

# Evaluations of vertical P-wave axis in the diagnosis of emphysema and assessment of its severity

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Date Submitted:14.5.2014

Date Accepted:3.7.2014

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## Abstract

**Background:** Emphysema is chronic obstructive pulmonary disease that result in an abnormal permanent enlargement of air spaces distal to the terminal bronchioles. This leads to presence of increased air between the heart and the ECG recording electrodes that may alter ECG findings in patient with emphysema.

**Aims:** To evaluate the vertical P-wave axis in the diagnosis of emphysema and assessment of its severity.

**Patients and Methods:** This is a case - control study conducted at Al Yarmouk Teaching Hospital and The Medical City in Baghdad during the period from the 1<sup>st</sup> of February 2012 to 31<sup>st</sup> of January 2013. A total of 100 emphysematous patients compared with other well matched 100 non emphysematous patients as a control group.

The diagnosis of pulmonary emphysema was based on clinical history , physical examination , chest radiographs finding, High resolution chest CT scan and pulmonary function test. Full history including age, sex, occupation, history of smoking was taken and complete physical examination was done on both groups, ECG and PFT done for all emphysema patient and control group and P-wave axis calculated.

**Results:** Demographic characteristics of emphysema patients & non emphysema controls were comparable apart from significant association between smoking and emphysema ( $P < 0.001$ ). Our emphysematous patients show that mean P-wave axis were significantly ( $P < 0.01$ ) higher than that of control group. There is 86% of emphysema patient with vertical ( $>60^\circ$ ) P-wave axis in comparison to 9% of control group. There is a significant inverse correlation between P wave axis and FEV1 that decrease in FEV1 is associated with increase in P wave axis and vice versa. Those with FEV1 less than 50% significantly have higher P wave axis mean

**Conclusions:** This study revealed clearly that p-wave axis deviation to the right is the most characteristic ECG change that occur in emphysema. Moreover, There is a significant inverse correlation between P wave axis and FEV1.

**Keywords:** Emphysema, P wave axis , pulmonary function test

## INTRODUCTION

Emphysema is chronic obstructive pulmonary disease (COPD) that is defined pathologically as an abnormal permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of alveolar

walls and without obvious fibrosis (1). Emphysema frequently occurs in association with chronic bronchitis. These 2 entities have been traditionally grouped under the umbrella term COPD which is a heterogeneous condition embracing several overlapping pathological processes including chronic bronchitis, chronic bronchiolitis and

emphysema (2). Patients have been classified as having COPD with either emphysema or chronic bronchitis predominance. The current definition of COPD put forth by (GOLD) does not distinguish between emphysema and chronic bronchitis (1), and defines COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. (3)

The Burden of Obstructive Lung Disease (BOLD) study showed that the worldwide prevalence of COPD (stage II or higher) was 10.1%. This figure varied by geographic location and by sex. Pooled prevalence among men was 11.8% (8.6-22.2%) and among women was 8.5% (5.1-16.7%). It has been estimated that COPD will rise from the sixth to the third most common cause of death worldwide by 2020. (3)

Smoking is by far the single most clearly established risk factor for emphysema and chronic bronchitis. One in 5 persons who smoke develops COPD, and 80-90% of COPD patients have a smoking history (1).

#### **P-wave axis**

In sinus rhythm when the SA node is the pacemaker, the mean direction of atrial depolarization (the P wave axis) points downward and to the left, in the general direction of lead II within a coordinate between 15° and 60° (75°) and away from lead aVR. On this count the P wave is always positive in lead II and always negative in lead aVR during sinus rhythm. A P wave that is positive in lead II and negative in lead aVR indicates normal P wave axis & sinus rhythm (4). ECG changes occur in emphysema due to:

1. The presence of hyperexpanded emphysematous lungs within the chest.
2. The long-term effects of hypoxic pulmonary vasoconstriction and increases the resistance of the pulmonary vascular bed upon the right side of the heart causing pulmonary hypertension and subsequent right atrial and right ventricular hypertrophy (i.e. cor pulmonale).(5)

#### **Effects of Emphysema on the Heart**

- Lung hyperinflation and hyperexpansion causes external compression of the heart, rotation,

medialisation of the heart and lowering of the diaphragms, with consequent elongation and vertical orientation of the heart.

