PRE-OPERATIVE PULMONARY ASSESSMENT



Gerald Weinhouse, MD
Assistant Professor of Medicine, Harvard Medical School
Associate physician, Brigham and Women's Hospital



Disclosures

• None

- 72 yo male with COPD,CAD, HFpEF
- Pre-op LV aneurysm/thrombus repair/removal. Thrombus "large and mobile".
- FEV1 1.15 -> 1.44 (41%): (25% increase)
- FVC 2.55 -> 3.07 (66%) (20% increase)
- Able to walk > 100 ft and climb a flight of stairs before stopping.
- RVSP 30 + RA

- 50 yo woman with BOS s/p BMT pre-op for resection and RND for SCCA buccal mucosa.
 Procedure anticipated to be 8 hours.
- FEV1 is 0. 45 liters (16%)
- FVC is 1.86 liters (61%)
- Echo without elevated PA pressure

Introduction

 Postoperative pulmonary complications are equally prevalent and contribute similarly to morbidity and mortality compared with cardiac complications.

- Pulmonary complications are:
 - 1. more likely than cardiac complications to predict long-term mortality
 - 2. more costly than the other major postoperative complications including cardiac, thromboembolic and infectious
 - 3. result in the longest length of stay
- Which definition is used determines the prevalence.

Post-operative pulmonary complications

- Atelectasis
- Infection
- Bronchospasm
- Respiratory failure/prolonged mechanical ventilation
- Exacerbation of chronic lung disease

- Definition:
 - Pulmonary abnormality that produces identifiable disease or dysfunction that is:
 - Clinically significant
 - Affects clinical course

RISK STRATIFICATION Non-lung resection surgery

Patient-related issues

- POOR COUGH
- INCREASES ATELECTASIS

Surgery-related issues

WORSE V/Q MATCHING

Upper abdominal surgery, for example, may be associated with reduced vital capacity 50-60%. May be decreased for a week.

RISK ASSESSMENT

Patient-related issues

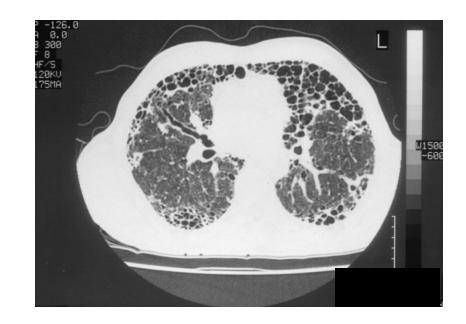
•COPD

- One of the most frequently identified patient-related risk factor
- No prohibitive level of pulmonary function (<u>for non-lung</u> <u>resection surgery</u>)



Other chronic lung disease

- Insufficient data to quantify the risk of restrictive lung diseases
- Abnormal findings on chest exam, however, have been shown in 2 small studies to be predictive of postoperative pulmonary complications



Preoperative Evaluation of Patients With Interstitial Lung Disease

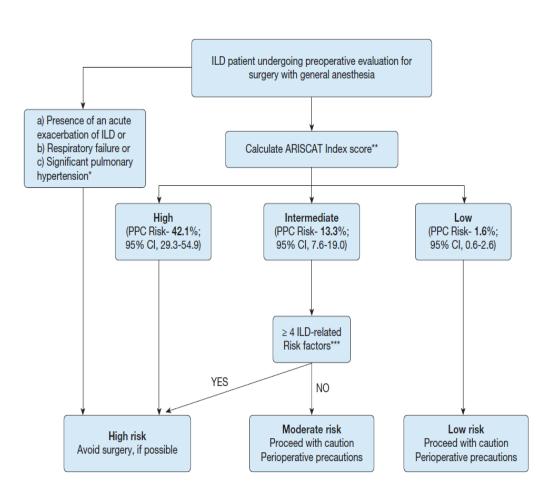
Note: based on published data and expert opinion

