

EDITORIAL

Integration of Clinical Findings and Physiology in Respiratory Disease

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Received: October 5, 2015

Revised: November 13, 2015

Accepted: November 17, 2015

Published online: December 28, 2015

ABSTRACT

Respiratory diseases have broad category from allergic disease to diffuse lung diseases. In approach for these diseases, we should collect many useful clinical information with physiological, imaging, and pathological point of view. Using focused clinical approach and physiological thinking will contribute to arrive adequate diagnosis with imaging and pathology. I show integrated approach of clinical findings and physiology for representative respiratory diseases such as community acquired pneumonia, chronic obstructive lung disease, bronchial asthma and interstitial lung disease.

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Key words: Integration, detailed history, physical findings, physiology, dyspnea

Kishaba T. Integration of Clinical Findings and Physiology in Respiratory Disease. *Journal of Respiratory Research* 2015; 1(1): 1-4 Available from: URL: <http://www.ghrnet.org/index.php/jrr/article/view/1408>

Abbreviation

FVC: forced vital capacity; DLco: Diffusing capacity of the lung for carbon monoxide; 6MWT: 6 minute walking test distance; 6MWT; mMRC: modified Medical Research Council.

EDITORIAL

Diagnosis and management of respiratory disease is based on detailed history, physical examination and physiology. However, there are scarce reports about integration of clinical information and physiological findings.

I describe practical approach for common respiratory diseases using clinical findings and physiological data.

First, I show approach for community acquired pneumonia. In history taking, clinical course is most crucial. I divide into three courses such as acute, subacute and chronic. These clinical scenario is associated with likely infection. For example, representative acute pneumonia are pneumococcus, Klebsiella, Legionella, influenza virus and aspiration pneumonia^[1]. Subacute community acquired pneumonia are Hemophilus influenzae, Moraxella catarrhalis and mycoplasma pneumonia (Table 1)^[2].

If we see chronic pneumonia, important differential diagnosis are tuberculosis, lung abscess and actinomycosis.

In terms of physical examination, oral hygiene contribute to respiratory infection especially anaerobic infection such as aspiration pneumonia, lung abscess and empyema^[3]. Lung auscultation provide useful information for physician. When we hear pan-inspiratory crackles, our priority diagnosis is typical pneumonia with non segmental distribution such as pneumococcal pneumonia and Klebsiella pneumonia. On the other hand, if we hear late inspiratory crackles, we usually consider atypical agent such as mycoplasma, legionella or viral pneumonia^[4]. Extra-pulmonary symptoms such as joint pain, muscle ache and rash reminds us about mycoplasma and viral infection^[5].

Regarding physiology of respiratory infection, chest echo is recent useful tool. It clarifies definite pleural effusion with internal structure^[6]. When we see patients who has persistent fever with adequate antibiotics, one of the differential diagnosis is parapneumonic effusion. With echo, I recommend thoracentesis if free fluid is over 2 cm and fibrin like material within fluid suggest

empyema.

In laboratory findings, WBC and CRP are main items^[7]. We should watch trend of these data. Both inflammatory markers with vital signs and physical findings have positive relationship. Recently, utility of procalcitonin (PCT) have been reported. It has high sensitivity. However, distinction of bacterial infection and non-bacterial infection such as viral infection is moderate^[8]. After using antibiotics, decrease trajectory of inflammatory markers usually means clinical success.

Second, we show approach for obstructive disease such as bronchial asthma and chronic obstructive pulmonary disease (COPD). On history taking, most important symptoms are progressive exertional dyspnea and cough^[9]. In social history, smoking and occupation are essential^[10]. In phenotype of COPD, I divide into emphysema dominant type or chronic bronchitis. The meaning of classifying these two types are different clinical presentation^[11]. Emphysema dominant type have thin and more dyspnea with preserved arterial blood gas value^[12]. On the contrary, chronic bronchitis patients are more obese, and report, less dyspnea and more hypoxemia (Table 2).

