asthma (5.4%)
Acute coronary syndrome (3–4%)	Atrial fibrillation or flutter (4.9%)	COPD (5.4%)
Pulmonary embolism (2%)	Malignant tumor (3.3%)	Heart failure (5.4%)
Lung cancer (1–2%)	Pulmonary embolism (3.3%)	Hypertension (4.3%)

Frese T et al. J Clin Med Res. 2011;3:239–246
Prekker ME et al. Acad Emerg Med; 2014;21:543–550
Hüfner A, Dodt C. Med Klin Intensivmed Notfmed. 2015;110:465–481

Playing the Odds:
2) What do you see?

Chart from: Walls S, Am Fam Physician. 2012 Jul 15;86(2):173-180

Playing the Odds: 3) When did it/does it happen?

- Temporal
  - acute onset, vs. chronic (present for more than four weeks), vs. acute worsening of pre-existing symptoms
  - intermittent vs. permanent
  - episodic (attacks)
- Situational
  - at rest
  - on exertion
  - accompanying emotional stress
  - depending on body position
  - depending on special exposure(s)

Berlinger D. et al. Dtsch Arztebl Int. 2016 Dec; 113(49): 834–845

Protocolize the Workup
“Don’t miss the easy stuff”

Example of Protocolized Chronic Dyspnea Workup

H&P with dyspnea index.

Labs: Chem Complete, CBC, TSH, BNP

PFTs: Spirometry, Lung Volumes, DLCO, BPC

CXR

Cardiopulmonary Exercise Testing (CPET)

Pulmonary: CT Chest, V/Q, Bronchoscopy, Thoracentesis

Cardiac: Stress Echo, Nuclear Stress Test, Cardiac Catheterizaion

Others: GI

Adapted from: Pratter MR et al. *Respir Med.* 2011;105(7):1014–1021

Typical Dyspnea Evaluation and Differential Diagnosis

Alternate “Level” Testing Algorithm

- Step 1
  - CBC with differential cell count, a chemistry panel that includes
  - renal and liver function tests, thyroid function tests
  - Chest radiograph
  - Electrocardiogram
  - Spirometry with pulse oximetry
- Step 2
  - Complete pulmonary function tests (spirometry before and after
  - Administration of a bronchodilator, measurement of lung volumes,
  - Diffusing capacity, and flow volume curves)
  - Chest CT scan (high resolution and/or CT arteriography)
  - B-type natriuretic peptide measurement and transthoracic
  - Echocardiography
- Step 3 - CPET

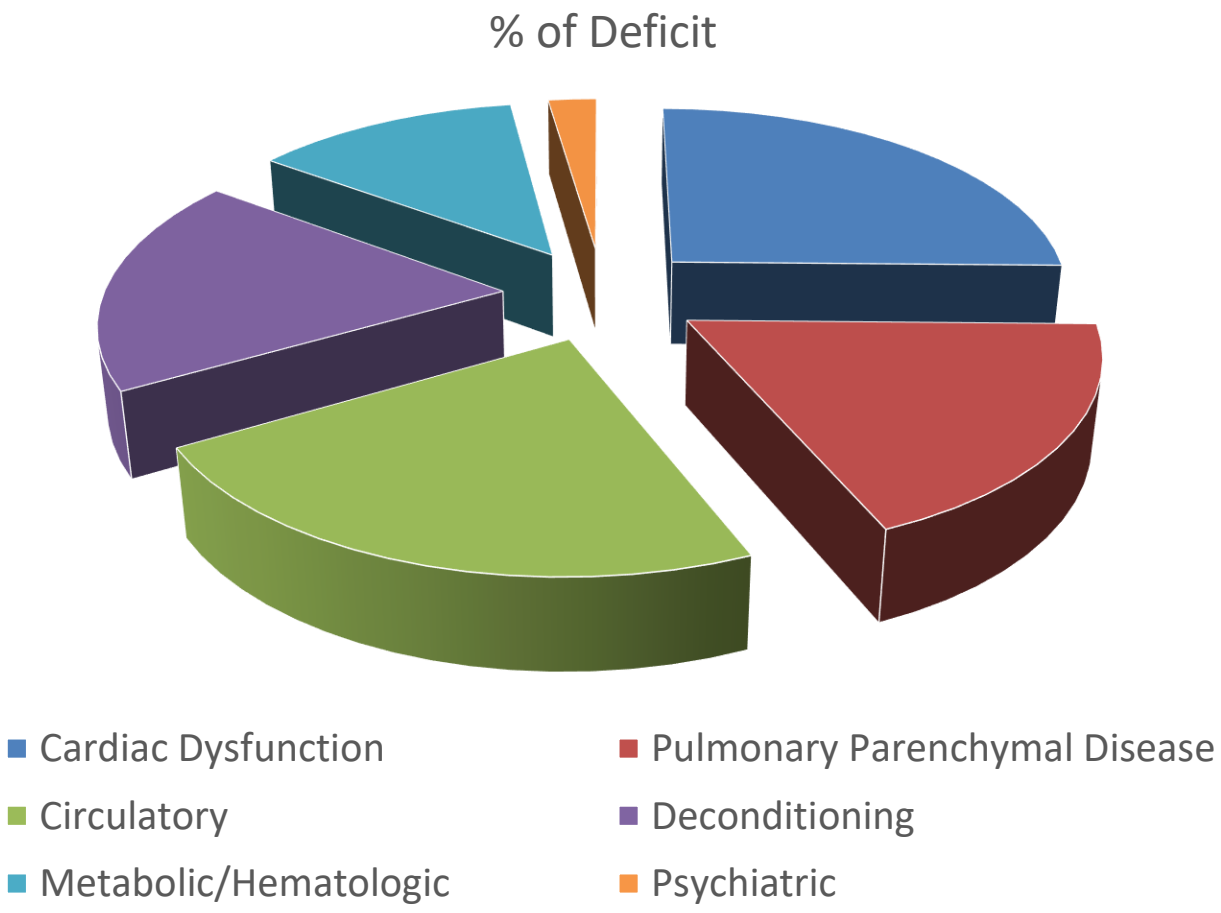
Peters SP. J Allergy Clin Immunol: In Practice 2013;1:129-36