Nina M. Patel, MD, FCCP; Tejaswini Kulkami, MD, MPH; Daniel Dilling, MD, FCCP; and Mary Beth Scholand, MD, FCCP; the Interstitial and Diffuse Lung Disease Network Steering Committee*

CHEST 2019; 156(5):826-833

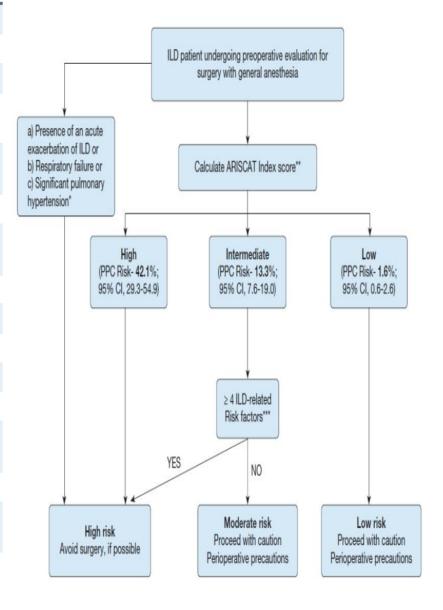
ARISCAT Index

Independent Predictor of PPC Risk	Risk Score		
Age, y			
≤ 50	0		
51-80	3		
> 80	16		
Preoperative Spo ₂ %			
≥ 96	0		
91-95	8		
≤ 90	24		
Respiratory infection in the last month	17		
Preoperative anemia (< 10 g/dL)	11		
Surgical incision site			
Peripheral	0		
Upper abdominal	15		
Intrathoracic	24		
Duration of surgery, h			
≤ 2	0		
> 2 to 3	16		
> 3	23		
Emergency procedure	8		
PPC Risk (Based on Cumulative Score)	ARISCAT Score		
Low risk: 1.6% PPC risk	0-25		
Intermediate risk: 13.3% PPC risk	26-44		
High risk: 42.1% PPC risk	45-123		



Patient- and Procedure-Related Risk Factors for ILD-Related PPCs

Factor	Reference(s)
Patient-related factors	
Male sex	3, 15
DLco < 60% predicted	14, 16, 17
Preoperative home oxygen requirement	18, 19
Presence of acute exacerbation of ILD	13, 20
Pulmonary hypertension ^a	18
Charlson Comorbidity Index score ≥ 2	3
Immunosuppressed status	13, 15
OSA ^b	
Procedure-related factors	
General anesthesia	25, 26
Emergency surgery	1, 3
Longer duration of anesthesia/ longer operative time (> 2 h)	1, 14, 15
Pulmonary/thoracic surgery	1
Open rather than thorascopic surgery	3
Pneumonectomy or lobectomy (vs wedge resection) ^c	14, 15



RISK ASSESSMENT

Patient-related issues

Age

>50 is an independent risk for complications.

>50-59: OR 1.5

≻60-69: OR 2.28

≻70-79: OR 3.9

> or = 80: OR 5.63

• Metabolic:

- Albumin < 3 g/dL
- Blood urea nitrogen > 30 mg/dL

RISK ASSESSMENT Patient-related issues

Smoking

- Increased risk if actively smoking at the time of surgery
- No increased risk if stopped > 6 months
- Smoking cessation of at least four weeks prior to surgery begins to lower the measureable risk but the true benefits may begin earlier.
- There may be a relationship between risk and the amount of smoking.

RISK ASSESSMENT

Patient-related issues

 Functional dependence/ASA class: has been shown to correlate with post-op pulmonary complication.
 ASA class > 2 associated with 4.87 fold increased risk.

Class I: Normally healthy patient

Class II: Patient with mild systemic disease

Class III: Patient with systemic disease that is not

incapacitating

Class IV: Patient with an incapacitating systemic

disease that is a constant threat to life

Class V: Moribund patient not expected to survive for 24 hours

or without an operation

RISK ASSESSMENT Patient-related issues

• Pulmonary hypertension: associated with higher risk postoperatively (CHF, resp failure, dysrhythmia, renal insufficiency, sepsis) regardless of etiology and even in patients with mild-moderate disease.