- Due to its fixed attachments to the great vessels, the heart undergoes clockwise rotation in the transverse plane, with movement of the right ventricle anteriorly and displacement of the left ventricle posteriorly.
- The presence of increased air between the heart and recording electrodes has a dampening effect, leading to reduced amplitude of the QRS complexes.

#### **The most typical ECG findings in emphysema are:**

- Rightward shift of the P wave axis with prominent (large upright) P waves in the inferior leads II and III and flattened or inverted (negative) P-wave in leads I and aVL.(6)
- Frontal P-wave axis 'verticalisation' between 60° and 90°. (6)

## **PATIENTS AND METHODS**

#### **Study design**

A case - control study was conducted at Al Yarmouk Teaching Hospital and The Medical City in Baghdad during the period from the 1<sup>st</sup> of February 2012 to 31<sup>st</sup> of January 2013.

#### **Patients' selection**

100 emphysematous patients compared with other 100 non emphysematous patients as a control group, the patients and controls were well matched demographically. Both groups were randomly selected from the patients attending the out patients clinics and those who enrolled in the medical wards in Al Yarmouk Teaching Hospital and The Medical City.

Inclusion criteria for (emphysema group); patients enrolled in the study include those who are with previous documented diagnosis of COPD with emphysema predominance or diagnosed recently as COPD with emphysema predominance. The diagnosis of pulmonary emphysema in this study depend on;

- (1) Clinical history and physical examination; usually smoker, more than 40 years age, dyspnea associated with reduced chest expansion, reduction or loss of cardiac and hepatic dullness, increased anteroposterior chest diameter or barrel shaped chest.

(2) Chest radiographs (X-ray) which shows (i) hyperlucency of the lung fields, (ii) retrosternal space greater than 4.5cm, (iii) low or flat diaphragms below the level of the seventh rib anteriorly, (iv) peripheral pruning of blood vessels, and (v) long tubular heart. Items (iv) and (v) were made optional in those with cor pulmonale as it is known that they disappear with its development (7,8).

These criteria were entertained only after the exclusion of upper airway obstruction or the presence of isolated asthma.

(3) High resolution chest CT scan ( HRCT) was mainly used for the diagnosis of emphysematous changes, as it is highly specific for diagnosing emphysema and outlines bullae .

(4) Pulmonary function tests (PFT).

The control group including; healthy or patient with disease other than emphysema. Exclusion criteria for both groups were: Chronic bronchitis without or with minimal emphysema, asthma, bronchiectasis patients with non-sinus rhythm, pacing rhythm, congenital heart disease, valvular heart disease and cardiomyopathy because all these may cause abnormal P-wave axis.

Informed consent was obtained from each participant included in this study according to the declaration of Helsinki on research in human subjects. Official approvals were granted from the officials in the study setting.

#### **Data collection**

Full history including age, sex, occupation, history of smoking was taken and complete physical examination was done on both groups, ECG and PFT done for all emphysema patient and control group and P-wave axis calculated.

#### **Data entry**

Data entry of each patient was done using paper clinical research form (CRF), this special designed questionnaire filled by the researcher through a standardized approach of history, examination and investigation for both cases and control.

#### **Methods of data monitoring**

1. The standard 12-lead ECG using a standard technique was performed at rest in the semi- supine position for emphysematous and control then electrocardiograms were analyzed individually by the author using a handheld loop magnifier to determine the frontal P wave axis/frontal P vector by accounting for the P

wave amplitudes in leads I, III, and aVL, aVF. The standard hexaxial modification of the Bailey's reference system is used for plotting the derived frontal plane p-wave axes; the frontal plane P-wave axis was calculated manually using the hexagonal reference system. An axis greater than + 60° was taken to be abnormally vertical , A vertical P wave axis was also determined by the following criteria: when the P wave was flat in lead 1, of equal heights in leads 2 and 3, and definitely negative in aVL, the axis was taken to be abnormally vertical <sup>5</sup>.

2. Emphysema patients underwent pulmonary function testing and post bronchodilator FEV1 were determined either by use of a Vitalograph or spirometry. As per ATS guidelines, all spirometry maneuvers were repeated at least three times, the highest value being accepted when the operator was satisfied that a maximum effort was obtained. The FEV1, were expressed as a percentage of the predicted normal value for each individual patient. These were all estimated from sex, height, and age. The values for FEV1 were taken from the monogram of Kory, Callahan, and Boren.