Problems with These Approaches

- No accounting for difficulties in some diagnoses
  - HFPEF
  - Pulmonary Arterial Hypertension
  - Coronary Disease
  - Vocal Cord Dysfunction
- No accounting for diversions of diagnoses due to comorbidities
- Tests are performed at rest!
- Some patients will still remain undiagnosed

Specialty Referral to a Dyspnea Center: Approach to the Patient with Chronic Undefined Dyspnea After Initial Testing

Alternate Approach to Cardiopulmonary Dysfunction



The Dyspnea Spiral

from Haas F, Salazar-Schicchi J, Axen K. Desensitization to dyspnea in chronic obstructive pulmonary disease. In: Casaburi R, Petty TL, eds. Principles and Practice of Pulmonary Rehabilitation. Philadelphia, PA, WB Saunders Company;1993:241-25.

Differential Diagnosis of Chronic Dyspnea

- Cardiac
  - Heart failure
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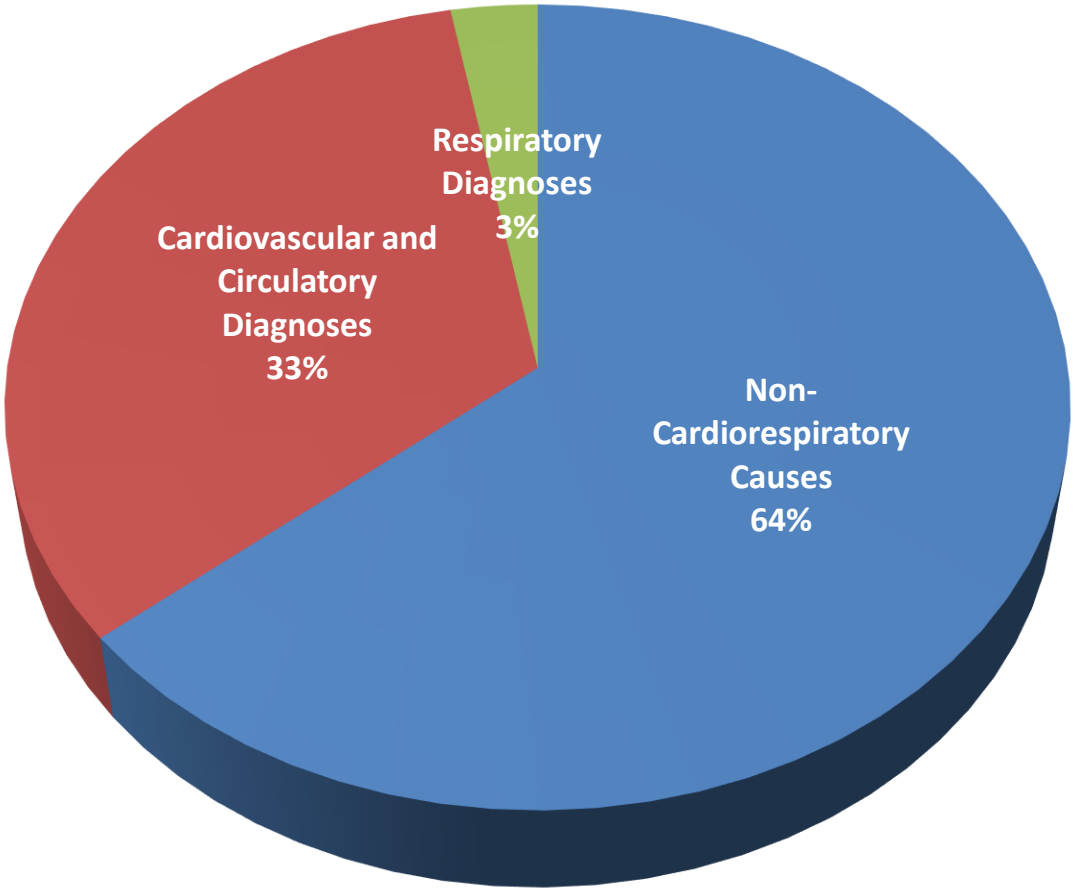
  - Obesity
  - Anemia
  - GERD
  - Metabolic conditions
  - Cirrhosis
  - Thyroid disease
  - Neuromuscular
  - Chest wall
  - Upper airway
  - Medications