Risk predictors: h/o PE, NYHA class > or = 2, anesthesia > 3hr

• Congestive heart failure: risk for post-op pulmonary complications is as high or higher then those with COPD (the Goldman risk index predicts postop pulmonary complications).

RISK ASSESSMENT

Patient-related issues

- Obesity
 - No added risk even with morbid obesity

HOWEVER

 Obstructive sleep apnea IS a risk for complications including hypoxemia and unplanned reintubation and possibly pneumonia and respiratory failure.

RISK ASSESSMENT: (NON-LUNG RESECTION)

- Significance controversial:
 - Asthma
 - Well-controlled vs. poorly controlled

Upper respiratory infections

RISK ASSESSMENT: (NON-LUNG RESECTION)

Table 3. Summary Strength of the Evidence for the Association of Patient, Procedure, and Laboratory Factors with Postoperative Pulmonary Complications*

Factor	Strength of Recommendation†	Odds Ratio‡	
Potential patient-related risk factor			
Advanced age	A	2.09-3.04	
ASA class ≥ II	A	2.55-4.87	
CHF	A	2.93	
Functionally dependent	A	1.65-2.51	
COPD	A	1.79	
Weight loss	В	1.62	
Impaired sensorium	В	1.39	
Cigarette use	В	1.26	
Alcohol use	В	1.21	
Abnormal findings on chest examination	В	NA	
Diabetes	C		
Obesity	D		
Asthma	D		
Obstructive sleep apnea	ı		
Corticosteroid use			
HIV infection	İ		
Arrhythmia			
Poor exercise capacity	l		
Aortic aneurysm repair	A	6.90	
Thoracic surgery	A	4.24	
Abdominal surgery	A	3.01	
Upper abdominal surgery	A	2.91	
Neurosurgery	A	2.53	
Prolonged surgery	Α	2.26	
Head and neck surgery	Α	2.21	
Emergency surgery	A	2.21	
Vascular surgery	A	2.10	
General anesthesia	A	1.83	
Perioperative transfusion	В	1.47	
Hip surgery	D		
Gynecologic or urologic surgery	D		
Esophageal surgery	ı		
Esophagear surgery	•		
Laboratory tests			
Albumin level < 35 g/L	A	2.53	
	В	4.81	
Chest radiography			
	В	NA	
Chest radiography	В	NA	

Smetana, G. W. et. al. Ann Intern Med 2006;144:581-595

RISK ASSESSMENT:

Surgery-related issues

Site

• Complications inversely related to distance from incision to diaphragm.

Duration

• < 2 hr/8% vs > 4 hr/40%

Anesthesia

GA > regional/spinal

RISK ASSESSMENT NON-LUNG RESECTION

- History
- Physical exam Labs: albumin, BUN
- Pulmonary function testing?
- Arterial blood gas?
- Chest x-ray?

ACP guidelines

- "Preoperative spirometry and chest radiography should not be used <u>routinely</u> for predicting risk for postoperative pulmonary complications"
- Since publication of the guidelines in 2006, physicians have become more selective in their use of preop PFT's but still are less inclined to adhere to guidelines for chest xray.
 - 20% of preop chest xrays are abnormal but less then 3% influence perioperative management.

RISK ASSESSMENT

• ABG: Not routinely necessary.

pCO2 not an independent predictor of postop pulmonary complications.

Pulmonary Function Test

May have a role in determining cause of dyspnea, suspected COPD, etc. prior to surgery in order to better assess risk and also optimize patients pre-op.

RISK <u>MODIFICATION</u> PRF-OP

Smoking cessation at least 4 weeks (8+ would be better) preop

Optimize the treatment of COPD and asthma.