In terms of physical examination, general appearance is crucial. Therefore, COPD patients show distress especially in acute phase. Palpebral conjunctiva are generally congested because of polycythemia due to chronic hypoxemia. Neck has much information of chronic respiratory diseases. COPD patients show hypertrophy of sterno-cleido muscles because of dysfunction of diaphragm and impairment of inspiratory muscle activity. Percussion of lung reveal more tympanic. Lung auscultation of COPD patients typically show distant or early crackles, and early-to-mid inspiratory crackles^[13]. These sound correspond to hyperinflation, severe air-trapping and chronic inflammation of more central airways. In peripheral muscle, pigmentation of distal part of quadriceps muscles is called thinker's sign and this means chronic lean forward posture of patients^[14]. Facial and leg edema is associated with cor pulmonale or chronic hypercapnia. Hypercapnia play a role for absorption of free water accompanied with bicarbonate from proximal renal tubule^[15]. In addition, ankle edema have relationship with pulmonary hypertension (PH) especially in COPD patients.

Regarding physiology of COPD, most important tool for diagnosis of COPD is pulmonary function test (PFT). Key issue is under 0.70 of ratio of forced expiratory volume in one second (FEV1)/forced vital capacity (FVC). Next step is evaluation of severity. It is based on the Global Initiative for chronic obstructive pulmonary disease (GOLD) staging^[16]. They propose four stages according to the percent predicted FEV1. All these values are obtained after bronchodilator. And inspiratory capacity (IC) is crucial surrogate index for severity of air-trapping. In management point of view, long acting bronchodilator is effective for increase of IC. Besides, if ratio of IC/total lung capacity (TLC) is under 25%, it predicts poor prognosis^[17]. Needle to say, body weight loss also have relationship with worse prognosis^[18].

In laboratory findings, there are some reports that fibrinogen and surfactant protein D (SP-D) are associated with acute exacerbation of COPD^[19].

Third, I describe approach for bronchial asthma. On history taking, cardinal symptoms are wheezy dyspnea, cough and chest tightness^[20]. In terms of asthma on set, age of 12 is important^[21]. Before 12, childhood asthma is likely and usually associated with atopy and environmental factors. After 12, adult on set asthma is possible, obesity and chronic sinusitis contribute (Table 3)

In terms of physical examination, orthopnea is significant in asthma

Table 1 Respiratory Infection based on clinical scenario.

Clinical course		Possible Infection
Acute	Within one week	Pneumococcus
		Klebsiella
		Legionellosis
		Influenza virus
		Aspiration
Subacute	A couple of weeks	Haemophilus Influenzae
		Moraxella catarrhalis
		Mycoplasma
Chronic	Over one month	Tuberculosis
		Lung abscess
		Actinomycosis

Table 2 Phenotype of COPD.

	Body shape	Dyspnea	Edema	Blood gas
Emphysema	Thin	More dyspnea	Less often	Preserved
Chronic bronchitis	Obese	Less dyspnea	More often	More hypoxemia

Table 3 Disease type of bronchial asthma.

	Atopy	Environment	Obesity	Smoking	ENT disease
Childhood	Yes	More often	No	No	No
Adult	No	Usual	Yes	Yes	Yes

Table 4 Useful marker and signs of ILD.

	Physical Findings	Physiology
Baseline	Clubbing	%FVC
	Heliotrope Rash	%DLco
	Gottron sign	6MWT
	Mechanic hand	
Trend	mMRC	%FVC
	breathlessness	%DLco
	scale	%KCO
	Extent of fine crackles	6MWT

attack. Jugular vein show variable dilatation accompanied with respiration.

In short, jugular vein show more distention in expiratory phase. On the other hand, jugular vein show more collapse in inspiratory phase. Lung auscultation of asthma patients typically show polyphonic wheezes expiratory or both phases^[22]. In status asthmatics, auscultation demonstrates silent because of severe air flow limitation. In extremities, edema is absent and this is important differential point from congestive heart failure.

Regarding physiology of asthma, one of the important item is airway reversibility in PFT. However, over half of the COPD patients also show reversibility. Therefore, comprehensive approach is crucial for secure diagnosis of asthma.

In laboratory findings, evaluation of absolute value of peripheral eosinophils and IgE are important for allergic status^[23]. If significant eosinophilia or marked elevation of IgE is identified, we should consider allergic broncho-pulmonary aspergillosis (ABPA) or eosinophilic granulomatosis with polyangiitis (EGPA). Exhaled nitric oxide (eNO) is useful marker of eosinophilic airway inflammation^[24]. If over 35 ppm of eNO, inhaled corticosteroid (ICS) is recommended to relief eosinophilic airway inflammation. Smoking usually decrease the value of eNO.