#### **Statistical Analysis**

Statistical Package for Social Sciences version 20 (SPSS 20) was used for data input and analysis. Continuous variables presented as mean and standard deviation (SD). Discrete variables presented as numbers and percentages. t test for two independent samples used to test the significance of difference in mean between two independent samples. Pearson's correlation coefficient (r) used to quantify the relationship between continuous variables. Receiver Operating Characteristics (ROC) curve used to determine the test performance at different cut off point levels. P value used for all tests was asymptotic and all tests were two sided. Findings with P value less than 0.05 considered statistically significant.

## **RESULTS**

Demographic characteristics of 100 emphysema patients & 100 non emphysema controls are shown in (Table 1). The mean age was (66.4±6.4) ;( 65.6±7.4) years for emphysema and control peoples respectively and the distribution was (41%) of patients and (39%) of control in the age range (55-64) year old, with (59%) of patients and (61%) of control in the age range (≥ 65) year. (66%) of emphysema patient are males and (34%) are females while

(64%) of control group are male and (36%) are female. (51%) of emphysema were current smoker while (49%) were ex-smoker. Non emphysema group distributed as 16% smoker, 17% ex-smoker and 67% were non smoker. There was significant association between smoking and emphysema (P value< 0.001) (Table 1).

**Table 1.** Demographic and social characteristics of study sample.

	Emphysema	No Emphysema	
Variables	N=100 (100.0%)	N=100 (100.0%)	P value
Age (year); mean ± SD	66.4±6.4	65.6±7.4	0.064
Age Category (year)			0.053
• 55-64	41 (41.0)	39 (39.0)	
• ≥ 65	59 (59.0)	61 (61.0)	
Sex			0.767
• Male	66 (66.0)	64 (64.0)	
• Female	34 (34.0)	36 (36.0)	
Smoking			< 0.001
• Smoker	51(51.0)	16 (16.0)	
• Ex-smoker	49(49.0)	17 (17.0)	
• Non-smoker	0(0.0)	67 (67.0)	

Our emphysematous patients show that mean P-wave axis were significantly (P < 0.01) higher than that of control group with mean P-wave axis of (72.0±11.1) degree for emphysema and (47.6±9.6) degree for control (Table 2).

There is 86% of emphysema patient with vertical (>60 °) P-wave axis, the other 14% with P-wave axis of (<60).While , 9% of control group with vertical (>60 °) P-wave axis and 91% with P-wave axis of (<60) (Table 2) .

The mean P-wave axis showed very highly statistical significant difference between emphysema and control group (P < 0.05).

Categorization of the p-wave axis show 46% of emphysema patient and 0% of control with p-wave axis in the category (75-90) ° , 40% of emphysema and 9% of control in the category of (61-74) ° , while 14% of emphysema and 91% of the control in the category of (60 °) and less. Table 2.

**Table 2.** Categorization of study sample according to P wave axis degrees.

	Emphysema	No Emphysema	
P wave axis	N=100 (100.0%)	N=100 (100.0%)	P value
P wave axis; mean ± SD	72.0±11.1	47.6±9.6	< 0.001
P wave Axis Classification			< 0.001
• Vertical (P wave axis > 60°)	86 (86.0)	9 (9.0)	
• Not vertical (P wave axis up to 60°)	14 (14.0)	91 (91.0)	
P wave Axis Categories			< 0.001
• 75-90	46(46.0)	0(0.0)	
• 61-74	40(40.0)	9(9.0)	
• Up to 60	14(14.0)	91(91.0)	

Findings are significant (P < 0.05, table 4-A) that vertical p-wave axis (>60 °) were sensitive and specific ECG criterion for diagnosis of emphysema and sensitivity unlike specificity, it decreases as P wave axis increase (table 4-B).

There is a significant inverse correlation between P wave axis and FEV1 that decrease in FEV1 is associated with increase in P wave axis and vice versa ( table 5).