- Minimize wheezing:
 - Beta-agonists
 - Systemic corticosteroids if persistent wheezes despite usual outpatient meds.

RISK **MODIFICATION**PRE-OP

- Use of perioperative systemic corticosteroids:
 - For asthmatics with wheezing, productive cough, chest tightness, SOB on usual treatment.
 - Peak flow or FEV1 < 80% of their best despite their usual treatment.

RISK **MODIFICATION**PRE-OP

- Use of perioperative antibiotics:
 - If clinically apparent infection
 - ? If bronchiectasis or immunodeficiency

RISK ASSESSMENT INDICES

- Cardiopulmonary risk index
- Lawrence risk index
- Brooks-Brunn risk index
- Multifactorial risk index (Arozullah)
- ARISCAT preoperative risk index

ARISCAT risk index

Post-op pulmonary complications

- Age
 - \bullet < or = 50 (0 pts)
 - 51-80 (3 pts)
 - > 80 (16 pts)
- Preoperative oxygen saturation
 - > or = 96% (0 pts)
 - 91-95% (8 pts)
 - < or = 90% (24 pts)
- Other clinical risk factors
 - Resp infection in the last month (17 pts)
 - Preop anemia with Hgb < or = 10 g/dl (11 pts)
 - Emergency surgery (8 pts)

- Surgical incision
 - Upper abd (15 pts)
 - Intrathoracic (24 pt)
- Duration of surgery
 - < or = 2 hr (0 pts)
 - 2-3 hr (16 pt)
 - > 3 hr (23 pt)

• 0-25 pt: Low risk (1.6%)

• 26-44 pt: Intermediate (13.3 %)

• 45-123 pt: High risk (42%)

Multifactorial risk index: Predicting postop <u>pneumonia</u> after major noncardiac surgery

Preoperative Risk Factor	Point Value	
Type of surgery		
Abdominal aortic aneurysm repair	15	
Thoracic	14	
Upper abdominal	10	
Neck	8	< or = 15 points: risk = < 0.3%
Neurosurgery	8	101 10 points: 1101x 10.070
Vascular	3	> or = 55 points: risk = $16%$
Age		/ 01 - 33 points: 11sk - 10/0
≥80 y	17	
70–79 y	13	
60-69 y	9	
50-59 y	4	
Functional status		
Totally dependent	10	
Partially dependent	6	
Weight loss > 10% in past 6 months	7	
History of chronic obstructive pulmonary disease	5	
General anesthesia	4	
Impaired sensorium	4	
History of cerebrovascular accident	4	
Blood urea nitrogen level		
<2.86 mmol/L (<8 mg/dL)	4	
7.85-10.7 mmol/L (22-30 mg/dL)	2	
≥10.7 mmol/L (≥30 mg/dL)	3	
Transfusion > 4 units	3	
Emergency surgery	3	
Steroid use for chronic condition	3	
Current smoker within 1 year	3	Arozullah et al. Ann Intern Med 2001;135:847-857
Alcohol intake > 2 drinks/d in past 2 weeks	2	11102ullali ci al. Allii Illicili Mcu 2001,133.047-037
-		

Multifactorial risk index: Predicting postop <u>respiratory failure</u> after major noncardiac surgery

RESPIRATORY FAILURE RISK INDEX

Preoperative Predictor	Point Value
Type of surgery	
Abdominal aortic aneurysm	27
Thoracic	21
Neurosurgery, upper abdominal, or peripheral vascular	14
Neck	11
Emergency surgery	11
Albumin (<30 g/L)	9
Blood urea nitrogen (>30 mg/dL)	8
Partially or fully dependent functional status	7
History of chronic obstructive pulmonary disease Age (years)	6
≥70	6
60–69	4

RESPIRATORY FAILURE RISK INDEX SCORES FOR PHASE I AND PHASE II PATIENTS

Class	Point Total	n (%);*	Predicted Probability of PRF	Phase I (% RF)	Phase II (% RF)	
1	≤10	39,567 (48%)	0.5%	0.5%	0.5%	
2	11-19	18,809 (23%)	2.2%	2.1%	1.8%	
3	20-27	13,865 (17%)	5.0%	5.3%	4.2%	
4	28-40	7,976 (10%)	11.6%	11.9%	10.1%	
5	>40	1,502 (2%)	30.5%	30.9%	26.6%	

Arozullah, et al. Ann Surg. 2000; 232(2): 242–253.

