VALIDATION OF THE TAGALOG TRANSLATION OF THE CHRONIC RESPIRATORY DISEASE QUESTIONNAIRE FOR USE IN STABLE COPD PATIENTS UNDERGOING PULMONARY REHABILITATION

LENORA C FERNANDEZ, MD, FPCCP,[1] RHODERICK IAN G. REYES, MD, [1] LEAH IGAYA, PhD, [1] ELLEN VILLANUEVA, RN[1]

OBJECTIVES: It is the objective of this study to test the validity of the Tagalog translation (CRQ-T) of the original Canadian English CRQ in a clinical trial. Specifically, we aim to determine whether both versions yield similar results in subjects undergoing a similar intervention. Furthermore, we aim to test the ability of both versions to detect a change after the subjects undergo a specific intervention.

METHODS: The subjects of the study were stable COPD patients enrolled in the Pulmonary Rehabilitation Program of the Comprehensive Ambulatory Respiratory Rehabilitation (CARE) Center of the University of the Philippines - Philippine General Hospital (UP-PGH). The post-bronchodilator FEV_1 and FVC, six-minute walk test, PaO_2, $PaCO_2$, smoking history (pack years) and Borg's dyspnea score of each subject were determined at baseline and at 4 weeks after completing the pulmonary rehabilitation program. All patients underwent a twice a week 4-week outpatient pulmonary rehabilitation program at the UP-PGH CARE Center. The original Canadian English version of the CRQ was translated into Tagalog. The Tagalog version (CRQ-T) was translated back into English by 5 patients with adequate comprehension of both the English and Tagalog language. Any error or words that needed clarification or modification were noted. This process was repeated until the questionnaire was deemed satisfactory and the final version was the one administered to the subjects included in the study. The patients were randomized into two groups. One group was administered the original CRQ followed by the CRQ-T after a lapse of 15 minutes. The other group was given the CRQ-T first followed by the original CRQ after a lapse of 15 minutes. Both versions of the CRQ were administered to the subjects prior to the start of and 4 weeks after they have completed the Rehabilitation Program. Analysis of differences in baseline characteristics was done using the t-test for continuous data and Fisher's exact test for ordinal data. The values at baseline and after intervention were compared using t-test for means with equal proportions and *p* values less than 0.05 were considered statistically significant. The correlations of the domains and of the total score for both questionnaires were compared using the Spearman Rank Correlation Coefficient and their ability to detect changes after the intervention was analyzed using the paired t-test. Values of $p < 0.05$ were considered significant.

RESULTS: A total of 23 patients enrolled in the CARE Program were included in the study. Eleven patients were randomized to receive the original CRQ before the CRQ-T and 12 patients were to receive the CRQ-T prior to the CRQ. Baseline characteristics of both groups were similar. When the post rehabilitation characteristics of the two groups were compared, no significant difference was noted. There was a statistically significant improvement in the FVC and the distance covered in the six minute walk test in both groups after undergoing Pulmonary Rehabilitation. No improvement was noted with the FEV_1 and the Borg's dyspnea scale.

The CRQ-T and CRQ had very high correlation scores implying that both versions measure the same parameters. All subjects showed a significant improvement in their domain scores and in their total scores after undergoing Pulmonary Rehabilitation. This was reflected in the scores of the subjects in both the CRQ-T and CRQ. Both versions detect a similar intervention effect.

CONCLUSION: This study reinforces the conclusion of previous works showing that pulmonary rehabilitation not only improves exercise capacity of COPID patients but more importantly, it significantly improves their perception of the quality of their lives. We have proven that the CRQ-T can be used to measure the quality of life perception of Filipino patients in clinical trials. The CRQ-T measures the same parameters as the original English version. It yields similar results in subjects undergoing a similar intervention. Furthermore, both versions have the ability to detect a change or an improvement after the subjects underwent pulmonary rehabilitation. We recommend that the CRQ-T be utilized to assess the quality of life scores of Filipino patients in future clinical trials. *Phil Jour Chest Diseases Vol 11 No 1 pp: 1-5*

Keywords: COPD, Pulmonary rehabilitation, Respiratory Questionnaire

INTRODUCTION

Quality of life has been identified as an important attribute of clinical investigation and patient care.[1] In public health and in medicine, the concept of health-related quality of life refers to a person's or group's perceived physical and mental health over time. Physicians have often used health-related quality of life to measure the effects of chronic illness in their patients in order to better understand how an illness interferes with a person's day-to-day life. Similarly, public health

[1] Comprehensive Ambulatory Respiratory Rehabilitation Unit, University of the Philippines - Philippine General Hospital

professionals use health-related quality of life to measure the effects of numerous disorders, short- and long-term disabilities, and diseases in different populations. Tracking health-related quality of life in different populations can identify subgroups with poor physical or mental health and can help guide policies or interventions to improve their health. Health-related quality of life represents the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient. One of the aims of treating patients must be to enable them to feel better and to function better in their day-to-day activities. Many clinicians and clinical investigators now recognize the importance of incorporating health-related quality of life into their routine clinical practice and into clinical studies.

Health related quality of life measurement has become a central feature of studies in Chronic Obstructive Pulmonary Disease (COPD). One driving force for this is the recognition that treatments for this condition are largely symptomatic.[2] Over the last decade, the potential value of incorporating disease specific quality of life questionnaires into clinical trials evaluating medical interventions for COPD has become well established. Since the associations between spirometric values and disease specific quality of life questionnaires have been shown to be weak, it is generally recognized that these instruments contribute valid additional information about the daily functioning and well being of patients with COPD.[3] Several questionnaires *have* been developed to measure quality of life in patients with COPD including the Chronic Respiratory Disease Questionnaire (CRQ) by Guyatt and colleagues.[4]

With the growing local interest in quality of life research in the field of pulmonary medicine, an instrument suitable for local utilization is very much needed. Unfortunately, there are no disease specific quality of life questionnaires that have been validated for use in our setting. It is the objective of this study to test the validity of the Tagalog translation (CRQ-T) of the original Canadian English CRQ in a clinical trial. Specifically, we aim to determine whether both versions yield similar results in subjects undergoing a similar intervention. Furthermore, we aim to test the ability of both versions to detect a change after the subjects undergo a specific intervention.

METHODS

Study Population. The subjects of the study were stable COPD patients enrolled in the Pulmonary Rehabilitation Program of the Comprehensive Ambulatory Respiratory Rehabilitation (CARE) Center of the UP-PGH. They fulfill the following criteria:

Inclusion Criteria. The patients included in the Pulmonary Rehabilitation Program meet all of the following criteria: COPD patients as defined by the American Thoracic Society;[5] the patients have symptoms of COPD; the patients have stable disease (as defined by the following: No acute lower respiratory tract infections for the past 2 weeks; no increase in the use of COPD medications for the past 2 weeks); no exacerbations which warranted medical consult/ confinement for the past two weeks; willingness to attend all of the pulmonary rehabilitation sessions; gives informed consent to participate in the program; and adequate comprehension of both English and Tagalog.

Exclusion Criteria. Patients with the following characteristics were not included in the pulmonary rehabilitation program: Patients with conditions that may interfere with the patient undergoing the rehabilitative process (which may include but will not be limited to: advanced arthritis; cognitive defects; disruptive behavior; uncorrectable congenital or acquired physical defects limiting performance of measured parameters; patients with conditions that might place them at undue risk during exercise training such as: severe pulmonary hypertension, Congestive heart failure, unstable angina, acute myocardial infarction within the past 6 months, cerebrovascular accident and its residua which hinders ambulation, debilitating malignancies); Acute respiratory failure necessitating intubation or upper abdominal/thoracic surgery during the past 3 months; lack of compliance and unwillingness to participate in the pulmonary rehabilitation program.

The post-bronchodilator FEV_1 and FVC, six minute walk test, PaO_2, $PaCO_2$, smoking history (pack years) and Borg's dyspnea score of each subject were determined at baseline and at 4 weeks after completing the pulmonary rehabilitation program.

Pulmonary Rehabilitation. All of the patients underwent a twice a week 4-week out patient pulmonary rehabilitation program at the UP-PGH CARE Center. The program includes health education focusing on respiratory anatomy and the pathology of COPD, dietary instruction, exercise techniques, techniques on performance of activities of daily living, sexuality, stress management, proper use of medications, recognition and management of exacerbations and psychosocial counseling.[6]

Quality of Life Questionnaire.

Translation and Pretesting of Questionnaire. A language expert from the University of the Philippines-

Table I. Comparison of baseline characteristics using t-test. (Mean ± SD)

Characteristics	English – Tagalog N = 11	Tagalog – English N = 12	p Value
Age (years)	63 ± 9.83	62.17 ± 9.09	0.7981
Range	49 - 81	48 - 80	
Sex			0.2610
Male	8	11	
Female	3	1	
FEV_1 (li)	0.99 ± 0.43	1.12 ± 0.38	0.4601
FVC (li)	2.02 ± 0.71	2.28 ± 0.38	0.2796
Six-minute walk test (ft)	319.91 ± 173.32	345.75 ± 113.12	0.6736
PaO_2 (mmHg)	69.53 ± 25.25	79.95 ±27.75	0.3584
$PaCO_2$ (mmHg)	34.56 ± 12.13	35.0 ± 11.52	0.9303
Pack years	46.27 ± 38.17	53.76 ± 31.29	0.6111
Borg's Dyspnea Scale	1.22 ± 1.68	1.0 ± 1.48	0.7439

Table II. Parameters tested after completion of pulmonary rehabilitation

Characteristics	English – Tagalog N = 11	Tagalog – English N = 12	p Value
FEV_1 (li)	1.10 ± 0.45	1.16 ± 0.42	0.7995
FVC (li)	2.35 ± 1.02	2.46 ± 0.59	0.0924
Six-minute walk test (ft)	414.55 ± 113.36	471.58 ± 107.20	0.8520
Borg's Dyspnea Scale	0.682 ± 0.87	0.583 ± 1.15	0.4036

Table III. Comparison of pre and post-rehabilitation parameters

Characteristics	Pre-Rehabilitation N = 23	Post-Rehabilitation N = 12	p Value
FEV_1 (li)	1.06 ± 0.40	1.08 ± 0.48	0.7400
FVC (li)	2.15 ± 0.57	2.31 ± 0.92	0.0259*
Six-minute walk test (ft)	333.39 ± 142.22	444.30 ± 111.52	0.0026*
Borg's Dyspnea Scale	1.04 ± 1.55	0.063 ± 1.00	0.2240

Manila translated the original Canadian English version of the CRQ by Guyatt and colleagues[4] into Tagalog. The Tagalog version (CRQ-T) was translated back into English by five patients with adequate comprehension of both the English and Tagalog language. Any error or words that needed clarification or modification were noted. Modifications on the CRQ-T were made based on these observations. This process was repeated until the questionnaire was deemed satisfactory and the final version was the one administered to the subjects included in the study. The aim of the pre-testing phase is to ensure that the questionnaire had the same intended meaning as the original English version; that the Tagalog version is free from wording errors and is easily understood and that the complete range of response options is used and understood.

Validation of the CRQ-T. The patients were randomized into two groups. One group was administered the original CRQ followed by the CRQ-T after a lapse of 15 minutes. The other group was given the CRQ-T first followed by the original CRQ after a lapse of 15 minutes. Both versions of the CRQ were administered to the subjects prior to the start of and 4 weeks after they have completed the Rehabilitation Program. The instructions of the authors on how to administer the questionnaire were closely adhered to.

Analysis of Data. Analysis of differences in baseline characteristics was done using the t-test for continuous data and Fisher's exact test for ordinal data. The values at baseline and after intervention were compared using t-test for means with equal proportions and p values less than 0.05 were considered statistically significant.