Finally, I describe approach for interstitial lung disease (ILD). On history taking, progressive exertional dyspnea and non-productive cough are main symptoms^[25]. Modified medical research council (mMRC) breathlessness scale are often used for evaluation of chronic

dyspnea^[26]. Trend of these symptoms reflect for disease activity. For example, stable FVC is linked with small change of dyspnea. And significant decline of FVC is usually associated with worse dyspnea.^[27] In addition, cough predicts of prognosis of ILD^[28]. Therefore, when we see intractable cough, it is quite important for distinction of ILD itself from infection, gastro-esophageal reflux disease (GERD) and lung cancer^[29].

In terms of physical examination, detailed examination is required. Among the ILD patients, many candidate diseases can be listed such as connective tissue disease(CTD),vasculitis and sarcoidosis^[30]. Therefore, detection of extrapulmonary findings is key issue. Scalene muscle hypertrophy means chronic moderate to severe restrictive disorder^[31]. Lung auscultation usually show bilateral fine crackles at lung base^[32]. If lung sound is normal with diffuse nodular shadow, we should consider any granulomatous diseases such as sarcoidosis, hypersensitivity pneumonitis (HP) and occupational lung diseases. In heart examination, elevation of S2 and pansystolic murmur at parasternal area suggest PH. If accentuation of pansystolic murmur is reproduced when inspiratory phase, tricuspid valve regurgitant murmur is most likely. In addition, parasternal lift is confirmed, the patient's systolic pulmonary arterial pressure (PAP) may be over 50mmHg.

In extremities, clubbing is most crucial finding which means chronicity of lung disease. Among the diffuse lung diseases, idiopathic pulmonary fibrosis (IPF) and Rheumatoid arthritis (RA) associated ILD more often show clubbing^[33]. COPD and tuberculosis (TB) rarely have clubbing. In addition, heliotrope rash and Gottron's sign are careful findings. Because these findings with ILD suggest amyopathic dermatomyositis (ADM) associated ILD which often have relentless course such as progressive respiratory failure^[34]. On the contrary, mechanic hand and proximal muscle ache are associated with anti-Aminoacyl tRNA synthetase (Anti-ARS) syndrome which usually show good response to systemic steroid and good survival^[35]. Therefore, detection of specific findings in ILD patients is important for management and prediction of clinical course. And if we see palpable purpura and systemic symptoms such as fever, vasculitis such as Myeloperoxidase Anti-neutrophil cytoplasmic antibody (MPO-ANCA) associated disease is possible.

Physiological point of view, FVC is most important surrogate marker for prediction of clinical course in ILD^[36]. Over 10% decline of percent FVC(%FVC) within one year is related with worse survival. In IPF patients, over 5% decline of %FVC within three months predicts of short-term mortality^[37]. Diffusing capacity of the lung for carbon monoxide (DLco) is rather sensitive parameter of activity of ILD especially early phase. And over 15% decline of percent DLco (%DLco) is associated with poor prognosis. (Table 4) However, if vital capacity of patient is less than 1500ml, we usually cannot evaluate DLco precisely in single breath method. And DLco is sometimes affected by respiratory infection. Therefore, FVC is more reproducible, reliable and robust physiological marker than DLco. When we see combined pulmonary fibrosis and emphysema (CPFE) patients, FVC are preserved^[38]. Therefore, I recommend to use composite physiological index(CPI) when we evaluate disease activity of CPFE^[39]. Besides, DLco/alveolar volume (KCO) is useful indicator. Over 15% decline of KCO is important threshold for PH prediction^[40]. In systemic sclerosis (SSc) associated ILD patients, %FVC/%DLco over 1.6 means existence of PH^[41].

6 minute walking test distance (6MWTd) is classic useful physiological test for chronic lung disease. In IPF patients, over 25 m decline of 6MWTd within 6 months predicts short-term mortality^[42].

And heart rate recovery after one minute (HRR1) after 6MWT is crucial parameter. If less than 13 of HRR1 is associated with poor prognosis of ILD^[43].