PRF, postoperative respiratory failure.
* Number of phase I subjects in each risk class.

Canet risk index

Table 1. Definitions of Postoperative Pulmonary Complications

Complication	Definition
Respiratory infection	When a patient received antibiotics for a suspected respiratory infection and met at least one of the following criteria ^{4,9,10} : new or changed sputum, new or changed lung opacities, fever, leukocyte count >12,000/μ
Respiratory failure	When postoperative Pao ₂ <60 mmHg on room air, a ratio of Pao ₂ to inspired oxygen fraction <300 or arterial oxyhemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy
Pleural effusion	Chest x-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved
Atelectasis	vascular shadows ¹¹ Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung ^{12,13}
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura ¹⁴
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents ¹⁵

Table 6. Independent Predictors of Risk for PPCs Identified in the Logistic Regression Model

Multivariate Analysis OR (95% CI) n = 1,624*	eta Coefficient	Risk Score†
1		
1.4 (0.6–3.3)	0.331	3
	1.619	16
,		
1		
2.2 (1.2-4.2)	0.802	8
10.7 (4.1–28.1)	2.375	24
5.5 (2.6-11.5)	1.698	17
3.0 (1.4–6.5)	1.105	11
4.4 (2.3–8.5)	1.480	15
11.4 (4.9–26.0)	2.431	24
•	1 500	10
		16 23
,		23 8
2.2 (1.0-4.5)	0.766	
	Analysis OR (95% CI) n = 1,624* 1 1.4 (0.6-3.3) 5.1 (1.9-13.3) 1 2.2 (1.2-4.2) 10.7 (4.1-28.1) 5.5 (2.6-11.5)	Analysis OR (95% CI) β Coefficient 1 1.4 (0.6–3.3) 0.331 5.1 (1.9–13.3) 1.619 1 2.2 (1.2–4.2) 0.802 10.7 (4.1–28.1) 2.375 5.5 (2.6–11.5) 1.698 3.0 (1.4–6.5) 1.105 1 4.4 (2.3–8.5) 1.480 11.4 (4.9–26.0) 2.431 1 4.9 (2.4–10.1) 1.593 9.7 (4.7–19.9) 2.268

^{*} Because of a missing value for some variables, three patients were excluded. Logistic regression model constructed with the development subsample, c-index = 0.90; Hosmer-Lemeshow chi-square test = 7.862; P=0.447. † The simplified risk score was the sum of each β logistic regression coefficient multiplied by 10, after rounding off its value.

 $CI = confidence interval; OR = odds ratio; PPC = postoperative pulmonary complications; <math>Spo_2 = oxyhemoglobin saturation by pulse oximetry breathing air in supine position.$

Table 7. PPC Risk Score: Distribution of Patients and Rates by Intervals

		Risk Score Intervals*	
	Low Risk <26 Points	Intermediate Risk 26–44 Points	High Risk ≥45 Points
Development subsample, No. (%) of patients†	1,238 (76.2)	288 (17.7)	98 (6.0)
Validation subsample, No. (%) of patients	645 (77.1)	135 (16.1)	57 (6.8)
PPC rate, development subsample, % (95% CI)	0.7 (0.2-1.2)	6.3 (3.5-9.1)	44.9 (35.1-54.7)
PPC rate, validation subsample, % (95% CI)	1.6 (0.6–2.6)	13.3 (7.6–19.0)	42.1 (29.3–54.9)