The correlation of the domains and of the total score for both questionnaires were compared using the Spearman Rank Correlation Coefficient and their ability to detect changes after the intervention was analyzed using the paired t-test. Values of $p < 0.05$ were considered significant.

RESULTS

A total of 23 patients enrolled in the CARE Program were included in the study. Eleven patients were randomized to receive the original CRQ before the CRQ-T and 12 patients were to receive the CRQ-T prior to the CRQ. Baseline characteristics of both groups were similar (*Table I*). When the post rehabilitation characteristics of the two groups were compared, no significant difference was noted (*Table II*). There was a statistically significant improvement in the FVC and the distance covered in the six minute walk test in both groups after undergoing Pulmonary Rehabilitation. No improvement was noted with the FEV_1 and the Borg's dyspnea scale (*Table III*).

We compared the correlation of the CRQ-T with the CRQ and found that all domains of the questionnaire and the questionnaire as a whole had very high correlation scores implying that both versions measure the same parameters (*Table IV*). All subjects showed a significant improvement in their domain scores and in their total scores after undergoing Pulmonary Rehabilitation. This was reflected in the scores of the subjects in both the CRQ-T and CRQ. (*Table V*) and (*Table VI*) show that both versions of the questionnaire detect an improvement after the subjects underwent pulmonary rehabilitation. The CRQ and CRQ-T were designed so that higher scores reflect favorable patient condition. The negative values obtained after subtracting the post-intervention scores from the pre-intervention scores (pre-intervention minus post-intervention) implies improvement in the condition of the subjects. Both versions detect a similar intervention effect.

Table IV Correlation coefficient of the CRQ-T compared to CRQ using Spearman Rank Correlation Coefficient

Domain	Pre-intervention	Post-intervention
Dyspnea	0.9517	0.8062
Fatigue	0.8850	0.8735
Emotional function	0.8523	0.9549
Mastery	0.8703	0.9121
Total Score	0.9541	0.8979

Table V. Ability of the CRQ to detect an intervention effect using paired t-test

Domain	Mean Difference in Score	p Value	95% CI
Dyspnea	- 6.57	0.0001	- 9.25, - 3.89
Fatigue	- 5.14	0.0001	- 7.29, - 2.99
Emotional function	- 7.76	0.0002	- 11.24, - 4.28
Mastery	- 3.71	0.0039	- 6.09, - 1.34
Total Score	- 23.19	0.0000	31.06, - 15.32

Table VI Ability of the CRQ-T to detect an intervention effect using paired t-test

Domain	Mean Difference in Score	p Value	95% CI
Dyspnea	- 6.09	0.0003	- 9.02, - 3.17
Fatigue	- 5.38	0.0000	- 7.54, - 3.22
Emotional function	- 11.95	0.0000	-14.97, - 8.94
Mastery	- 5.14	0.0000	- 7.21, - 3.08
Total Score	- 28.57	0.0000	- 36.38, - 20.76

DISCUSSION

Guyatt and colleagues[4] originally wrote the CRQ in Canadian English. This measure is an interviewer-administered questionnaire measuring both physical and emotional aspects of chronic lung disease. It has 20 items and has four domains: dyspnea, fatigue, mastery and emotional function. The responses are in numerical form with a 7-point Likert Scale that takes approximately 15 to 25 minutes to administer. Its reliability,[7,8] validity[4,9] and responsiveness[10,11] has been tested in various clinical trials particularly among patients undergoing pulmonary rehabilitation. A change in the score of 0.5 on the 7-point scale reflects a clinical significant small change. A change of 1.0 represents a moderate change and a change of 1.5 represents a large change.[10,12] It has been translated into other languages and these versions have been validated.[13-16] To date, the CRQ has been used as the sole quality of life measure in a number of pulmonary rehabilitation interventions.[1,3,11,13,14] Results from these studies have generally demonstrated significant improvements in each domain of the CRQ after various forms of pulmonary rehabilitation.

The subjects had similar baseline characteristics so that the resulting improvement in exercise capacity, as reflected by the increased distance covered in the six-minute walk test; and the improved FVC can be attributed to the intervention (pulmonary rehabilitation). Significant improvements emerged in overall quality of life scores as well as in each domain. The rehabilitation program appears to have produced the minimal clinically important difference. The enhanced perceptions after the program may be secondary to improvements in exercise tolerance in addition to diminished COPD symptoms. The improved dyspnea scores in our subjects after the intervention is similar to other studies.[4,14] Dyspnea has been the most limiting symptom of most COPD patients. It is possible that the improved dyspnea symptoms were the result of improvements derived from the exercise intervention. The improved emotional function scores was also seen in previous studies.[4,14,17]

Comparing the CRQ-T to the CRQ showed a very high correlation when the questionnaire was taken as a whole as well as when the domains were considered separately. This implies that the CRQ-T measures the same parameters that the CRQ intended to measure. Our method of randomizing the subjects into two groups with each group using both versions of the questionnaire, albeit, in a different order; and thereafter obtaining similar results further reinforced this hypothesis. Further testing also showed that both versions measured the improved quality of life perception of the subjects after they underwent pulmonary rehabilitation.

CONCLUSION

This study reinforces the conclusion of previous works showing that pulmonary rehabilitation not only improves exercise capacity of COPD patients but more importantly, it significantly improves their perception of the quality of their lives. Also, we have proven that the CRQ-T can be used to measure the quality of life perception of Filipino patients in clinical trials. The CRQ-T measures the same parameters as the original English version. It yields similar results in subjects undergoing a similar intervention. Furthermore, both versions have the ability to detect a change or an improvement after the subjects underwent pulmonary rehabilitation. We recommend that the CRQ-T be utilized to assess the quality of life scores of Filipino patients in future clinical trials.

REFERENCES

1 Lox CL, Freehill AJ. Impact of Pulmonary Rehabilitation on Self-Efficacy, Quality of Life and Exercise Tolerance. *Rehabilitation Psychology 1999;* 44: 208-221.

2 Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax 2001; 56: 880-887.

3 Rutten-van Mollken M; Roos B, Van Noord JA. An empirical comparison of the St. George's Respiratory Questionnaire and the Chronic Respiratory Disease Questionnaire in a clinical trial setting. Thorax 1999; 54: 995-1003.
4 Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987; 42: 773-778.
5 Standards for the Diagnosis and Care of Patients with Chronic obstructive Pulmonary Disease. Official Statement of the American Thoracic Society. Am J Respir Ctit Care Med 1995; 152: S77 - S 120.
6 Facilitator's Manual. Comprehensive Ambulatory Respiratory Rehabilitation Center. Section of Pulmonary Medicine. UP-Philippine General Hospital. 1999.
7 Martin LL. Validity and reliability of a quality of life instrument. The chronic respiratory disease questionnaire. . Nurs Res 1994; 3: 146-156.
8 Lacasse Y, Wong E, Guyatt G. A systematic overview of the measurement properties of the Chronic Respiratory Questionnaire. *Canadian* Respiratory Journal 1997; 4: 131-139.
9 Harper R, Brazier JE, Waterhouse JC, Waiters SJ, et al. Comparison of outcomes measure in patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. Thorax 1997; 52: 879-887.
10 Jaeschke R, Singer J, Guyatt GH. Measurement of health status ascertaining the minimal clinically important difference. Controlled Clin Trials 1989; 10: 407-415.
11 Goldstein, RS, Gort, EH, Stubbing D, Avendano MA, Guyatt, GH. Randomised controlled trial of pulmonary rehabilitation. *Lancet* 1994; 344: 1394-7.
12 Redelmeier DA, Guyatt GH, Goldstein RS. Assessing the minimal important difference in symptoms: a comparison of two techniques. J Clin Epidemiol 1996*;* 49:1215-1219.
13 Guell R, Casan P, Sangenis M, Morante F, Belda J, Guyatt GH. Quality of life in patients with chronic respiratory disease: the Spanish version of the Chronic Respiratory Questionnaire (CRQ). Eur Respir J 1998;11(1):55-60.
14 Wijkstra PJ, Tenvergert EM, VanAltena R, Otten V, Postma D, Kraan J, et al. Reliability and validity of the Chronic Respiratory Questionnaire (CRQ). Thorax 1994;49:465-7.
15 Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax 1998;53:477-82.
16 Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:785-90.
17 Reardon J, Patel K, ZuWallack R. Improvement in quality of life is unrelated to improvement in exercise endurance after outpatient pulmonary rehabilitation. J Cardiopul Rehab 1993; 13: 51-54.

DEVELOPMENT & VALIDATION OF THE TAGALOG VERSION OF THE ST. GEORGE RESPIRATORY QUESTIONAIRE

NORBERTO FRANCISCO, MD, FPCCP,[1] VINCENT BALANAG, MD, FPCCP,[1] SULLIAN SY-NAVAL, MD, FPCCP,[1] CALIXTO ZALDIVAR, MD, FPCCP,[1] RUEL REVILLA, MD, FPCCP[1]

The St. George Respiratory Questionnaire (SGRQ), a widely accepted, fixed format standardized and self-administered questionnaire measuring health in chronic airflow limitation, was translated to colloquial Tagalog by linguistic experts. Conceptual equivalence was ascertained through meticulous discussions with a panel of content experts, namely, Dr. Paul Jones, the original SGRQ developer, and three practicing bilingual pulmonologists from the study team. Cognitive testing of the Tagalog instrument was done on 10 patients to determine time and ease of administration. Thirty literate, stable, moderate to severe COPD patients were enrolled for the validation proper, mean age 68.8 years (range 52 to 86 years), post-bronchodilator FEV_1 % predicted 42.5% (range 19% - 76%). Most patients reported significant breathlessness belonging to MRC grades 2 and 3. Patients randomly completed either the Tagalog or English SGRQ three days apart. Scale equivalence (validity) between translated and original English versions was shown with SGRQ component and total score intra-class coefficients (Rr) ranging from 0.76 to 0.89, (*p<0.0001*). One way ANOVA showed significant association between mean SGRQ total score (Tagalog) and dyspnea grade. Spearman rank test established a significant correlation between SGRQ total score (Tagalog) and MRC Dyspnea Grade. Poor correlation was seen between SGRQ total score (Tagalog) and spirometric parameters and COPD severity. Data from this study show that a conceptually equivalent, valid, user friendly, Tagalog version of the SGRQ has been successfully developed. *Phil. Journal Chest Diseases. Vol. 11 No. 1 pp: 6-9*

Keywords: COPD, QOL, Tagalog version

INTRODUCTION

Health-related quality of life (HRQOL) questionnaires allow clinicians to measure directly the impact of disease on a patient's daily life and can be especially valuable in clinical trials designated to assess benefits, side effects, and costs of different treatments. Increased recognition of the importance and value of understanding and measuring HRQOL has resulted in measures being developed and/or validated for use in conditions such as COPD, asthma and cystic fibrosis.[1]

The St. George Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to measure impact of overall health, daily life, and perceived well-being. It was developed by the group of Jones, Quirk, Baveystock and Littlejohns from the St. George's Hospital Medical School in London for use by patients with fixed and reversible airway obstruction. It can be given as a self-administered questionnaire or by face-to-face or telephone interview; test time is about 10 minutes. The SGRQ consists of 76 items divided into three sections: Section 1: Symptoms (frequency and severity); Section 2: Activity (activities that cause or are limited by breathlessness) and Section 3: Impacts (social functioning, psychological disturbances resulting from airways disease). Section 1 is answered using a 5-point Likert scale while Sections 2 and 3 are answered by Yes or No. Scores for each section is weighed based on empirical data. Scores range from 0 to 100, with higher scores indicating poor health.[1]

The reliability and validity of the SGRQ has been determined in a series of four different studies using the final version of the questionnaire.[1] Repeatability of total SGRQ scores was 0.91 in asthmatic patients and 0.92 in 20 COPD patients. The coefficient of variation for the difference between the measurements done 2 weeks apart was 19%. The repeatability of the component sections was also very similar in both groups of patients, so correlations for repeated measures of the section scores are represented using combined data. These were Symptom, r = 0.91; Activity r = 0.87; and Impact, 0.88. Studies on the validity of the SGRQ show significant correlation between total score and presence of cough (r^2 = 0.11, *p=0.0001*); sputum (r^2 = 0.06, *p=0.002*); and

[1] Department of Research & Development, Lung Center of the Philippines

wheeze (r^2 = 0.25, *p=0.0001*). Significant correlation was likewise shown between SGRQ total scores and FEV_1, (r^2 = 0.05, *p=0.001*); FVC (r^2 = 0.07, *p=0.002*); SaO_2 (r^2 = 0.05, *p=0.01*); 6-MWD (r^2 = 0.13, *p = 0.0001*); MRC dyspnea grade (r^2 = 0.22, *p=0.001*) anxiety score (r^2 = 0.03, *p = 0.033*); depression score (r^2 = 0.12, *p=0.0001*); SIP total score (r^2 = 11.10, *p=0.0002*); SIP physical domain (r^2 = 0.02, *p=0.09*); and SIP psycho-social domain (r^2 = 0.09, *p=0.0005*). The SGRQ was also shown to reflect changes in the patient's health status, with a mean change of 4 units associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment.[2,3] It has been utilized as an assessment of QOL in at least 2 clinical trials.[3,4]

The original English version has been translated to Finnish, Dutch, Italian, Thai, Japanese, Danish, French, Portuguese, Spanish, Swedish and Polish. This study will deal with the development of the Tagalog version of the SGRQ and subsequent validation of the final version.