Those with FEV1 less than 50% significantly have higher P wave axis mean (P<0.05, table 6)

The degree of P-wave verticalisation was found to have a strong inverse relationship with FEV1; Pearson correlation coefficient being (-0.796); P < 0.001) (Table 5). The prevalence of a high degree of verticalisation (mean p-axis (80.2±5.9 °) was strikingly higher in emphysema patients with severe obstructive lung disease as defined by GOLD criteria (FEV1 < 50%) as compared to those with mild or moderate severity as defined by GOLD criteria (FEV1 > 50% associated with a less vertical (mean P-axis (64.5±9.4 °) (Table 6).

Other ECG findings among emphysematous patients show that most of the patients (55.0%) do not exhibit

related changes in ECG, 30% show right axis deviation, 6.0% show P pulmonale, while 9.0% show both P pulmonale and right axis deviation ( $P < 0.05$ , table 3). There is no significant association between age and emphysema ( $P > 0.05$ , table 1).

There is no significant association between sex and having emphysema ( $P > 0.05$ , table 1).

**Table 3.** ECG and FEV1 characteristics of emphysema group.

Variables	N=100 (100.0%)	P value
<b>Other ECG Findings</b>		<b>&lt; 0.001</b>
• P pulmonale	6 (6.0)	
• Right Axis Deviation of QRS	30 (30.0)	
• Both	9 (9.0)	
• Non/Others	55 (55.0)	
<b>FEV1 Category</b>		0.689
• < 50%	48 (48.0)	
• 50%-80%	52 (52.0)	

It is significant to find that smoking is associated with emphysema ( $P < 0.05$ , table 1). P wave axis significantly higher in emphysematous patients ( $P < 0.05$ , table 2). ECG findings among emphysematous patients significantly show most of patients (55.0%) do not exhibit related changes in ECG, 30% show right axis deviation, 6.0% show P pulmonale, while 9.0% show both P pulmonale and right axis deviation ( $P < 0.05$ , table 3)

The distribution of FEV1 was not significant ( $P > 0.05$ , table 3). ECG findings among emphysematous patients significantly show most of patients (55.0%) do not exhibit related changes in ECG, 30% show right axis deviation, 6.0% show P pulmonale, while 9.0% show both P pulmonale and right axis deviation ( $P < 0.05$ , table 3)

The distribution of FEV1 was not significant ( $P > 0.05$ , table 3). Findings are significant ( $P < 0.05$ , table 4-A) that sensitivity unlike specificity, it decreases as P wave axis increase (table 4-B).

There is a significant inverse correlation between P wave axis and FEV1 that decrease in FEV1 is associated with increase in P wave axis and vice versa. Those with FEV1 less than 50% significantly have higher P wave axis mean ( $P < 0.05$ , table 6).

**Table 4.** Performance of P wave axis as a test for detecting emphysema.

**A. Area under the Curve**

Area	Standard Error	P value
0.939	0.016	<b>&lt;0.001</b>

**B. Test performance**

Cut Point (Positive if P wave axis is greater than or equal to...)	Sensitivity	Specificity
41.00	1.000	0.260
51.00	0.920	0.620
60.00	0.860	0.910
64.50	0.820	0.930
70.50	0.570	1.000
81.00	0.240	1.000

**Table 5.** Correlation between P wave axis and FEV1

	Pearson Correlation Coefficient (r)	P value
Correlation between P wave & FEV1	- 0.796	<b>&lt;0.001</b>

**Table 6.** Mean P wave axis degree according to FEV1 category among emphysematous group.

	FEV1 Category				P value
	< 50%		50%-80%		
	N	Mean ±SD	N	Mean ±SD	
<b>P wave axis (degrees)</b>	4	80.2±	5	64.5±	<b>&lt; 0.001</b>
	8	5.9	2	9.4	

**DISCUSSION**

This study has been shown high prevalence of vertical P-wave axis ( $>60^\circ$ ) in emphysema group and low prevalence of vertical p wave axis in control group with mean P-wave axis of ( $72.0 \pm 11.1^\circ$ ) in emphysema group and ( $47.6 \pm 9.6^\circ$ ) in non emphysema group ,vertical( $>60^\circ$ ) p-wave axis found in 86% of emphysema group and only 9% in control group, while non-vertical( $\leq 60^\circ$ ) p-wave axis found in 14% of emphysema and 91% of control group .This results demonstrated that this lone criterion was associated with emphysema and can be used in aiding the diagnosis of pulmonary hyperinflation occur in emphysema , using a few simple parameters. In this study the sensitivity and specificity of this criterion was 86% and