Causes of Dyspnea in a Pulmonary Clinic



Pratter et al. Respiratory Medicine Volume 105, Issue 7, Pages 1014–1021

Our Approach To The Patient with Chronic Cryptogenic Dyspnea – Initial Testing and Review

- History and physical
- ECG
- Spirometry, Lung volumes, pulse oximetry rest and ambulatory
- CXR/CT scan
- Echocardiogram with bubble contrast if hypoxia or desaturation, +/- exercise
- Cardiopulmonary exercise testing with spirometry

Why evaluate with exercise?

- "Dyspnea is a complex symptom that potentially warns of a critical threat to homeostasis and thus frequently leads to adaptive responses (such as rest)".[1]

- Exercise is the ideal stimulus to interrogate the cardiovascular system
  - Increases oxygen consumption and minute ventilation by 3 – 15x baseline utilization
  - Improves signal to noise ratio of test

- Most patients are not dyspneic at rest. Why not test them when they have symptoms?

[1]Parshall, AJRCCM 2012:185;435

Consider Advanced Non-Invasive/Minimally Invasive Studies in Dyspnea Evaluation

- Complete PFTs (Dco, Lung volumes, Flow-volume loops, Resp. pressures, ABG)
  - During exercise
  - Methacholine testing
  - Positional
- Airway inspection +/- Exercise
  - Endoscopic
  - Dynamic CT
- Echocardiogram
  - Exercise
  - Bubble studies

Consider Invasive Procedures in Dyspnea Evaluation

- Cardiac Catheterization
  - RHC
    - Volume Loading
    - Nitroprusside
    - NO Challenge
    - Simple Exercise
  - LHC
  - iCPET
- Muscle Biopsy
- Open Lung Biopsy

Non-Invasive Cardiopulmonary Exercise Testing

Cardiopulmonary Exercise Test (CPET)

http://www.medgraphics.com/download/UltimaCardiO2_4pg_060105-001rA.pdf

Common Variables Measured

Variable	Definition	Clincial Signficance
VO_2 Peak (O_2 ml/kg/min)	Highest demonstrable VO_2	Expression of aerobic exercise capacity
VT (O_2 ml/kg/min)	VO_2 at which there is an accelerated rise in VE & VCO_2 relative to VO_2	Measure of fitness (usually about 50-65% of VO_2 Max)
RER (VCO_2 / VO_2)	Ratio at max exercise	Indicator of subject effort (RER >1.10)
VE / VCO_2 (Ventilatory efficiency) (VE = minute ventilation)	Efficiency of pulmonary clearance of CO2 during exercise	Reflects V/Q matching (can be used for severity index)
Breathing reserve	Relation of max VE and pre-test max voluntary ventilation (MVV)	Index of physiologic reserve of lung (low in COPD and trained athletes)
Oxygen Pulse (VO_2/HR)	Ratio of oxygen consumption to HR	Surrogate Marker for Stroke Volume

Modified from: Siestema Circ. 2011;123:668-680

Diagnostic Patterns of Abnormal CPET Results

Arena Am J Lifestyle Med 2008

Exercise Echo Testing

What Does DHF Look Like On Echo?