METHODOLOGY

A. Translation: Following initial consultations with the questionnaire developer, Dr. Paul Jones, a copy of the SGRQ in English was obtained. A colloquial Tagalog translation was produced by the Department of Linguistics of the University of the Philippines which was then back translated by another member of the staff of the same Department.

Conceptual equivalence of the backward translation and the original version was evaluated by a panel composed of 3 bilingual "content experts" (3 local practicing pulmonologists), Professor Consuelo Paz, the linguistic expert, and Dr. Paul Jones himself, the original questionnaire developer. Conceptual equivalence is said to be present when the original and the translated versions have the same meaning. Items and response scales assessed to be non-equivalent were clarified further from Dr. Paul Jones and reworded in English until they were assessed to be acceptable and the Tagalog translation revised accordingly. The forward translation was then finalized based on the panel's feedback.

The resulting translation was field tested in a sample of 10 persons consisting of COPD patients and asthmatic individuals to test the interpretation of the translation (cognitive testing) and to determine time and ease of administration. The self-administered Tagalog questionnaire was distributed to 2 groups of 5 subjects, after which their interpretation and responses to each item were discussed in a round table format together with the facilitators and recorders from the study team. The time of completion by each subject was recorded.

Following cognitive testing, the items and response options were revised accordingly by the study team until the final version of the Tagalog translation emerged.

B. Validation. The translated and the original version of the SGRQ were administered to a sample (N=30) of bilingual COPD patients to allow for direct comparison of responses for the same patient. The patient randomly answered either original or translated version during the first session and made to answer the other version after 3 days, making sure there was no significant change in the patient's medical status within the period.

The same group of patients was classified according to COPD severity using GOLD Criteria, and MRC Dyspnea Grade.

Statistical Analysis. The intra-class correlation (RI) coefficients of the component and total scores derived from the responses in English and Tagalog translation were obtained to determine scale equivalence between the two versions. To determine concurrent validity, Spearman Rank correlation coefficient (r) of the SGRQ total score (Tagalog) with COPD severity and MRC Dyspnea Grade were derived. Pearson's correlation coefficient between SGRQ total score (Tagalog) and means of the following spirometric parameters FEV_1, FEV_1 % Predicted, FEV_1/FVC, and FVC were computed. Analysis of Variance (ANOVA) was done to compare the mean total scores among Dyspnea grades and COPD severity grades.

RESULTS

A. Translation. The original SGRQ was submitted to Prof Consuelo Paz, a linguistic expert at the University of the Philippines for colloquial Tagalog translation. Another linguistic expert who has not seen the original version of the SGRQ then did a backward translation.

A panel composed of three practicing pulmonologists (content experts), Prof. Consuelo Paz, and Dr. Paul Jones himself, the original questionnaire developer evaluated the original and the backward translated questionnaire for conceptual equivalence. One item was assessed to be non-equivalent. This is the last item of section 4 of part 2 of tile questionnaire. This was clarified further from Dr. Paul Jones and was reworded in English until they were assessed to be acceptable. The Tagalog translation was also revised accordingly.

Table I. Demographic data of the 30 COPD patients

Parameter		
BMRC Grade	No. of pts	Percent
0	2	6.67
1	4	13.33
2	11	36.67
3	10	33.33
4	3	10.00
COPD Severity (GOLD)	No. of pts	Percent
2	23	76.67
3	7	23.33
Spirometry	Mean	SD
FVC actual	2.099	0.528
FEV_1 actual	1.034	0.332
FEV_1 % predicted	42.571	14.606
FEV_1/FVC	49.107	8.422

Table II. Mean SGRQ component and total scores in English and Tagalog translation and their intra-class correlation coefficients

Component	English	Tagalog	R_1	SE	95% CI
Symptom	48.2 (22.6)	46.0 (20.3)	0.76	0.08	0.61, 0.91
Acitivty	66.0 (17.7)	62.5 (18.1)	0.80	0.07	0.67, 0.93
Impact	36.7 (24.1)	35.4 (21.2)	0.88	0.04	0.80, 0.96
TOTAL	47.5 (19.6)	45.4 (17.8)	0.89	0.03	0.82, 0.97

Table III. Correlation coefficients (r) of SGRQ total score (Tagalog) and COPD severity and MRC dyspnea grade

	Spearman Correlation Coefficient	*p* Value
COPD Severity	0.2	0.29
MRC Dyspnea grade	0.45	0.0131

The field-testing of the Tagalog translation resulted to an average test time of 21 minutes. The 10 subjects completed the questionnaire with ease. Following cognitive testing by the study team, the items and response options were revised accordingly until the final version of the Tagalog translation was deemed ready for the validation phase.

B. Validation. Thirty subjects, all previously diagnosed with Chronic Obstructive Pulmonary Disease (COPD) participated in the study. There were 29 males and 1 female with ages ranging from 52 to 86 years old with a mean age of 68.8 $\pm$ 8.6 years. Spirometric testing done upon entry to the study revealed that mean FEV_1 (actual) is 1.03 L and mean FEV_1 percent predicted is 42.5%. Further classification of disease severity using the 2001 GOLD criteria show that 23 patients have moderate disease while 7 has severe disease. Moderate disease was further subdivided into FEV_1 % predicted of 50-79 and 30-49. BMRC grading of dyspnea clustered in Grades 2-3, i.e., they walk slower than people of the same age or actually have to stop after a few minutes because of breathlessness. *Tables I-IV* summarize these demographic data. The patients completed the English questionnaire in 19 minutes on the average, (range = 8 - 41 minutes). Comparative figures for the Tagalog version are 21 minutes and 10-3.8 minutes, respectively. All patients completed both versions easily.

Scale equivalence (validity) between the translated and original versions of the SGRQ was established with computed intra-class correlation coefficient of component and total scores ranging from 0.76 - 0.89 (*Table II*).

Correlation coefficients (r) of SGRQ total score (Tagalog) and COPD severity, MRC Dyspnea Grade, FEV_1, FEV_1 % predicted, FEV_1/FVC, and FVC are tabulated in *Tables III and IV*. No significant correlation was found between SGRQ total scores (Tagalog version) and spirometric parameters. Likewise, there was no significant correlation between SGRQ total score (Tagalog version) and disease severity using the GOLD criteria (r = -0.2, *p=0.29*). However, a significant correlation (r = 0.45, *p=0.01*) was found between SGRQ total score (Tagalog version) and MRC Dyspnea Grade. Using One Way ANOVA, mean SGRQ total score (Tagalog version) was significantly different in the dyspnea groups, (*p=0.035*) most evident in the extremes of severity, i.e., between groups reporting a Dyspnea Grade of 0-1 and 3-4. No significant difference in SGRQ total score (Tagalog) and the different COPD severity grades was seen using ANOVA (*p=0.25*) (*Tables V* and *VI*).

DISCUSSION

The St. George's Respiratory Questionnaire (SGRQ) is a fixed format, self-complete, and standardized questionnaire for measuring the impact of diseases of chronic airflow limitation on health and well-being. Several studies have proven that the SGRQ is a valid and repeatable instrument. Moreover, it is sufficiently sensitive to respond to changes in disease activity. The present study seeks to develop an equivalent Tagalog version of the SGRQ with all the mentioned attributes of the English version, valid, repeatable and sensitive, for use by Tagalog proficient individuals.

The method of translation into colloquial Tagalog ensures its widespread applicability among Filipinos who maybe more comfortable in their own spoken dialect but can also understand Tagalog. The participation of experts from the Department of Linguistics of the University of the Philippines for the

Table IV. Correlation coefficients of SGRQ Total score (Tagalog) and spirometric indices

	Pearson Product Moment Correlation Coefficient	*p* Value
FVC	0.29	0.11
FEV_1 actual	0.17	0.38
FEV_1 % predicted	0.17	0.37
FEV_1/FVC	0.09	0.60

Table V. Mean SGRQ total score (Tagalog) of the different dyspnea groups

Dyspnea Group	Mean	Standard Deviation
0 – 1	31.98	21.46
2	42.91	10.48
3 – 4	53.63	17.80
TOTAL	45.37	17.84

Table VI. Mean SGRQ total score (Tagalog) of the different COPD severity grades

COPD Severity (FEV_1)	Mean	Standard Deviation
1 (50-79)	45.19	18.87
2 (30-49)	50.35	17.86
3 (<30)	36.37	14.78
TOTAL	45.37	17.84

forward and backward translation assures precision. Face to face consultation and panel (3 bilingual practicing pulmonologists and linguistic expert) discussion with the original author of the SGRQ, Dr. Paul Jones, guarantees a high degree of conceptual and content equivalence. Cognitive testing performed in ten patients with chronic airflow limitation and consequent minor refinement produced a questionnaire that is easy to understand and accomplish.

Validity of the final Tagalog version of the SGRQ produced by the study team has been established in the current paper. Intra-class coefficients between the original English questionnaire and the Tagalog translation ranging from 0.76 - 0.89 for all the SGRQ component (Symptom, Activity, and Impact) and total scores confine this equivalence and makes it valid for use for measuring impact of disease as well as assessing treatment outcomes.

Validation against external references like MRC dyspnea grade and spirometric parameters were done. The findings in the present study confine earlier reports of low predicted correlations between SGRQ total score and spirometric measures FEV_1, FEV_1 % predicted, FEV_1/FVC, and FVC. Expectedly, no significant correlation was shown between SGRQ total score and severity of disease using spirometric criteria. Earlier validation of the original English questionnaire did not include the FEV_1 and FVC from a multivariate model testing for their effect on SGRQ total score. This stemmed on the observation that only the Six Minute Walking Distance (6-MWD) accounted for nearly all the effect of spirometry on the SGRQ scores.[1] This conclusion is anticipated as the SGRQ total score is a global estimate of the patient's respiratory health and the impact of airflow limitation to the patient's life. As such, a number of different areas of disease activity contribute to this score, not limited alone to physiologic measures.