In laboratory findings, Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) are most useful biomarker for ILD. KL-6 is sensitive for prediction of disease activity and usually associated with extent of fibrosis. And over > 1000 is related with acute exacerbation (AE) of CPFE^[44]. And if seasonal variation of KL-6 is shown, chronic hypersensitivity pneumonitis (CHP) is possible^[45]. Marked elevation of KL-6 is associated with NSIP, CHP and pulmonary alveolar proteinosis (PAP)^[46]. On the other hand, SP-D is sensitive marker of more acute or subacute ILD such as acute eosinophilic pneumonia (AEP) and organizing pneumonia (OP). And SP-D have negative associated with VC and positive relationship with ground glass opacity (GGO) in high resolution computed tomography (HRCT) of the chest^[47].

In conclusion, approach for respiratory diseases require both clinical and physiological viewpoints. It will lead to adequate evaluation of imaging and pathology.

CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

REFERENCES

1. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44: Suppl 2: S27-S72.
2. File TM Jr, Marrie TJ. Does empiric therapy for atypical pathogens improve outcomes for patients with CAP? *Infect Dis Clin North Am* 2013; 27: 99-114.
3. Fukuyama H, Yamashiro S, Tamaki H, et al. A prospective comparison of nursing and healthcare-associated pneumonia (NHCAP) with community-acquired pneumonia (CAP) *J Infect Chemother* 2013 Aug;19(4): 719-26.
4. Norisue Y, Tokuda Y, Kiozumi M, et al. Phasic characteristics of inspiratory crackles of bacterial and atypical pneumonia. *Postgrad. Med. J* 2008;84: 423-436.
5. Elena Prina, Otavio T Ranzani, Antoni Torres. Community-acquired pneumonia. *Lancet* 2015;386:1097-1108.
6. Chavez MA, Shams N, Ellington LE, et al. Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. *Respir Res* 2014; 15:50.
7. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008; 121: 219-25.
8. Aabenhus R, Jensen JU, Jrgensen KJ, et al. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014; 11: CD010130.
9. Bartolome R, Celli, Marc Decramer, Jadwiga A. Wedzicha, et al. An Official American Thoracic Society/European Respiratory Society Statement: Research Questions in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015;191(7):e4-e27.
10. Rostron BL, Chang CM, Pechacek TF. Estimation of cigarette smoking attributable morbidity in the United States. *JAMA Intern Med* 2014;174:1922-1928.
11. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347-365.
12. Bettoncelli G. Errata Corrige: The clinical and integrated man-