Nagueh. JASE, 2009.

Diastolic Stress Echo

E/e’ 17

E/e’ 24

Peteiro, JASE 2008;21:178

Pulmonary Hypertension Stress Echo

Rest 4 Chamber View

Peak Exercise 4 Chamber View

Additional Exercise Echo Studies

- Assess wall motion abnormalities
- Assess valvular gradients and function with exercise
- Check bubble study to assess PFO shunting during exercise with hypoxic patients with minimal shunt during rest

Invasive Cardiopulmonary Exercise Testing

UH iCPET

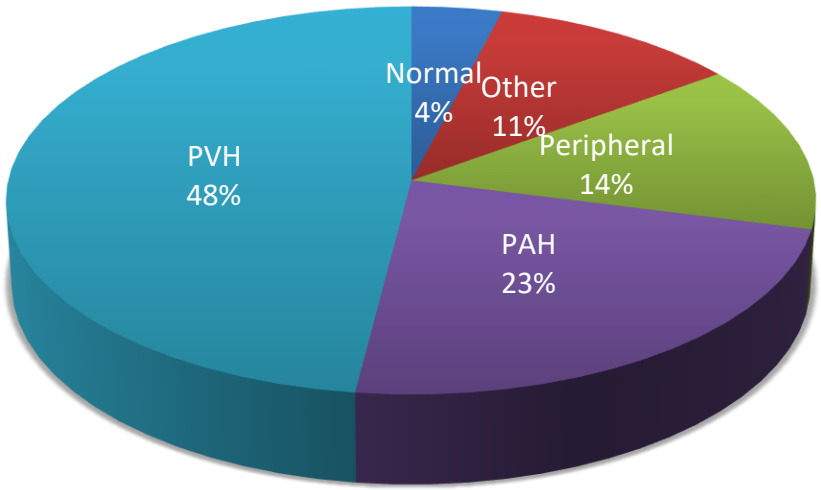
I-CPET Allows for Hemodynamic Phenotyping

- Peak Exercise mean PAP and LAP (via PCWP)
- Peak Exercise mixed venous O2 saturation
- Δ CaO_2 – CvO_2 gradient
- Fick Cardiac Output
- Pulmonary Vascular Resistance: PVR = (mPAP – LAP)/CO
- Δ mPAP (mm Hg) / Δ Cardiac Output (L/min)

Exercise-Induced Pulmonary Arterial Hypertension

James J. Tolle, MD; Aaron B. Waxman, MD, PhD; Teresa L. Van Horn, BA;
Paul P. Pappagianopoulos, MEd; David M. Systrom, MD

CPET Diagnoses



- The MGH CPET lab performed 406 studies over 3 year period
- Each patient had RHC, A-line placed and CO calculated by first pass radionuclide ventriculography
- 75% of studies performed to evaluate dyspnea of uncertain etiology

Tolle, Circulation 2008;118:2183

PA pressure normal response to exercise

Lewis, Circ 2013:128;1470

A diagnostic algorithm for interpreting iCPET results.

Maron B A et al. Circulation 2013;127:1157-1164

Exercise Hemodynamics of HFpEF

Borlang, BA et al. Circ Heart Fail. 2010 Sep;3(5):588-95

UH Dyspnea Program, Summary and Conclusions

Case Revisited

- Patient underwent Left Heart cath through wrist. Normal coronaries with LVEDP of 14.
- iCPET with Arterial Line and Swan Ganz catheter in place with gas exchange.
  - MVO2 = 16 ml/kg/min (60% predicted)
  - Normal BP and HR response
  - Normal Vt, RR and Respiratory Reserve, normal spirometry at peak exercise
  - Anaerobic Threshold Consistent with Deconditioning

Case Revisited

- Ve/CO2 = 35
- Normal CI, PAP 35/13, RAP = 6 mm Hg
- PCWP 13->28 mm Hg with exercise

- Diagnosis = Heart Failure with Preserved Ejection Fraction (HfPEF)