Earlier reports have stated that dominant factors determining the SGRQ total score were wheeze, dyspnea, and anxiety.[1] The present study confirms this finding with SGRQ total score (Tagalog) correlating significantly with MRC dyspnea grade. A closer scrutiny shows that significant differences in mean SGRQ total scores were more evident in the groups exhibiting extremes of severity, that is, lower mean SGRQ total scores are expected for less dyspneic/impaired patients.

In conclusion, a conceptually equivalent, valid, user-friendly, Tagalog version of the SGRQ has been successfully developed. This instrument is highly recommended for use in the Filipino patient with chronic airways limitation for measuring impact of disease as well as assessing treatment outcomes.

REFERENCES

1 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis* 1992; 145: 1321- 1327.

2 Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. *Resp Med* 1991: 85 (Suppl): 25-31.

3 Jones PW and the Nedocromil Sodium Quality of life Study. Quality of life, symptoms, and pulmonary function in asthma: long-term treatment with nedocromil sodium examined in a a controlled multicentre trial. Li ur *Respir.11994;* 7: 55-G2.

4 Lahdensuo A. Hushtela T, Herrala J, et al. Randomised comparison of guided self-management and traditional treatment of asthma over one year. *BA111996;* 312: 748-752.

CORRELATION BETWEEN A SELF-ADMINISTERED QUESTIONNAIRE AND SPIROMETRIC STUDIES IN THE EARLY DETECTION OF OBSTRUCTIVE AIRWAY DEFECT AMONG CHRONIC SMOKERS AT ST. LUKE'S MEDICAL CENTER

JERRY T. SY, MD,[1] LINUS JOHN H. STO. TOMAS, MD, FPCP, FACCP,[1] MERCY ANTONINETTE S. GAPPI, MD, FPCP, FPCCP[1]

BACKGROUND COPD is a leading cause of mortality and morbidity, yet it remains to be underdiagnosed. Most often, a patient only seeks medical advice when he becomes dyspneic enough that it interferes with his daily level of activity. By that time, his ventilatory reserves are irreparably lost. It is therefore imperative that early detection be made so that subsequent intervention can be instituted in order to improve patient care.

OBJECTIVE To determine whether a self-administered simple questionnaire on symptoms and risk factors can be used to detect airflow limitation among chronic smokers when compared to spirometric study

STUDY DESIGN Prospective, cross-sectional study

SETTING Spirometry laboratory of the Institute of Pulmonary Medicine, St. Luke's Medical Center

SUBJECTS 100 consecutive patients age >_ 40 years of age with at least 10 pack year of smoking history. Eighty (88%) were males. The mean age was 60.4 years (range 45 - 86).

RESULT Only 94 patients were analyzed and they have on average 30.3 pack years of smoking history (range 10 - 70 pack years). Fifty patients showed obstructive defect by spirometry while 44 had no findings. Data regarding symptoms (presence or absence of cough, shortness of breath, sputum production and wheezing) coupled with the duration of smoking history failed to show any statistically significant correlation with the spirometric findings of obstructive airway disease.

CONCLUSION Various limitations make it difficult to come up with a definite conclusion. *Phil Journal Chest Diseases. Vol 11 No. 1 pp: 10-13*

Keywords: COPD, SAQ, Smoking

INTRODUCTION

COPD is a disease state characterized by airflow limitation that is not fully reversible and is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gasses.[1] It is the fourth' leading cause of death among those over 45 years of age and was reported to have a prevalence of 9.34/1,000 men and 7.33/1,000 women and is highest in countries where cigarette smoking is still common.[2] Although it is said to be the 12th leading cause of disability adjusted life years lost worldwide in 1990, it is estimated to be ranked fifth by the year 2020.[3]

It is apparent that COPD is a major cause of mortality and a significant drain on health care resources but is widely underdiagnosed.[4] Most patients are still first identified when they present to the hospital with an exacerbation. Those requiring intensive care are clearly at an advanced state of their illness with > 30% dying one year after admission.[5] The assessment of large patient cohorts in COPD intervention studies has shown that many are symptomatic with a prevalence of 54% for wheezing, 73% for cough, 54%for sputum production, 36% for difficulty of breathing on exertion. However, most patients do not attribute particular significance to these symptoms, which often worsen during periods of upper respiratory tract infection.

The key indicator for considering a diagnosis of COPD are the presence of chronic cough, chronic sputum production and/or dypsnea with positive history of exposure to risk factors (such as cigarette smoking) and is confirmed by spirometry ($FEV_1/FVC < 70\%$ with post bronchodilator $FEV_1 < 80\%$).'

In 1995, Donald R. Hollerman, reviewed 158 articles regarding the use of history in predicting airflow limitation and found out that patients with at least a 70

[1] Institute of Pulmonary Medicine St. Luke's Medical Center

Table I. Patient characteristics

Sex	94
Male	83 (88%)
Female	11 (12%)
Education	
Elementary	1 (1%)
High School	16 (17%)
College	66 (70%)
Post graduate	11 (12%)

Table II. Distribution of patient characteristics based on questionnaire and correlation with spirometry findings

Patient Characteristic	N (%)	*p* Value
Smoker		
Previous	62 (66)	0.1875
Current	32 (34)	
Range	10-70 pack yrs	
Average	30.3 pack yrs	0.3204
Sputum production		
(+)	54 (57)	0.4386
(-)	40 (43)	
Duration of sputum production		
0-2 weeks	25 (46)	0.7421
2-4 weeks	11 (20)	
> 1 month	8 (15)	
Years	10 (19)	
Cough		
(+)	63 (67)	0.5126
(-)	31 (33)	
Cough Severity		
Everyday	38 (60)	0.5584
Intermittent	25 (40)	
Cough duration		
0-2 weeks	23 (37)	0.5584
2-4 weeks	13 (21)	
> 1 month	16 (25)	
Years	1 (1.7)	
Shortness of breath		
(+)	52 (55)	0.4902
(-)	42 (45)	
Shortness of breath severity		
Intermittent	16 (31)	
Progressive	16 (31)	
Persistent	20 (31)	
Shortness of breath duration		
0-5 years	42 (81)	0.3716
6-10 years	6 (12)	
11-20 years	3 (6)	
> 20 years	1 (1)	

pack year history of smoking are much more likely to have airflow obstruction (40% sensitivity, 95% specific). Symptoms of chronic bronchitis, sputum production or wheezing are associated with a moderate increase in the likelihood of airflow limitation. However, symptoms of cough or exertional dyspnea are associated with only a slight increase in the likelihood of airflow obstruction.[8] It was noted that varying reference standards where used in these studies (mostly $FEV_1/FVC < 60\%$). In our study, the ATS standard cut-off of $FEV_1/FVC < 75\%$ was used in the hope of increasing the sensitivity thereby identifying those in the early stages of the obstructive airway disease. Needless to say, easy access to spirometry is essential for the objective diagnosis of COPD, but in practice, a significant proportion of our health sector and patients have very limited exposure to this very important diagnostic tool, thus diagnosis was basically done on clinical grounds alone. The use of a simple questionnaire, which contains most of the basic respiratory symptoms coupled with the smoking history, would greatly help promote patient awareness and provide feedback to physician about the scale of the problem within their clinic. It is therefore the objective of this study to find out whether a simple self-administered questionnaire would predict airflow limitation among chronic smokers > 40 years of age when compared to spirometric studies alone.

METHODOLOGY

This is a prospective, cross-sectional, questionnaire based study.

One hundred consecutive patients who were at least 40 years of age with at least 10 pack years of smoking history who underwent spirometry were asked to fill up a questionnaire. The questionnaire was arbitrarily prepared as a checklist of symptoms of chronic cough, chronic sputum production, dyspnea and wheezing together with the smoking history. The basis for such questions were the items mentioned in the GOLD guidelines as key indicators for a diagnosis of COPD and that of a proposed questionnaire by Norbert F. Vollkel.[4] The questions were modified to suit our setting and contain mostly the inquiries of a clinician whenever he suspects a diagnosis of COPD in a high-risk group of patients. Patients who had a history of pulmonary tuberculosis, asthma, bronchiectasis, congestive heart failure and COPD were excluded.

Airflow limitation is defined as FEV_1/FVC of < 75% with an FEV_1 of < 80% predicted.

Data were then collected and analyzed statistically using multiple and logistic regression analysis. A *p* value of < 0.05 for a given variable is considered significant.

RESULTS

Out of the 100 consecutive patients examined, six patients were excluded: two had incomplete date, one had history of asthma, one with COPD, and two with PTB. Of the 94 who were analyzed, 83 (88%) were males with an average age of 60.4 years (range 45 - 86).

Most of them (70%) have reached college degree level (*Table I*) and are mostly previous smokers (66%) with an average of 30.3 pack year of smoking history (range 10 - 70 pack years).(*Table II*)

Fifty out of the 94 subjects had airflow limitation by spirometry. Fifty-four patients (57%) had chronic sputum production with most of them (46%) of about 0 - 2 weeks duration while 63 (67%) reported chronic cough which they mostly experience daily for about 0 - 2 weeks at the time of the study.

Fifty-two patients (55%) reported shortness of breath which was mostly persistent (38%) for about 0 - 5 years in 81% of the subjects.

Wheezing was only noted in 13% of our patients and mostly (42%) between 0 - 2 weeks duration.

None of the variables mentioned showed any significant correlation with the finding of airflow limitation by spirometry when statistically analyzed using multiple and logistic regression analysis.

DISCUSSION

A quick and inexpensive method of detecting COPD could lead to more aggressive secondary prevention, earlier treatment to ameliorate symptoms and improve evaluations of pulmonary complaints.[9]

Previous investigators have studied the role of medical history and physical examination in detecting COPD, however, the reproducibility of the pulmonary physical examination has been questioned[10-12] and because of this limitation, the use of the peakflow meter or spirometer has been recommended as a standard part of the pulmonary physical examination. The latter is presently the preferred diagnostic tool because compared to the former, it is less effort dependent, more accurate, reproducible, prognostic and validated in other studies.[13,14] However, spirometry is not as easily accessible and cost more than the peakflow meter. Thus efforts to come up with a diagnosis of airflow obstruction by clinical means alone will greatly benefit those who do not have access to spirometry.

Most of the studies on the diagnosis of COPD based on clinical history were geared towards detecting "clinically significant airflow limitation" or "moderate COPD" rather than focusing on its early detection before significant pulmonary function was lost. It is quite obvious that detecting early disease is of little value unless some form of effective intervention can be offered. This may not always prevent progression of the illness, but can still be applied even when the disease is established, to limit its impact on the patient's life. A range of approaches is available, most of which are supported by substantial clinical evidence.[15] Example is the removal of cause versus stimuli like tobacco and environmental exposure.

Tobacco smoking is by far the most important initiating factor in COPD and stopping smoking is the only intervention known to modify the natural history of airway obstruction.[6] The use of bronchodilators[16] and anticholinergics[17] have been shown to improve the patient's health status presumably by preventing episodes of breathlessness and improving exercise tolerance and ability to undertake daily activity. The use of oral corticosteroids increased the resolution rate of COPD exacerbations,[18,19] thus include the prevention of exacerbations through timed immunization against influenza, treatment of extrapulmonary complications through pulmonary rehabilitation, long term oxygen therapy and surgical approaches in carefully selected patients which may improve exercise tolerance dramatically.

Our study did not show any statistically significant correlation between the clinical variable obtained from the questionnaire and the spirometric study results. This could be due to a lot of flaws and limitations in our study design per se.