- 50 yo woman with BOS s/p BMT for resection and RND for SCCA buccal mucosa. Procedure anticipated to be 8 hours.
- FEV1 is 0. 45 liters (16%)
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- FVC 2.55 -> 3.07 (66%) (20% increase)
- Able to walk > 100 ft and climb a flight of stairs before stopping.
- RVSP 30 + RA

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EVALUATION FOR LUNG RESECTION



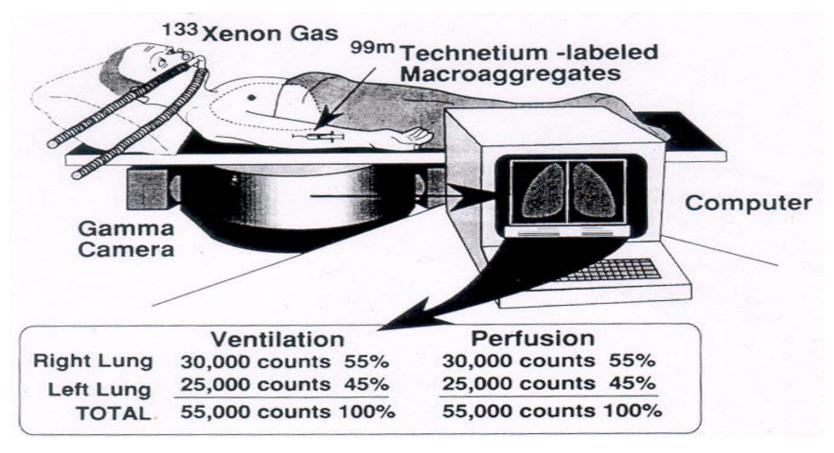
EVALUATION FOR LUNG RESECTION

- All patients undergoing lung resection need pulmonary function studies (FEV1 and DLCO)!
 - FEV1 < 60% strongest predictor of postop complication

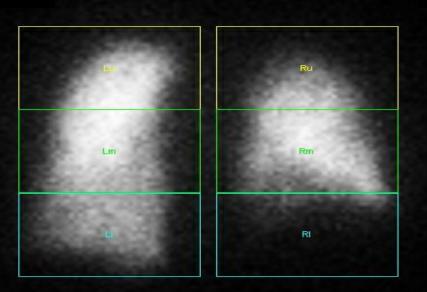
EVALUATION FOR LUNG RESECTION

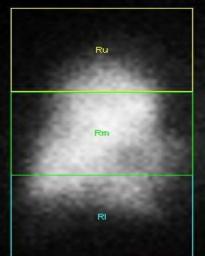
- BTS guidelines:
 - FEV₁ > 2 liters (or >80% predicted) adequate for pneumonectomy
 - FEV₁ > 1.5 liters adequate for lobectomy
- ACCP: focus on predicted postoperative values.

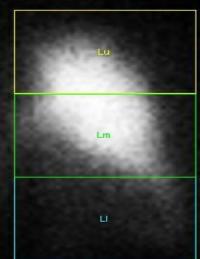
PREDICTING POSTOPERATIVE PULMONARY FUNCTION



Quantitative ventilation-perfusion scan







2/20/2012 VQ QUANT ANT - POST POST Perf Quant. 2/20/2012 VQ QUANT ANT - POST ANT Perf Quant.

Posterior Kct			Geometric Mean Kct			Anterior Kct						
	Left		Right		Left Lung		Right Lung		Right		Left	
	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct	%	Kct
Upper Zone:	18.7	62.86	11.1	37.26	18.2	60.07	9.8	32.42	8.4	28.21	17.0	57.40
Middle Zone:	25.9	86.94	25.2	84.82	27.4	90.44	27.9	92.10	29.6	100.01	27.9	94.08
Lower Zone:	14.3	47.90	4.8	16.27	9.1	30.17	7.6	25.23	11.6	39.11	5.6	19.00
Total Lung:	58.8	197.70	41.2	138.35	54.7	180.68	45.3	149.75	49.5	167.34	50.5	170.48