91% respectively. Previous studies on this subject have found a close correlation between P-wave verticalisation and COPD/emphysema. In a study by Chhabra et al,(9) the vertical p- wave axis was highly correlated with emphysema with mean P-wave axis ( $69.71 \pm 11.87^\circ$ ) and ( $36.1 \pm 20^\circ$ ) in emphysema and non-emphysema group respectively and the sensitivity and specificity of a vertical P axis for diagnosing emphysema was 94.7% and 86.4%, respectively and this goes with result of this study. In a study by Thomas et al, (10) those with vertical P axis had a strikingly greater incidence of emphysema than did the controls (86% vs 4%, respectively). The sensitivity of a P axis ( $>60^\circ$ ) was (96%) and the specificity was 87%. In the study by Baljepally et al.(11) the vertical P-wave axis ( $70^\circ$  to  $+90^\circ$ ) found in 89 of the 100 patients with demonstrated emphysema and in only 4 of those without emphysema, the sensitivity and specificity was ( 89%) and( 96%) respectively, this result goes with our result. Spodick et al, also showed that P loop vectors were vertical in most of 25 cases with COPD emphysema. Chappell analyzed 112 patients with emphysema (assessed radiologically) and chronic bronchitis, the 24 emphysematous subjects all were associated with P axis verticalization, the P axis (vertical P axis) occurred more frequently in the 24 patients with widespread emphysema than in the 88 chronic bronchitis with possible slight, localized, or no emphysema. (The differences are statistically significant).

Calatayud et al: reported that the P wave in 173 patients with chronic obstructive pulmonary disease had been demonstrated a good correlation between P wave verticalization and the amplitude of increasing obstruction. They also showed that as the P wave axis shifted rightward. It is clear that a vertical P axis on an electrocardiogram can be used in aiding the diagnosis of emphysema with high sensitivity and specificity at a simple glance. Its simplicity makes it user-friendly(13).

In this recent study the degree of P-wave verticalisation has a strong inverse relationship with FEV1 which quickly provides a gross quantification of severity of the obstructive lung disease, increasing verticality of the P-wave axis correlated with increasing degrees of obstruction and the degree of depression of the diaphragm. Those emphysematous patient with ( $FEV1 < 50\%$ ) significantly have higher P wave axis mean ( $80.2 \pm 5.9^\circ$ ) ( $P < 0.05$ , table 6), while in emphysema with ( $FEV1 > 50\%$ ) a less vertical mean P-axis ( $64.5 \pm 9.4^\circ$ ) (Table 6). Pearson correlation coefficient being ( $-0.796$ );  $P < 0.001$ ) (Table 5). The prevalence of a high degree of verticalisation was strikingly higher in emphysema

patients with severe obstructive lung disease as defined by GOLD criteria ( $FEV1 < 50\%$ ) as compared to those with mild or moderate severity as defined by GOLD criteria ( $FEV1 > 50\%$ ) associated with a less vertical P wave axis (Table 6).

There is a significant inverse correlation between P wave axis and FEV1 that decrease in FEV1 is associated with increase in P wave axis and vice versa.

This is similar and in the range of other previous studies Baljepally et al, (11) show that vertical P-axis and forced expiratory volume (FEV1) were inversely correlated (Pearson correlation coefficient =  $-0.683$ ). Prevalence of severe COPD was strikingly higher in patients with P-axis  $> 75^\circ$  as compared to the group with P-axis  $60^\circ$ – $75^\circ$ : 96.3% vs 4.6%. Close to 80% of the emphysema patients with P-axis  $> 85^\circ$  had very severe disease ( $FEV1 < 30\%$ ). The degree of P-wave verticalisation might also have a significant correlation with the radiological severity of the emphysematous changes/lung hyperinflation which is the basic mechanism for a vertical P-wave axis. Chhabra L *et al* the orientation of the P vector positively correlates with computed tomographic visually scored emphysema (VSE) in patients with established diagnosis of COPD/emphysema. Both P-wave axis and VSE are strong reflectors of qualitative lung function in patients with emphysema.