Firstly, the questionnaire was not in any way validated. Most of the reported symptoms were only between 0 - 2 weeks in duration and may not actually reflect chronic airway pathology even though the patient is at risk due to the smoking history and age. Our sample size is quite small and selection errors may have occurred when we decided to include those patients who were already referred to the spirometric laboratory for spirometry by their respective attending physicians. We were not able to negate the other differential diagnosis of COPD such as asthma, PTB, bronchiectasis because not all patients had chest x-ray nor post-bronchodilator determinations. The use of FEV_1/FVC as a parameter for the early detection of airflow limitation may not be that accurate. Other proposed measurements of peripheral airway function in individuals with relatively normal FEV_1 have been extensively studied and these included the closing volume and closing capacity, the density-dependence of expiratory flow, nitrogen and oxygen washout testing and the frequency dependence of compliance. All have an excellent physiological rationale, work well in carefully selected individuals but are relatively complex and expensive to perform and, of course, the problem of availability and/or accessibility.[13]

The use of $FEF_{25-75\%}$ may be considered since it reflects the "small airways disease" and may be reduced early even before the FEV_1/FVC declines, but there are

questions regarding its reproducibility for which reason it is not widely used.

Thus, the early detection of COPD is difficult and no simple test can be applied with 100% sensitivity or specificity. However, this is not a justification to abandon all attempts at early intervention. Targeting groups where airflow limitation is likely will undoubtedly improve the present poor situation with regard to early detection.

The economic and social impact of COPD is immense and simply waiting until the affected individuals are noticed by the health care system is not an option. Changes in our attitude to cigarette smoking and the development of effective smoking cessation strategies should help prevent early disease progression, but even when established, much can be done to modify the effects of the disease on the patient long before decision about managing the end stage of the illness arise. In the next decade, improvements in our understanding of the continuing inflammation that characterizes this illness, and changes in our ability to modify it, will make early detection and intervention even more important than they are already.

CONCLUSION

This is a prospective, questionnaire based, cross-sectional study on 100 consecutive patients 40 years of age and above with at least 10 pack years smoking history who underwent spirometry at St. Luke's Medical Center in order to determine whether clinical symptoms and smoking history correlates with findings of airflow limitation in spirometry.

Only 94 patients were analyzed. Fifty patients had obstructive defect by spirometry. None of the data obtained from clinical symptoms and smoking history showed any statistically significant correlation with the spirometric study result.

Flaws in the study design together with various limitations make it difficult to come up with a definite conclusion.

REFERENCES

1 Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary disease, Executive summary, April 1998; Page 8

2 Murray CJL, Lopez AD, editors. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020 - Cambridge, MA: Harvard Press, 1996

3 Murray CVL, Lopez AD. Evidence based health policy - lessons from the global burden of disease study. Science 1996; 274:740-3

4 Vollkel N. Raising Awareness of COPD in Primary Care. Chest 2000 117: 3725 - 3755

5 Connors AFJ, et. al. Outcomes following acute exacerbations of severe chronic obstructive lung disease - The SUPPORT investigators (Study to Understand Progresses and Preferences for Outcomes and Risks of treatments),

6 Anthoniesen NR, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. JAMA 1994;272:1497 - 1505

7 Global strategy for the Diagnosis, Management, and prevention of COPD, April 1998, pp. 7.

8 Hollerman D. Does the Clinical Examination Predict Airflow Limitation? JAMA, Jan. 1995; 273: 313 - 319

9 Camille AE, Burrows B. Longitudinal changes in forced expiratory volume in one second in adults. Am Rev Respir Dis 1987; 135: 794 - 799

10 Mulrow CD, et al. Observer variability in the pulmonary examination. J Gen Intern Med 1986; 1 : 364 - 367

11 Smyllic HC. Observer disagreement in physical signs of the respiratory system. Lancet 1965; 2 : 412 - 413

12 Spiteri MA, Coak DG, Clarke SW. Reliability of eliciting physical signs in the examination of the chest. Lancet 1988; 1: 873 - 875

13 Calvuley P. COPD, early detection and intervention, CHEST 2000; 117: 3655 - 3715

14 Tweeddale PM. Short-term variability in FEV_1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. Thorax 987; 42 : 487 - 490

15 American Thoracic Society. Standards for the diagnosis and care of patients with COPD and asthma. Am Rev Respir Dis 1987; 136: 225 - 244

16 Jones PW. Quality of life changes in COPD patients treaded with salmeterol - Am J Respir Crit Care Med 1997; 155: 1283 - 1289

17 Mahler DA, et al. Efficacy of salmeterol xinaforte in the treatment of COPD - Chest 1999; 115: 957 - 965

18 Niewaehaer DE, et al. Effect of systemic glucocorticosteroids on exacerbations of COPD. N Eng J Med 1999; 340: 1941 - 1947

19 Davies L, Angus RA. Oral corticosteroids in patients hospitalized with exacerbations of COPD - a randomized controlled trial. Lancet 1999; 354: 456 - 460

SMOKING CESSATION INTERVENTION IN A TERTIARY HOSPITAL: The UP-Philippine General Hospital Stop Smoking Program Experience

RHODERICK IAN G. REYES, MD,[1] LENORA C. FERNANDEZ, MD, FPCCP[1]

OBJECTIVES. It is the aim of this study to assess the effectiveness of the UP-PGH Stop Smoking Program in terms of abstinence rates measured at 3 months and 6 months after the actual quit date set for each subject. We also aim to describe the socio-demographic characteristics of the subjects and try to assess if any of these factors correlate with continued abstinence from smoking after 6 months from the actual quit date.

METHODS. Smokers aged 18 years and older who have decided to quit smoking were included in the program. Screening was done at least 2 weeks prior to the first session day on which date, the enrollees were asked to answer a questionnaire that included questions on demography such as age, sex, marital status, educational attainment and employment status. Questions on smoking history such as age when smoking was started, average number of sticks consumed per day for the past year, number of pack years, number of quit attempts in the past, longest time off cigarettes in the past, methods/techniques used in quitting, presence of smokers in the household and Fagerstrom test for nicotine dependence score were also included. A medical history, particularly the presence of important medical illnesses was also elicited.

The enrollees were divided into classes of 5-6 members each and they all attended a 2-3 hour weekly group session for 4 weeks held at the Comprehensive Ambulatory Rehabilitation (CARE) Center of the UP-PGH. The course content of the sessions were patterned on the *StartSmarta* program. The volunteers were followed up at 3 months and 6 months after their actual quit date and their smoking status was reassessed.

The main outcome variable was sustained smoking cessation for 6 months or more. A descriptive analysis was performed first, with categorical variables expressed as proportions and continuous variables as mean (SD) values unless otherwise specified. Fishers exact test and t-test were used when appropriate and a p value less than 0.05 was considered significant.

RESULTS. A total of 22 subjects were enrolled in the SSP from November 2000 to March 2001. Majority of the subjects were males and the mean age was 53.9 years. Most of our patients are married. Half of the subjects had at least a college level education and majority of them are employed. The subjects started smoking at a mean age of 18.27 years and they consumed a mean of 21 sticks of cigarettes per day for the past year. They had a significant smoking history with a mean of 40 pack years and mean Fagerstrom nicotine dependence score of 72. Most of our subjects (86.4%) attempted to quit in the past with a mean of 2.5 attempts. A majority (31.8%) had stayed off cigarettes for one to four weeks with most of them (72.7%) using only self-control techniques. Only a few (13.6%) have ever tried any form of nicotine replacement therapy in their past quit attempts. Majority (63.6%) had housemates who also smoked. All our patients had at least one co-morbid medical illness.

Eleven (50%) of than subjects were still abstaining after three months but this number was reduced to ten (45.5%) after 6 months. A comparison of the demographic characteristics and smoking status of those who were in continuous abstinence versus those who failed to abstain showed no significant difference except for the number of pack years which showed that those who succeeded had a significantly higher number of pack years as compared to those who failed.

CONCLUSIONS. The smoking abstinence rate of patients enrolled at the UP-PGH SSP is 50% and 45.5% at 3 months and 6 months, respectively. This is comparable with those observed in other intensive smoking cessation programs. The demographic characteristics of our subjects reflect the prevalence of smoking in the Philippines. Specifically, males outnumber females, the median age is in the 6th decade and they have started smoking at a mean age of less than 20 years. Those who were able to maintain abstinence for 6 months or more had a significantly higher number of pack years than those who failed. All other demographic and pre-intervention smoking characteristics were similar for both groups. *Phil Journal Chest Diseases. Vol 11 No 1 pp: 14-18*

Key words: smoking cessation, smoking, smoking cessation

INTRODUCTION

In the United States and the United Kingdom, tobacco use is the number one cause of preventable diseases.[1,2] It is estimated that current cigarette smoking trends will cause about 450 million deaths worldwide in the next 50 years.[3] It has been estimated that a heavy smoker at age 25 can expect a life expectancy at least 25% shorter than a nonsmoker.[4] In the Philippines, it was estimated that 33% of adults were current smokers

[1] Section Of Pulmonary Medicine, Department of Medicine, UP-Philippine General Hospital

and another 13% were ex-smokers. At least 40 diseases are known to be definitely linked to smoking. Lung cancer, COPD, coronary artery disease and cerebrovascular disease are among the top 4 in the lists. Consequently, smoking will cause suffering from these diseases in approximately 252,640 Filipinos.[5]

Reducing current smoking by half would avoid 20 - 30 million premature deaths in the first quarter of the century and about 150 million in the second quarter.[3] Smoking cessation has immediate and substantial health benefits, both symptomatically and pathophysiologically, and dramatically reduces the risk of most smoking-related diseases.[6,7] There is evidence that some form of treatment aids an increasing number of successful attempts to quit.[8] A range of tobacco control measures can be effective in reducing tobacco use, and there is now clear evidence that effective support for smoking cessation, delivered through the health care system, would be a substantial and worthwhile addition to these measures. Smoking cessation interventions are guaranteed to bring population health gains for relatively modest expenditure and in the long term reduce health care costs related to smoking. Such interventions remain much more cost effective than many medical interventions.[9] The updates to the British Health Education Authority smoking cessation guidelines for health professionals stipulates that whenever 2nd wherever possible, smokers should have access to a specialist smokers' clinic and that these clinics should offer both and group treatment.[10]

It is in consideration of these data that the Section of Pulmonary Medicine of the UP-Philippine General Hospital (UP-PGH) realized that it was imperative to organize and spearhead the establishment of a multidisciplinary Smoking Cessation Program to serve the patients of the institution as a part of its mission of fostering optimal health care delivery to the masses. The program, known as the UP-PGH Stop Smoking Program (SSP), became operational in November 2000. Since then, it has served and catered to referrals from both the pay and service division of the UP-PGH as well as from other nearby government institutions.

It is the aim of this study to assess the effectiveness of the UP-PGH Stop Smoking Program in terms of abstinence rates measured at 3 months and 6 months after the actual quit date set for each subject. We also aim to describe the socio-demographic characteristics of the subjects and try to assess if any of these factors correlate with continued abstinence from smoking after 6 months from the actual quit date.

METHODS

Patients enrolled at the SSP where either volunteers who signed up in response to advertisements posted in the hospital premises or referrals from the various outpatient clinics within the hospital. Later on, enrollees also came from referrals from nearby private outpatient clinics and institutions. Smokers aged 18 and above who have decided to quit smoking were included in the program. Screening was done at least 2 weeks prior to the first session day on which date the enrollees were asked to answer a questionnaire that included questions on demography such as age, sex (male or female), marital status (single, married, separated, widowed or widower), educational attainment (elementary, high school, college or postgraduate) and employment status (employed, unemployed, retired, homemaker).

Questions on smoking history such as age when smoking was started, average number of sticks consumed per day for the past year, number of pack years (number of sticks smoked per day divided by 20 multiplied by the number of years the patient has smoked), number of quit attempts in the past, longest time off-cigarettes in the past, methods/techniques used in quitting, presence of smokers in the household and Fagerstrom test for nicotine dependence score ((1-11) were also included. A medical history, particularly the presence of important medical illnesses was also elicited.