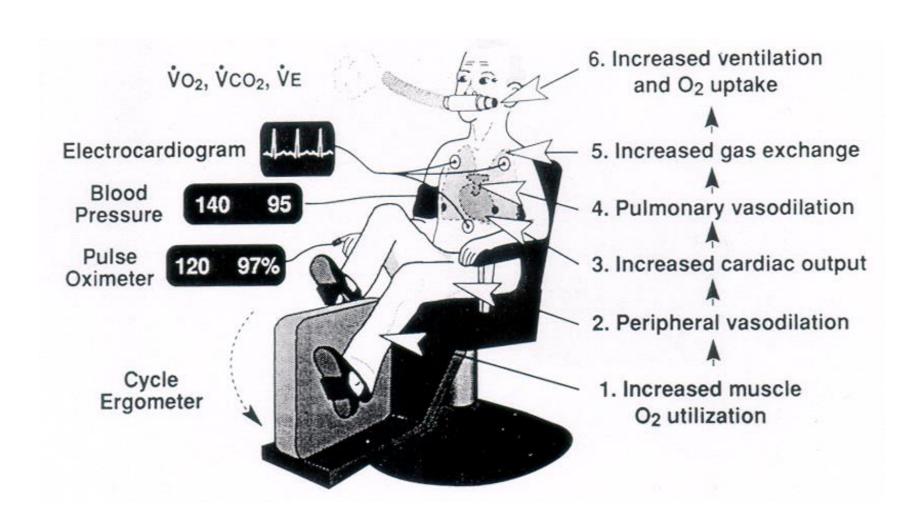
PRE-OP QUANTITATIVE VENTILATION/PERFUSION SCAN

Predicted post-op FEV1=
 pre-op FEV1 x (1 – fraction of total perfusion in the resected lung).

ACCP:

- If either PPO FEV1 or PPO DLCO is < 60% but both are > 30%, recommend exercise testing (stair climbing for example).
- If either PPO FEV1 or PPO DLCO is < 30%, recommend a cardiopulmonary exercise test.

CARDIOPULMONARY EXERCISE TESTING



PRE-OP EXERCISE TESTING IN LUNG RESECTION SURGERY

- VO2max > 20 ml/kg/min suitable for surgery with "acceptable" morbidity and mortality.
- VO2 < 10 ml/kg/min appear to be at high risk of perioperative complication and death

Those between 10-20 ml/kg/min are at higher risk; all other factors including the predicted post-op values taken into account and the higher risk discussed with patient.

POST-OP RISK MODIFICATION

- Secretion clearance/lung expansion strategies are the only therapies proven to reduce post operative pulmonary complications. Implicit and necessary to this strategy is good pain control.
 - Deep breathing = incentive spirometry
 - Intermittent positive pressure breathing (IPPB) vs continuous positive airway pressure (CPAP)

Strength of the Evidence for Specific Interventions To Reduce the Risk for Postoperative Pulmonary Complications

Table 4. Strength of the Evidence for Specific Interventions To Reduce the Risk for Postoperative Pulmonary Complications

Risk Reduction Strategy	Strength of Evidence*	Type of Complication Studied
Postoperative lung expansion modalities	A	Atelectasis, pneumonia, bronchitis, severe hypoxemia
Selective postoperative nasogastric decompression	В	Atelectasis, pneumonia, aspiration
Short-acting neuromuscular blockade	В	Atelectasis, pneumonia
Laparoscopic (vs. open) operation	C	Spirometry, atelectasis, pneumonia, overall respiratory complications
Smoking cessation		Postoperative ventilator support
Intraoperative neuraxial blockade	_ 1	Pneumonia, postoperative hypoxia, respiratory failure
Postoperative epidural analgesia	1	Atelectasis, pneumonia, respiratory failure
Immunonutrition	1	Overall infectious complications, pneumonia, respiratory failure
Routine total parenteral or enteral nutrition†	D	Atelectasis, pneumonia, empyema, respiratory failure
Right-heart catheterization	D	Pneumonia