Spodick *et al.* in a series of studies (14,15,16) showed that, in patients with COPD (mainly emphysema), verticalization of the P wave axis is frequent. Of 301 patients with emphysema, 77% had such verticalization, which was well correlated with increasing degrees of airways obstruction assessed by the 2-second fraction of the timed vital capacity, this is also agreed with the result of this study.

Moreover, increasing verticality of the frontal P vector correlates with increasing degrees of airway obstruction, Chhabra L *et al*, (9) and also correlates with the degree of depression of the diaphragm, Shah NS et al (17) and radiographic quantification of the disease, Chhabra L et al (9). A prospective blinded investigation of patients with purely (fibrotic) restrictive, compared with purely obstructive pulmonary disease showed that the P axis to follow the level of the diaphragm, such that patients with restrictive lung disease and high diaphragms had horizontal and leftward P axes, while patients with low diaphragms and obstructive lung disease had vertical P axis. Shah NS *et al* (17).

ECG findings among emphysematous patients significantly show that most of patients (55.0%) do not exhibit related changes in ECG, 30% show right axis deviation, 6.0% show P pulmonale, while 9.0% show both P pulmonale and right axis deviation ( $P < 0.05$ ), this means that p-wave axis deviation to the right ( $>60^\circ$ ) is the most characteristic ECG change that occur in emphysema.

## REFERENCES

1. Dennis E. Niewoehner ; Chronic obstructive pulmonary disease in Cecil Textbook of medicine 24th Edition , chapter chapter 88 page 537-544.
2. J.A. Innes P.T. Reid; Respiratory disease; (COPD), Davidson's principles and practice of medicine 21th Ed.( 2010).
3. Steven D. Shapiro, M.D. Gordon L. Snider, M.D. Stephen I. Rennard, M.D. ,COPD in Murry J.F. and Nadal J.A., Textbook of Respiratory Medicine, 5th edition( 2005) . W.B Saunders, chap.39.page.947-983.
4. Holtzman D, Aronow WS, Mellana WM, et al. Electrocardiographic abnormalities in patients with severe versus mild or moderate chronic obstructive pulmonary disease followed in an academic outpatient pulmonary clinic. *Ann Non-invasive Electrocardiol* 2011; 16:30-2.
5. Chhabra L, Sareen P, Gandagule A, Spodick DH. Visual computed tomographic scoring of emphysema and its correlation with its diagnostic electrocardiographic sign: the frontal P vector. *J Electrocardiol*. 2012;45:136-140.
6. Thomas A J, Apiyasawat S, Spodick DH. Electrocardiographic detection of emphysema. *Am J Cardiol*. 2011;107:1090-1092
7. A. G. Chappell, The Electrocardiogram in Chronic Bronchitis and Emphysema From Bridgend General Hospital, Glamorgan.
8. Calatayud JB, Abad JM, Khoi NB, Stanbro WJ, Silver HM. P wave changes in pulmonary disease. *Am Heart J* 1970;79:445-53
9. Haruna A, Muro S, Nakano Y, et al. CT scan findings of emphysema predict mortality in COPD. *Chest*. Sep 2010;138(3):635-40.
10. Hubbard RC, Crystal RG. Augmentation therapy of alpha 1-antitrypsin deficiency. *Eur Respir J Suppl*. Mar 1990;9:44s-52s.
11. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;CD004403.
12. Sciruba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*. Sep 23 2010;363(13):1233-44.
13. Thurlbeck WM. Pathophysiology of chronic obstructive pulmonary disease. *Clin. Chest Med*. Sep 1990;11(3):389-403.
14. Sanders C. The radiographic diagnosis of emphysema. *Radiol Clin North Am*. Sep 1991; 29(5):1019-30.
15. O'Donnell R, Breen D, Wilson S, Djukanovic R. Inflammatory cells in the airways in COPD. *Thorax*. May 2006;61(5):448-54.
16. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. Sep 2006;28(3):523-32.
17. Mannino, DM, Homa, DM, Akinbami, LJ, et al (2002) Chronic obstructive pulmonary disease surveillance: United States, 1971-2000. *Respir Care* 47, 1184-1191WW..