The enrollees were divided into classes of 5-6 members each and they all attended a 2-3 hour weekly group session for 4 weeks held at the Comprehensive Ambulatory Rehabilitation (CARE) Center of the UP-PGH. The course content of the sessions were patterned on the StartSmart® program by Dr. Elbert Glover and Ms. Penny Glover. A multidisciplinary team of volunteer Pulmonologist, Psychiatrist and a nurse counselor conducted the sessions. The enrollees were required to stop smoking completely on the target day for quitting which was usually a week after the first session. The enrollees were offered *Bupropion* on the first session day; however, the use of this drug was purely voluntary. Those who opted to use *Bupropion* were advised to use it for 6 weeks and a free 2 -week supply of the drug was dispensed. The volunteers were followed up at 3 months and 6 months after their actual quit date and their smoking status was reassessed. The corroboration of at least one household member or caregiver was required to confirm a continued abstinence report.

The main outcome variable was sustained smoking cessation for 6 months or more. Subjects who did not fulfill this criterion or those lost to follow up were considered failures. A descriptive analysis was

Table I. Demographic characteristics of subjects in the Stop Smoking Program

Total number of patients	22
Sex (%)	
Male	17 (77.3)
Female	5 (22.7)
Age (years)	
Mean (± SD)	53.9 (12)
Range	25 – 69
Marital Status (%)	
Single	4 (18.2)
Married	16 (72.7)
Widow (er)	2 (9.1)
Educational attainment (%)	
Elementary	5 (22.7)
High school	6 (27.3)
College	10 (45.4)
Postgraduate	1 (4.6)
Employment status (%)	
Employed	13 (59.2)
Unemployed	3 (13.6)
Retired	3 (13.6)
Homemaker	3 (13.6)

performed first, with categorical variables expressed as proportions and continuous variables as mean (SD) values unless otherwise specified. Fishers exact test and West were used when appropriate and a *p* value less than 0.05 was considered significant.

RESULTS

A total of 22 subjects were enrolled in the SSP from November 2000 to March 2001. The demographic and smoking characteristics of the subjects are summarized in *Tables I* and *II*. Majority of the subjects were males and the mean age was 53.9 years. Most of our patients are married. Half of the subjects had at least a college level education and majority of them are employed. The subjects started smoking at a mean age of 18.27 years and they consumed a mean of 21 sticks of cigarettes per day for the past year. They had a significant smoking history with a mean of 40 pack years and mean Fagerstrom nicotine dependence score of 7.2. Most of our subjects (86.4%) attempted to quit in the past with a mean of 2.5 attempts. A majority (31.8%) had stayed off cigarettes for one to four weeks with most of them (72.7%) using only self-control techniques. Only a few (13.6%) have ever tried any form of nicotine replacement therapy in their past quit attempts. Majority (63.6%) had housemates who also smoked. All our patients had at least one co-morbid medical illness.

Eleven (50%) of the subjects were still abstaining after three months but this number was reduced to ten (45.5%) after 6 months. A comparison of the demographic characteristics and smoking status of those who were in continuous abstinence versus those who failed to abstain showed no significant difference except for the number of pack years which showed that those who succeeded had a significantly higher number of pack years as compared to those who failed (*Table III*).

Table II. Smoking characteristics of subjects in the Stop Smoking Program

Total number of subjects	22
Age started smoking (years)	
Mean (± SD)	18.27 (5.18)
Range	10 – 35
Average stick per day for the past year	
Mean (± SD)	21.2 (12.6)
Range	6 – 70
No. of pack years	
Mean (± SD)	39.6 (25.9)
Range	5 – 125
Fagerstrom nicotine dependence score	
Mean (± SD)	7.3 (2.1)
Range	4 – 11
No of quit attempts in the past	
Mean (± SD)	2.5 (2.3)
Range	0 – 10
Longest time off cigarettes (%)	
Never	3 (13.6)
< 24 hours	0
1 – 6 days	5 (22.7)
1 – 4 weeks	7 (31.8)
1 – 6 months	4 (18.2)
7 months – 1 year	1 (4.6)
> 1 year	2 (9.1)
Methods used in previous quit attempts (%)	
No quit attempts	3 (13.6)
Nicotine gum	2 (9.1)
Nicotine patch	1 (4.6)
Self-control	16 (72.7)
Presence of smokers in the household (%)	
Yes	14 (63.6)
No	8 (36.4)
Co-morbid medical conditions (%)	
CAD/AMI	3 (13.6)
Hypertension	11 (50)
Asthma	1 (4.5)
COPD	5 (22.7)
CVA	4 (18.2)
Others	14 (63.6)

DISCUSSION

Our patient population is composed of individuals in the older age group. This may be reflective of the greater prevalence of smoking in this age group in the Philippines as observed in the study of Dans, et al.[5] which showed that the highest prevalence of smoking (58%) was found in those aged 60 years and above. Similarly, our population showed a higher prevalence of males than females reflecting the national picture of a 75% smoking prevalence among males and 18% among females. Half of our subjects had at least a college level

Table III. Comparison of those who abstained for 6 months or more vs. those who failed to maintain abstinence

Factors	Abstained for ≥ 6 months n=10	Failures N=12	*p* Value
Educational attainment			
Elementary (5)	3	2	
High school (6)	1	5	0.239
College (10)	6	4	
Postgraduate (1)	0	1	
Sex			
Male (17)	8	9	1.000
Female (5)	2	3	
Marital status			
Single (4)	2	2	0.628
Married (16)	8	8	
Widow/er (2)	0	2	
Employment status			
Employed (13)	5	8	
Unemployed (3)	2	1	0.713
Retired (3)	1	2	
Homemaker (3)	2	1	
Use of bupropion			
Yes (16)	7	9	1.000
No (6)	3	3	
Fagerstrom Score (Mean ± SD)	7.5 (2.1)	7.2 (2.2)	0.726
Age started smoking (Mean ± SD)	17.7 (4.0)	18.7 (6.1)	0.648
No. of pack years (Mean ± SD)	52.4 (30.3)	29.0 (16.0)	0.031*
No. of quit attempts in the past (Mean ± SD)	2.5 (3.0)	2.6 (1.6)	0.934
Methods used in previous quit attempts			
No quit attempts (3)	2	1	0.668
Nicotine gum (3)	1	1	
Nicotine patch (1)	1	0	
Self control (16)	6	10	
Presence of smokers in the household			0.204
Yes (14)	8	6	
No (8)	2	6	

education. This is similar to the study of Monso and colleagues, which showed that 60% of those who enrolled in smoking cessation programs had education beyond the secondary level.[11] In that study, they surmised that subjects participating in smoking programs are self selected with an under representation of subjects with lower level of education. Our patients started smoking at an early age. This is similar to the findings in other studies, which show that 90% of smokers began to smoke regularly before the age of 20.[4,11] In the Philippines, a survey by Abundo et at. showed that 70% of smokers started to smoke regularly at age 15.[13]

Our abstinence rate of 50% at 3 months and 45.5% at 6 months is comparable to other intensive smoking cessation intervention programs.[11] On the average, most cessation programs yield between 20% to 40% abstinence rates at 6 to 12 months of follow up.[4] This is in contrast to the 2% to 5% quit rate observed if no intervention was ever used.[14] Various meta-analyses show a 13%-19% increase in quit rates after 6 months or more when intensive behavioral support with either nicotine replacement therapy or *Bupropion* was compared to intensive behavioral support alone. Similarly, a 7% increase in quit rate is observed if face to face intensive behavioral support from a specialist is given compared to no intervention at all.[10] All of our patients underwent intensive group sessions at the SSP. It is believed that group members can motivate each other to maintain an attempt to stop smoking. The Cochrane review found that group therapy was more effective than self help materials, however, there was no significant difference between group and individual therapy in trials where both modalities were compared. Group therapy has the advantage of being theoretically more cost effective.[8]

Our results showed no significant difference between those who maintained abstinence for 6 months as against those who failed to maintain abstinence save for the significantly higher number of pack years among those who remained smoke free for at least 6 months. We cannot find a satisfactory reason that may explain this relationship. It is possible that those who smoked most had the most number of smoking-related illnesses which may have provided them a stronger motivation to quit smoking. However, all of our subjects had at least one identified medical illness. Furthermore, it has been shown that cardiac or respiratory diseases are markers of severe nicotine dependence and may indicate a lower chance of success in smoking cessation among those who participate in smoking cessation programs.[11] This area needs further investigation. A study by Monso et al. showed that older subjects and males had higher quit rates. Furthermore, subjects who consumed fewer cigarettes per day and had lower scores in the Fagerstrom nicotine dependence test also had better chances of maintaining abstinence from smoking.[11] These relationships were not observed in our subjects. The Lung Health study did not observe any sex difference after one year of follow up but a higher relapse rate was observed for females after three years.[12] The use of a pharmacologic agent (*Bupropion*) as an adjunct did not affect the success or failure rate of our subjects. This is in contrast to most studies, which show that pharmacologic agents, specifically nicotine replacement therapy increased the rate of cessation from whatever baseline is set by other interventions.[8,11] A few studies have shown that the level of education [11,15-19] and

employment status[11,20] of smokers are not significant determinants of success in smoking cessation.

This study may be limited by the small population size and short follow up period, however, in as much as the UP-PGH SSP is one of the few structured smoking cessation programs that are operational in the country today, the results of these observations may give us knowledge and insights on how smoking cessation programs in the Philippines may benefit Filipino smokers who are willing to kick their habit but require professional help. Ideally, cessation of smoking should be supported by objective tests such as serum cotinine level determination or carbon monoxide determination. We were not able to perform these tests in our program due to non-availability of equipments in our institution; however, we thought that the corroboration of a concerned caregiver is sufficient to support the claim of continued abstinence or failure of our subjects.

CONCLUSIONS

The smoking abstinence rate of patients enrolled at the UP-PGH SSP is 50% and 45.5% at 3 months and 6 months, respectively. This is comparable with those observed in other intensive smoking cessation programs. The demographic characteristics of our subjects reflect the prevalence of smoking in the Philippines. Specifically, males outnumber females, the median age is in the sixth decade and they have started smoking at a mean age of less than 20 years. Those who were able to maintain abstinence for 6 months or more had a significantly higher number of pack years than those who failed. All other demographic and pre-intervention smoking characteristics were similar for both groups.

Finally, the role of physicians in the prevention and cessation of smoking can never be overly emphasized. Physicians should play an active role in the control of smoking. As smoking represents a threat to the public health, physicians must take a strong and active role seeking its control.[6]

REFERENCES

1 US Department of Health and Human Services. Healthy People 2000. Washington DC: US Government Printing Office; 1991. DHSS Publication (PHS) 91-50212.

2 Callum C. The Smoking Epidemic. London: Health Education Authority. 1998.

3 Peto R, Lopez AD. The future Worldwide Health Effects of Current Smoking Patterns. In: Koop CE, Pearson CE, Schwarz MR, eds. Critical Issues in Global Health. New York: Josey-Bass.

4 Cigarette Smoking and Health. Official Statement of the American Thoracic Society. *Am J Respir Criti Care Med* 1996; 153: 861-865.

5 Dans A, Canizares L, Fajutrao L, et al. The Economic Impact of Smoking in the Philippines. *Phil Journ !nt Med* 1999; 37 (6): 261-268.

6 Smoking and Health: Physician Responsibility. A Statement of the Joint Committee on Smoking and Health. *Chest* 1995; 108: 1118-21.

7 Okuyemi KS, Ahiuwalia JS, Harris KJ. Pharmacotherapy of Smoking Cessation. *Arch Fam Med* 2000; 9: 270 - 281.

8 Lancaster T, Stead L, Silagy C, Sowden A for the Cochrane Tobacco Addiction Review Group. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000; 321: 355 - 358.

9 West R, McNeill A, Raw M. Smoking Cessation: evidenced based recommendations for the healthcare system. *BMJ* 1999; 318: 182-185.