Causes of Dyspnea in UH Program

- Cardiac
  - Heart Failure (HFPEF)
  - Chronotropic incompetence
  - Undiagnosed critical coronary artery disease
  - Deconditioning
- Pulmonary and Airway
  - Asthma
  - IPF
  - Vocal Cord Dysfunction
  - Diaphragm Paralysis
- Others
  - Metabolic Acidemia
  - Probable mitochondrial abnormality
- Many Patients with multiple issues

Conclusions

- Dyspnea is a symptom with multi-organ system origins
- A step-wise approach to the dyspneic patient improves diagnostic accuracy
- Exercise is an important stressor to diagnose some cardiac and pulmonary causes of chronic dyspnea.
- In patients with both heart and lung disease, invasive cardiopulmonary exercise allows for determining which may be predominant.

Summary of Summary

- Know what you are up against
- Play the Odds
- Protocolize the Workup (Don’t miss the easy stuff)
- Be aware of advanced specialty diagnostics (Dyspnea Center Techniques)

History & Physical

- 75 y/o with years of dyspnea, worsening in last 2-3. Ex smoker 3 PPD, quit 20 years ago. Recently admitted with heart failure. History of OSA non-compliant with meds. No oxygen use. Occasional wheeze per patient. Difficulty breathing when lying flat on back. Chronic bronchitis
- BMI = 46, JVD 9 cm, absent BS right base, few scattered very soft wheezes, partially cleared with cough
- 2-3+ edema to knees

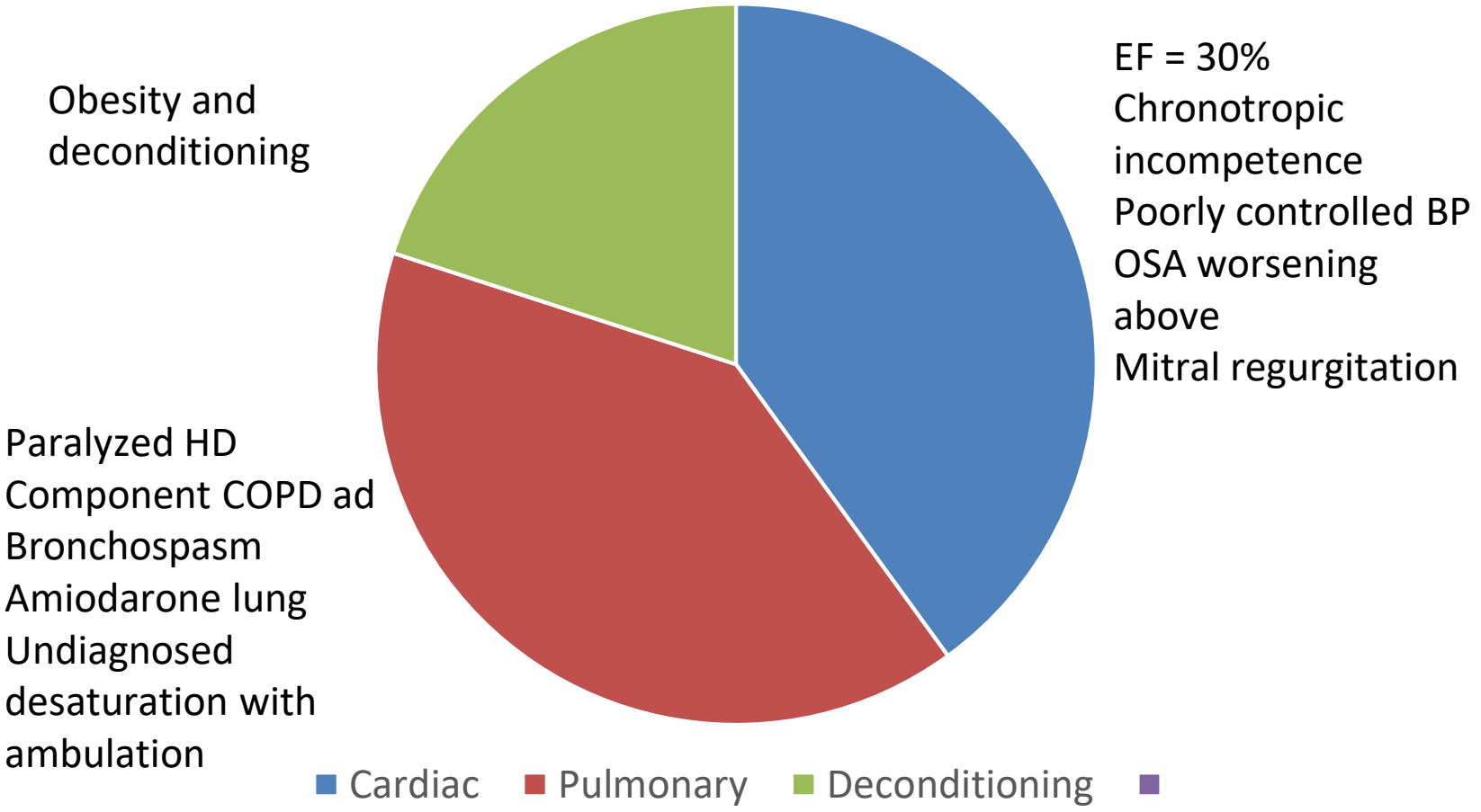
Summary of Workup (Old and New)