^{*} Definitions for categories of strength of evidence, modified from the U.S. Preventive Services Task Force categories (11). A = good evidence that the strategy reduces postoperative pulmonary complications and benefit outweighs harm; B = at least fair evidence that the strategy reduces postoperative pulmonary complications and benefit outweighs harm; C = at least fair evidence that the strategy may reduce postoperative pulmonary complications, but the balance between benefit and harm is too close to justify a general recommendation; D = at least fair evidence that the strategy does not reduce postoperative pulmonary complications or harm outweighs benefit; I = evidence of effectiveness of the strategy to reduce postoperative pulmonary complications is conflicting, of poor quality, lacking, or insufficient or the balance between benefit and harm cannot be determined.

[†] Evidence remains uncertain (strength of evidence I) on total parenteral or enteral nutrition for severely malnourished patients or when a protracted time of inadequate nutritional intake is anticipated.

POST-OP RISK MODIFICATION

- Pain control:
 - Epidural vs systemic opioids
- NG tubes not for routine use; only as necessary case-by-case

SUMMARY: PRE-OP

- Smoking cessation
- Appropriate/optimal treatment for COPD, asthma.
- Steroids if not optimally managed airway disease, especially if actively wheezing
- If respiratory infection, begin antibiotics, delay elective surgery

SUMMARY: INTRA-OP

- Short duration better then long
- Laparoscopic better then open
- Regional better then general anesthesia
- PA catheters don't help

SUMMARY: POST-OP

- Lung expansion maneuvers the only proven strategy:
 - Early mobilization or incentive spirometry

- A 75 yr old man is referred for a pre-operative evaluation in preparation for surgery to repair a 6.4 cm aortic aneurysm. He is a former smoker in the remote past and is known to have COPD/chronic bronchitis with an FEV₁ of 42% predicted. He has daily sputum production with a cough. He uses tiotropium and an inhaled corticosteroid daily.
- On exam you find him to be comfortable at rest with an O₂ saturation 94%. His breath sounds are clear but symmetrically diminished bilaterally.
- What should you tell his surgeon?

- A. He is a high risk patient for post-operative pulmonary complications and should be give peri-operative systemic corticosteroids.
- B. He is a high risk patient but his surgery is low risk so he should do fine.
- C. He is a high risk patient and should have aggressive postoperative lung expansion treatments to prevent complications.
- D. He is too high a risk and should not have surgery.
- E. Not enough information; need an arterial blood gas to adequately judge his risk.

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- E. Not enough information; need an arterial blood gas to adequately judge his risk.

- You are asked to evaluate a 57 yo woman with lung cancer who is undergoing concurrent chemotherapy and radiation therapy prior to resection of the tumor. It is anticipated she will need a left upper lobe resection. Her pre-op FEV₁ is 1.4 liters (55% predicted) and her diffusion capacity is 50% predicted.
- She undergoes a quantitative ventilation / perfusion scan which reveals that 40% of ventilation and perfusion goes to the left lung but only 15% of ventilation and 10% of perfusion goes to the left upper lobe.
- Which statement is true about this patient?

- A. Her post-op predicted FEV₁ and diffusion capacity will be too low to justify the risk of the surgery.
- B. She should have repeat pulmonary function testing after she stops smoking.
 - C. She should be scheduled for an exercise test to help determine if surgery is advisable.
- D. She is a high risk patient being considered for high risk surgery; palliative care should be offered instead.
- E. Surgery should only be offered if it can be done by videoassisted thoracoscopy.

References

- Ann Intern Med 2006;144:581-595
- BMJ 2000;321:1493
- Ann Intern Med 2006;144:575-80
- Anesthesiology 2010;113:1338
- JAMA Intern Med 2015;175:1352-9.