10 West R, McNeill A, Raw M. Smoking Cessation Guidelines for Health Professionals: An update. *Thorax* 2000; 5:987-999.

11 Monso E, Campbell J, Tonnesen P, Gustavsson G, Morera J. Sociodemographic predictors of success in smoking intervention. *Tobacco Control* 2001; 10: 165-169.

12 Bjornson W, Rand C, Connet JE, et al. Gender differences in smoking cessation after 3 years in the lung health study. *Am J Pub Health* 1992; 85: 223-230.

13 Abundo H, Novales ET, Abundo GP, et al. A survey of smoking among 640 medical students. Phil J Cardiology 1984; 12: 7-10.

14 Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to the physicians' smoking cessation counseling. *JAMA* 1996; 275: 1247-1251.

15 Osler M, Prescott E. Psychosocial, behavioral and health determinants of successful smoking cessation: a longitudinal study of Danish adults. *Tobacco Control* 1998; 7: 262-267.

16 Tilgren P, Haglung BJ, Lundberg M, et al. The sociodemographic pattern of tobacco cessation in the 1980s: results from a panel study of living condition surveys in Sweden. *J Epidemiol Community Health* 1996; 50625-630.

17 Olsen J. Predictors of smoking cessation in pregnancy. *Scand J Soc Med* 1993; 21.197-202.

18 Hymowitz N, Sexton M, Ockene J, et al. Baseline factors associated with smoking cessation and relapse. MRFIT research group. *Prev Med 1991;* 20: 590-601.

19 Nides MA, Rakos RF, Gonzales D, et al. Predictors of initial smoking cessation and relapse through the first 2 years of the lung health study. J *Consult Clin Psychol* 1995; 63: 60-69.

20 Morris JK, Cook DG, Shaper AG. Non-employment and changes in smoking, drinking and body weight. *BMJ 1992; 304: 536-541.*

SPIROMETRIC STUDY AND SMOKING AS PREDICTORS FOR MORBIDITY AND MORTALITY AMONG FILIPINO PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CHRISTINA A. UY, MD,[1] PERCIVAL PUNZAL, MD, [1] FPCCP, MARICAR BLANCO-LIMPIN, MD, FPCCP, [1] TERESITA S. DE GUIA, MD, FPCCP[1]

Several studies have been done abroad to determine the different factors affecting morbidity and mortality among patients with Chronic Obstructive Pulmonary Disease. However, to our knowledge, no study of this nature was done on Filipino patients. The objective of this study was to determine the association between spirometric values and smoking with morbidity and mortality among Filipinos with COPD. This is a preliminary report of an ongoing five year study. Forty-one out of 214 patients enrolled were qualified in this study. The study population was mainly males, with a mean age of 67 years and a mean smoking of 44 pack years. Initial data from the six month follow up showed no significant association between the amount of smoking, FEV_1 and FEV_1/FVC with morbidity (in terms of exacerbations) and mortality. Although this trend is observed in the preliminary data, a more conclusive report will be derived during the five year follow up. *Phil Journal Chest Diseases. Vol 11 No 1 pp: 19-23*

Keywords: COPD, smoking, spirometry

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as a disease state characterized by poorly reversible airflow limitation that is usually both progressive and associated with an abnormal inflammatory response of the lung.[1] Worldwide, millions of adults are afflicted with it, a slowly progressive condition that typically becomes symptomatic in the fifth and sixth decades of life.

Causes of COPD include smoking, genetic 'factors (including alpha-antitrypsin deficiency), passive smoking, occupational exposures, air pollution, and possibly hyperresponsive airways. Several outcome measures are used to assess disease severity and predict morbidity and mortality. The most common parameter utilized is FEV_1. It is considered the most important predictor of mortality, besides age. A recent study by Hansen, et al.[3] reported that age, smoking, and the best attainable FEV_1 % predicted are associated with mortality in COPD. However, no similar study was conducted locally to assess such factors among the Filipinos with COPD.

The diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production, or dyspnea and/or history of exposure to risk factors for the disease. The diagnosis is confirmed by spirometry. The presence of a post-bronchodilator FEV_1 <80% of the predicted value in combination with an FEV_1/FVC < 70% confirms the presence of airflow limitation that is not fully reversible.

In the Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD), disease severity is classified into four stages:[4]

Stage 0: At risk is characterized by chronic cough and sputum production. Lung Function, as measured by spirometry, is still normal.

Stage 1: Mild COPD is characterized by mild airflow limitation (FEV_1/FVC <70% but $FEV_1 \geq$ 80% of predicted) and usually, but not always, by chronic cough and sputum production. At this stage, the individual may not even be aware that his or her lung function is abnormal.

Stage II: Moderate COPD is characterized by worsening airflow limitation (30% $\leq FEV_1 \leq$ 80% of the predicted) and usually the progression of symptoms with shortness of breath typically developing on exertion. This is the stage at which patients typically seek medical

1 Division of Pulmonary and Critical Care Medicine, Philippine Heart Center

attention because of dyspnea or an exacerbation of their disease. The division in stages IIA and IIB is based on the fact that exacerbations are especially seen in patients with an FEV_1 below 50% predicted.

Stage III: Severe COPD is characterize by severe airflow limitation (FEV_1 < 30% predicted) or the presence of respiratory failure or clinical signs of right heart failure. Patients may have severe COPD even if the FEV_1 is > 30% predicted, whenever these complications are present.

Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors. The host factor is best documented by a rare hereditary deficiency of alpha-1 antitrypsin. Other risk factors include hyperresponsiveness and lung growth. On the other hand, environmental exposures include cigarette smoking, environmental dusts and chemicals, outdoor and indoor air pollution, infections, and socioeconomic status.[4]

Cigarette smoking is the most important risk factor for the development of COPD. It is now well accepted that this can elicit an inflammatory reaction involving an entire tracheobronchial tree even in the absence of an established airflow limitation. In smokers, the development of airflow limitation is associated with cellular and structural changes in both peripheral and central airways. In peripheral airways, these changes include airway inflammation, fibrosis, smooth muscle hyperplasia, goblet cell metaplasia and lumen occlusion by mucus plugging. Inflammation, fibrosis and smooth muscle hypertrophy, by increasing the thickness of the airway wall, may facilitate uncoupling between airways and parenchyma and promote airway narrowing. In central airways, the development of airflow limitation is associated with a further increase of macrophages and T-lymphocytes in the airway wall and of neutrophils in the airway lumen, suggesting a selective passage of neutrophils across the epithelium into the airway lumen. In a 15 year follow-up study, Stanescu and colleagues found that, in smokers, the accelerated decline in lung function was associated with an increased number of neutrophils in the airway lumen.[1]

Although smoking is the principal cause of COPD, quitting smoking does not appear to result in resolution of the inflammatory response in the airways. This suggests that there are perpetuating mechanisms that maintain the chronic inflammatory process once it has become established.

Lung function is a strong predictor of overall mortality in asthma and chronic obstructive pulmonary disease. FEV_1 is considered to be the "gold standard", whereas peak expiratory flow (PEF) is mostly used in the absence of FEV_1. Hansen et al.[5] compared the predictive power of PEF and FEV_1 measured after maximal bronchodilation. The results showed the best PEF is at least equal to best FEV_1 as predictor of overall mortality in subjects with COPD. In another study, reversibility of FEV_1 to bronchodilators and corticosteroids was shown to have no influence in the survival of subjects with COPD.[5]

In order to validate if indeed these are also true in the Filipino population, we undertook this study to determine the relationship of FEV_1, FEV_1/FVC, and smoking with morbidity and mortality in patients with COPD. We sought to correlate changes in spirometric values with periods of exacerbations (requiring either outpatient treatment or hospitalization) and mortality among COPD patients and to determine the relationship of smoking with periods of exacerbations and mortality among these patients.

Definition of Terms: Smoker - an individual smoking at least one cigarette, pipe, or cigar per day; Ex-smoker - complete cessation of the consumption of any type of tobacco from at least 6 months prior to the start of the study and acute Exacerbations - combination of any of the three clinical findings: worsening of dyspnea, increase in sputum purulence, and an increase in sputum production

METHODOLOGY

This is a five-year prospective, cohort study being conducted at the Outpatient Department of the Philippine Heart Center. The study population consists of 214 patients diagnosed to have Chronic Obstructive Pulmonary Disease (COPD). Informed consent was obtained from all the patients.

All patients fulfilled the following entry criteria: 1. Forty (40) years old and above; 2. Presence of symptoms such as chronic cough, sputum production, or dyspnea; 3. Current or ex-cigarette smokers (at least 5 pack years); 4. Post-bronchodilator FEV_1 < 80% of the predicted and an FEV_1/FVC < 70% of the predicted; 5. In stable condition for at least 2 weeks when the spirometry is performed.

Excluded in the study were: 1. Known asthmatics or history of atopy; 2. Those with an increase of 200 ml and $\geq$ 15% from the baseline FEV_1 after post-bronchodilator test; 3. Those with unstable cardiac disease and other medical problems or terminal illnesses.

Patient Information All patients were given questionnaire on initial visit after informed consent was

Table I. Characteristics of the study population

No. of patients (%)	41 (19.15)
Age (years)	67.15
Male gender	40 (97.6)
Height (cm)	160.6
Weight (kgs)	57.45
Educational Level	
Elementary	4 (9.75)
High School	16 (39.02)
College	21 (51.21)
With comorbidity	20 (48.78)
Smoking Status	
Current smoker	0
Ex-smoker	41 (100)
Smoking duration (pack years)	44.32
Severity of COPD	
Mild	1 (2.4)
Moderate (IIa)	12 (29.2)
Moderate (IIb)	18 (43.9)
Severe (III)	10 (24.3)
Pre-bronchodilator FEV_1	0.9898 ((41.94%)
Pre-bronchodilator FEV_1/FVC	48.138%
Post-bronchodilator FEV_1	0.9829 (43.75%)
Post-bronchodilator FEV_1/FVC	48.135%
Home Oxygen therapy	13 (31.7)
Pulmonary rehabilitation	12 (29.26)

Table II. Patient parameters at baseline and on initial visit.

Parameters	Baseline	Follow-up	Difference	p Value
FEV_1 actual	0.98 ± 0.42	0.92 ± 0.37	0.06 ± 0.215	0.104
FEV_1 % predicted	43.4 ± 19.4	41.38 ± 16.04	1.96 ± 9.11	0.226
FEV_1/FVC	48.58 ± 12.88	46.55 ± 11.77	2.04 ± 6.73	0.078
Symptoms				
DOB *	41 (100%)	25 (68%)		
EF *	37 (90.2%)	11 (30%)		
Cough	41 (100%)	41 (100%)		
Phlegm	41 (100%)	41 (100%)		
Dyspnea Scoring	7.22 ± 0.90	6.50 ± 1.25	0.72 ± 0.24	0.004

* DOB = difficulty of breathing
EF easy fatigability

signed. This included data such as age, gender, educational level, smoking history (current/ex-smokers), home environment and family history. Patients were also asked regarding their past and present respiratory symptoms (cough, dyspnea, sputum production) and current medications for their COPD and other co-morbidities. Co-morbidity is said to be present if the patient suffered from any other chronic disease (such as diabetes mellitus, hypertension, cardiovascular diseases, stroke, arthritis, etc). They were examined by the investigator and pertinent findings were recorded.

Pulmonary Function Test. During the initial visit, baseline spirometry was performed using *Microloop* Spirometer. Each patient underwent post-bronchodilator test with two inhalation of ipratropium-fenoterol (*Berodual*).