- Walks 69 m in 6 minutes , SpO_2 97-> 87%, BORG 2-5, HR 84->96
- Afib with ICD/Pacer, HfREF 30%, Mild MR
- OSA with AHI 35, (58 in REM)
- Combined restrictive and obstructive PFTs with TLC 55%
- Chest CT with evidence amiodarone changes
- V/Q (-) for matched perfusion defects
- Normal TSH, HCO3 , CBC, PO2 = 68 mm Hg
- Abnormal CXR

Abnormal CXR

Abnormal Diaphragm Flourography: “Sniff Test”

Subdivisions of Dyspnea



Case 3: History and Physical

- 52 y/o with approximately 1 year of insidiously increasing SOB. She feels that her heart ”races” when she performs heavier exercise. Denies edema, wheezing, chest pain, weakness.
- No previous cardiopulmonary disease
- PMHx only for Raynaud’s without other rheumatologic manifestations with the exception of pleurisy approximately 9 months ago evaluated by CTPA which was (-)
- Remote 2 pk/year ex-smoker
- Used to powerwalk 2 years ago, now walks more slowly, no more than 1 mile.
- Exam unremarkable except for trace pedal edema

Workup

- Spirometry – normal
- 6 Minute Walk Testing (532m [416 predicted], SpO2 99->96%, HR 60->122, BORG = 0->3, Heart Rate recovery not done.
- Stress testing – RVSP = 42 mm Hg, no wall motion abnormalities, normal LV, LA without evidence diastolic dysfunction
- R and L Heart Cath with simple exercise
  - No CAD
  - PCWP 12
  - Mean PAP = 20 mm Hg
  - Exercise with arm curls Mean PAP = 31 mm Hg, PAOP not done.

CPET

	Rest	AT	Peak VO_2	%Pred
Time	0	3.08	5:57	
Work (Watts)	0	42	98	
Vt (L)	0.55	0.93	1.41	
RR (br/min)	13	21	40	
VE (L/Min)	7.31	19.66	57	50%
Vd/Vt	0.17	0.15	0.12	
VO_2 (ml/kg/min)	2.8	7.5	15	68%
VO_2 (ml/min)	196	523	1038	
VCO_2 (ml/min)	183	523	1461	
RER	0.94	0.96	1.41	
METS	1	2.2	4.3	

	Rest	AT	Peak VO_2	%Pred
Time	0	3.08	5:57	
Work (Watts)	0	42	98	
HR (bpm)	70		163	97%
O_2 Pulse	3	5	7	
VE/VO2	37	38	55	68%
VE/VCO2	40	39	39	
PET O2 (mm Hg)	109	111	122	
PET CO2 (mm Hg)	32	31	29	
SBP	116		150	
DBP	64		90	
SpO2	100%		100%	

Simultaneous hemodynamics during the CPET confirm exercise precapillary pulmonary hypertension consistent with ”Exercise PAH”

	Rest	Peak VO_2
RAP	3	8
PAP (Systolic/Diastolic/Mean)	40/18/25	90/35/53
CO/CI	3.7/2.1	9.3/5.3
PAOP	9	14
HR	70	163
BP	116/64	150/90
SpO_2	100%	100%
SV (ml)f	52	87

PAH Workup Involves an Obligate V/Q Scan

Ventilation

Perfusion

Angiograms

Right

Left

SPECTRAL CT Images

Z- Images

CT Fusion with Spectral Perfusion

Images courtesy A Gupta MD

Diagnosis: Mimic of CTEPH, Sarcoid Related PA Compression -> Exercise PH