- agement of COPD. *Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31(2):3753.
13. Abraham Bohadana, Gabriel Izbicki, Steve S.Kraman. Fundamentals of Lung Auscultation. *New Engl J Med* 2014;370:744-51.
14. Sandeep M. Patel, Jay H. Ryu, H. Sekiguchi. Thinker's Sign. *Intern Med* 2011;50:2867-2868.
15. Hemlin M, Ljungman S, Carlson J, et al. The effects of hypoxia and hypercapnia on renal and heart function, haemodynamics and plasma hormone levels in stable COPD patients. *Clin Respir J* 2007 Dec;1(2):80-90.
16. U.S. Preventive Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry: U.S. Preventive Services TaskForce recommendation statement. *Ann Intern Med* 2008;148:529-534.
17. French A, Balfe D, Mirocha JM,et al. The inspiratory capacity/total lung capacity ratio as a predictor of survival in an emphysematous phenotype of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015; 10:1305-12.
18. Shan X, Liu J, Luo Y, et al. Relationship between nutritional risk and exercise capacity in severe chronic obstructive pulmonary disease in male patients. *Int J Chron Obstruct Pulmon Dis* 2015; 10:1207-12.
19. Mannino DM, Tal-Singer R, Lomas DA,et al. Plasma Fibrinogen as a Biomarker for Mortality and Hospitalized Exacerbations in People with COPD. *Chronic Obstr Pulm Dis (Miami)* 2015; 2(1):23-34.
20. Reddel HK, Bateman ED, Becker A,et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;46(3):622-39.
21. MooreWC,MeyersDA, Wenzel SE, et al.; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-323.
22. Gavriely N, Shee TR, Cugell DW,Grotberg JB. Flutter in flow-limited collapsible tubes: a mechanism for generation of wheezes. *J Appl Physiol* (1985)1989; 66:2251-61.
23. Mathur SK, Schwantes EA, Jarjour NN, et al. Age-related changes in eosinophil function in human subjects. *Chest* 2008; 133:412-419.
24. Chiappori A, De Ferrari L, Folli C,et al. Biomarkers and severe asthma: a critical appraisal. *Clin Mol Allergy* 2015; 13:20.
25. Ganesh Raghu, Harold R. Collard, Jim J. Egan,et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* 2-12;183:788-824.
26. Holland AE, Fiore JF Jr, Bell EC,et al. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology*. 2014; 19(8):1215-21.
27. Roland du Bois, Weycker D, Albera C,et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 2011; 184(12):1382-9.
28. Ryerson CJ, Abbritti M, Ley B, et al.Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology* 2011; 16 (6): 969-75.
29. Fahim A, Dettmar PW, Morice AH, Hart SP. Gastroesophageal reflux and idiopathic pulmonary fibrosis: a prospective study. *Medicina(Kaunas)* 2011; 47 (4): 200-5.
30. William D. Travis, Ulrich Costabel, David M. Hansell,et al. An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013;188(6):733-748.
31. Kishaba T Practical management of Idiopathic Pulmonary Fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32(2):90-98.
32. Bando M, Sugiyama Y, Azuma A,et al. A prospective survey of idiopathic interstitial pneumonias in a web registry in Japan. *Respir Investig* 2015;53(2):51-9.
33. Cai M, Zhu M, Ban C,et al. Clinical features and outcomes of 210 patients with idiopathic pulmonary fibrosis.*Chin Med J (Engl)* 2014;127(10):1868-73.
34. Fujisawa T, Hozumi H, Kono M, et al. Prognostic Factors for Myositis-Associated Interstitial Lung Disease. *Plos One* 2014; 9(6):e98824.
35. Takato H, Waseda Y, Watanabe S,et al. Pulmonary manifestations of anti-ARS antibody positive interstitial pneumonia--with or without PM/DM.*Respir Med* 2013; 107(1):128-33.
36. Banu A. Karimi-Shah, Badrul A. Chowdhury Forced Vital Capacity in Idiopathic Pulmonary Fibrosis —FDA Review of Pirfenidone and Nintedanib. *New Engl J Med* 2015; 372(13):1189-1191.
37. Taniguchi H, Kondoh Y, Ebina M, et al. The clinical significance of 5% change in vital capacity in patients with idiopathic pulmonary fibrosis: extended analysis of the pirfenidone trial. *Respir Res* 2011; 12:93.
38. Matthew D. Jankowich, Sharon I. S. Rounds. Combined Pulmonary Fibrosis and Emphysema Syndrome: A Review. *Chest* 2012;141:222-231.
39. Wells AU, Desai SR, Rubens MB,et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003; 167(7):962-9.
40. Moore OA, Proudman SM, Goh N,et al. Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease. *Clin Exp Rheumatol* 2015; 33(4 Suppl 91):S111-6.
41. HSU VM, Moreyra AE, Wilson AC,et al. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. *J Rheumatol* 2008; 35(3): 458-65.
42. Roland M. du Bois, Derek Weycker, Carlo Albera,et al. Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis. Test Validation and Minimal Clinically Important Difference. *Am J Respir Crit Care Med* 2011;183:1231-1237.
43. Swigris JJ, Swick J, Wamboldt FS, et al. Heart rate recovery after 6-min walk test predicts survival in patients with idiopathic pulmonary fibrosis. *Chest*. 2009; 136(3):841-8.
44. Kishaba T, Shimaoka Y, Fukuyama H, et al. A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema. *BMJ Open* 2012; 2(3). pii: e000988.
45. Okamoto T, Tsutsui T, Suhara K,et al. Seasonal variation of serum KL-6 and SP-D levels in bird-related hypersensitivity pneumonitis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 31(4):364-367.
46. Bonella F, Ohshimo S, Miaotian C, et al. Serum KL-6 is a predictor of outcome in pulmonary alveolar proteinosis. *Orphanet J Rare Dis* 2013 ; 8: 53
47. Ichiyasu H,Ichikado K,Yamashita A,et al. Pneumocyte biomarkers KL-6 and surfactant protein D reflect the distinct findings of high-resolution computed tomography in nonspecific interstitial pneumonia. *Respiration*.2012; 83(3):190-7.

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