Patient Follow-up. Patients was asked to follow up every six (6) months. Another set of questionnaires was given to obtain information regarding the interval symptoms and the number of exacerbations requiring either outpatient management or hospitalizations. Any diagnostic tests done (chest x-ray, arterial blood gas, complete blood count, sputum exam such as Gram stain, KOH mount and AFB smear and culture, electrocardiogram, etc) and medications added (antibiotics, bronchodilators, steroids, mucolytics, etc.) during periods of exacerbation were recorded. Hospitalized patients were asked whether they received mechanical ventilation (non-invasive such as intermittent positive pressure breathing, or continuous positive airway pressure, or invasive such as endotracheal intubation or tracheostomy) during their hospital stay.

In cases of deaths or mortality, the cause was recorded. Physical exam and spirometry will be performed every visit.

Statistical Analysis. Student's *t-test* was used to associate outcome (morbidity and mortality) with the spirometric studies. Spearman Rank Correlation was used to associate smoking with spirometric studies. Association between smoking and outcome (morbidity and mortality) was analyzed using Mann-Whitney or Wilcoxon Two-sample Test.

RESULTS

Patient Characteristics. Out of the 214 patients initially enrolled in this study, only 37 (17.3%) patients were able to complete the first follow-up visit (6 months after the initial visit). Four (1.9%) deaths were reported after the initial visit. Only these patients (41) are included in this preliminary report.

As shown above, the mean age of the COPD patients is 67.15 years old. All, except one, are males. The mean smoking duration was 44.32 pack years. All were ex-smokers. One (2.4%) patient had mild (Stage 1) COPD; 30 (73.1%) had moderate COPD 12 (29.3%) were stage IIa and 18 (43.9%) were in stage IIb and 10 (24.3%) had severe (Stage III) COPD.

There was a decline in the actual mean FEV_1 value and mean FEV_1 predicted from the initial visit (0.98 and 43.34%, respectively) as compared to follow up visit 6 months after (0.92 and 41.28%, respectively). However, this decline in FEV_1 is not statistically significant (*Table II)*.

Table III. Association of initial post-bronchodilator FEV_1 and FEV_1/FVC with adverse events (morbidity and mortality)

Baseline Parameters	With Adverse Events	Without Adverse Event	p Value
FEV_1	0.687 + 0.287	1.034 + 0.454	0.079
FEV_1/FVC	42.24 + 4.917	49.17 + 12.973	0.207

Table IV. Association of smoking duration and post-bronchodilator spirometric values

Spirometer Parameters	r	p Value
BASELINE		
FEV_1	0.098	0.542
FEV_1 % pred	- 0.0220	0.899
FEV_1/FVC	0.556	0.733
FOLLOW UP VISITS		
FEV_1	- 0.0149	0.931
FEV_1 % pred	- 0.1830	0.278
FEV_1/FVC	- 0.2336	0.170

Table V. Association of smoking duration and adverse events and home oxygen therapy

Parameter	Smoking Duration (pack years)	p Value
With adverse events	53 + 39.28	0.932
Without adverse events	54.2 + 30.82	
With Oxygen	60.09 + 38.53	0.462
Without oxygen	47.94 + 20.2	

The mean post- bronchodilator FEV_1/FVC was also lower in the follow up visit compared to baseline value however this was also not statistically significant.

There is persistence of cough and phlegm among these COPD patients from the initial visit; however, symptoms such as difficulty of breathing and easy fatigability were noted to have improved during the follow up visit.

The dyspnea score as assessed by patients themselves were lower on follow up compared to initial visit. It was statistically significant.

During the 6-month interval between the initial and follow up visits, only two patients were reported to have significant exacerbations (requiring either outpatient treatment or hospitalizations). Because the numbers are few, morbidity in terms of exacerbations was analyzed together with the number of mortalities (4) in this preliminary report. They were termed as Adverse Events.

All deaths (4) occurred before the first follow up visit hence no follow up spirometric study was done on these patients. Since this group comprised the majority of the patients included in Adverse Events, their baseline spirometric studies were used instead to associate them with morbidity and mortality. *Table III* showed that the mean baseline FEV_1 and FEV_1/FVC values (0.687 and 42.24%, respectively) were lower than in those with adverse events (exacerbations/mortality) than those without (1.34 and 49.17%, respectively). However, this was not statistically significant.

Table IV showed there is no significant correlation between the duration of smoking with the spirometric studies done during the initial and follow visit 6 months after.

The mean smoking duration was 53.0 pack years for those who developed an adverse event (exacerbation or mortality) compared to the 54.2 pack years for those without adverse event. This was not statistically significant (*Table V*).

The smoking duration was higher in patients who were given oxygen on follow up compared to those who did not. This is not statistically significant.

DISCUSSION

The natural history of airway obstruction is still only partially characterized. Longitudinal studies however show that ventilatory function as measured by the FEV_1 in nonsmokers without respiratory disease declines by 25 to 30 ml/year beginning at about 25 to 30 years. The rate of decline in FEV_1 with age is steeper for smokers than for non-smokers. It is also steeper for heavy smokers than light smokers. The decline in function occurs along a slowly accelerating curvilinear path.[9]

Non-smokers lose FEV_1 at an accelerating rate with age, the average loss is about 30 ml/ year. A small proportion of susceptible smokers (10-15% of the smoking population) lose function much more rapidly, 150 ml/ year and have an FEV_1 of 0.8 L at age 65 years. This was confirmed in a study done by Jimenez-Ruiz, et al.[10] showing that only approximately 15-20% of the smokers developed COPD.

This study showed that the mean FEV_1 and FEV_1/FVC had decreased on follow up visit from the baseline values; however, these were not statistically significant. Since the interval period between the baseline and follow up spirometry was less than a year (6 months), the results were expected.

All patients in the study had persistent cough and phlegm, as noted during the initial and follow up visits.

Majority complained of difficulty of breathing and easy fatigability. The dyspnea scores, as assessed by the patients themselves, were significantly lower on follow up compared to baseline.

Cough is the most frequent symptom reported by patients with COPD. It precedes onset of dyspnea or occurs at the same time. Most patients with COPD manifest cough, expectoration and dyspnea but it is usually dyspnea that causes them to seek medical attention.[9] This usually occur when the FEV_1 has fallen below about 60% of the predicted.[11] In this study, the mean FEV_1 was 43.75% with most patients belonging to the moderate to severe COPD groups. These groups were likely to develop above symptoms. On the other hand, Wijnhoven, et al.[12] found no association between the pulmonary function level and symptoms such as cough, sputum production, and days and nights disturbed by respiratory complaints.

Since the number pf patients included in this preliminary report are few, cases with exacerbations and mortalities were analyzed as one group. Analysis showed that although the spirometric values were lower. in patients who developed adverse events than those who did not, it was not statistically significant. Hence, in this study, no association was found between spirometric studies and morbidity and mortality. This is in contrast to most studies[12] where FEV_1 is considered to be the most important predictor of morbidity and mortality in patients with COPD.

In addition to FEV_1, prognosis in terms of all cause mortality was found to be strongly associated with age and smoking. However, in this preliminary report, no significant correlation between smoking and spirometric studies (after 6 months follow up) was noted. Smoking was also not associated with adverse events. However, the above data are inconclusive because the number of subjects are few and the duration of follow up is short. In another study by Vestbo, et al.[6] reported a higher impact on FEV_1 decline in women than in men. No such observation was noted in this report since majority of the subjects were males.

CONCLUSION

Results from the initial data obtained during the preliminary six months follow-up were too few and short to have a definite conclusion. A more conclusive result hopefully will be derived during the five year follow up.

REFERENCES

1 Saetta, M. Cellular and Structural Bases of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med Vol 163 pp. 1304 - 1309, 2001

2 McCrory, Douglas, et a1. Management of Acute Exacerbations of COPD. Chest 2001; 119; 1190-1209.

3 Hanse, E., et al. Reversible and Irreversible Airflow Obstruction as Predictor of Overall Mortality in Asthma. and Chronic Obstructive Pulmonary Disease. Am J Resp Crit Care Med Vol 159 pp 1267- 1271, 1999

4 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI. WHO

5 Hansen, E.F. , et al. Peak Flow as Predictor of Overall Mortality in Asthma and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med Vol 163. pp. 690- 693, 2001

6 Vestbo, J. Association of Chronic Mucus Hypersecretion with FEV_1 Decline and Chronic Obstructive Pulmonary Disease Morbidity. Am J Respir Crit Care Med Vol. 153 pp. 1530- 1535, 1996

7 Peto, R, et al. The Relevance in Adults of Air-flow Obstruction, but not of Mucus Hypersecretion, to Mortality from Chronic Lung Disease. Am Rev Respir Dis 1983: 128: pp. 491 - 500

8 Landbo, C., et al. Prognostic Value of Nutritional Status on Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med Vol 160. pp 1856- 1861, 1999

9 Murray, John. Textbook of Respiratory Medicine. 3rd edition. WB Saunders Company, USA 2000 pp. 1187-1235

10 Jimenez-Ruiz, C. Smoking Characteristics. Chest 119 (5) May 2001. pp. 1365-1370.

11 Fishman A., et al. Pulmonary Disease and Disorders. 3rd edition. McGraw-Hill Companies, Inc. USA. 1998 pp. 665-667.

12 Wijnhoven, Hanneke, et al. Determinants of Different Dimensions of Disease Severity in Asthma and COPD. Chest 119 (4) April 2001. pp. 1034 - 1042

VALIDITY OF THE RAND 36-ITEM HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRE (FILIPINO VERSION) AMONG PATIENTS WITH COPD IN A TERTIARY UNIVERSITY HOSPITAL

KO, M.A. MD;[1] DE LOS SANTOS, N. MD;[1] TRINIDAD, T.S.MD, FPCCP[1]

OBJECTIVE To determine the reliability and validity of our version of RAND 36 Item Health Related Quality of life questionnaire, translated into Filipino, administered among COPD patients.
DESIGN Hospital Based Cross Sectional Study
SETTING Out-Patient department and The Pulmonary Rehabilitation Unit of the Center for Respiratory Medicine, University of Santo Tomas Hospital
RECRUITMENT: 60 patients with a diagnosis of COPD were recruited from the period of March to September 2001
METHODOLOGY The RAND 36 item questionnaire is widely used worldwide and has been translated into many languages and has been successfully tested for reliability and validity. Our subjects were asked to answer this self-administered and translated questionnaire during their visits to the Out-Patient Department and COPD patients undergoing Pulmonary Rehabilitation Unit.
OUTCOME MEASURES Cronbach's Coefficient Alpha, Item-Total Correlation and Inter Item-Correlation were used to analyze the mean scores, reliability and construct validity of the questionnaire.
RESULTS Reliability of our version of the questionnaire were acceptable (alpha = 0.70) on four out of eight health concepts assessed by the questionnaire. These are Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems and social functioning. Cronbach's alpha coefficients increased after elimination of certain items in the concepts with low reliability coefficients. The item analysis also showed poor correlation among the items of these different concepts.
CONCLUSION This translated version showed to be reliable only on four domains. Low reliability coefficients in other domains may due to differences in age, gender, education, socio-economic status, cultural diversity and disease severity. Some items may need to be revised to improve the reliability and validity in other domains. *Phil Journal Chest Diseases. Vol 11 No 1 pp 24-27*

Keywords: COPD, QOL, Filipino version

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. It is usually progressive and associated with an abnormal response of the lungs to noxious gases and particles.[1] As patients become symptomatic in COPD, complaints of dyspnea, fatigue, and sleeplessness are common. These factors lead to physical deconditioning, decreased performance in daily activities and impaired quality of life.[2,3] Survival has been the main endpoint in several clinical trials for COPD but only few interventions have demonstrated to improve survival. Improving quality of life is another aspect of therapy to COPD.[2]

Health related quality of life (HQORL) refers to how health impacts an individual's ability to function and perception of well being in the physical, psychological and social domains of life. Interest in HRQOL over the past years has increased because of the following factors: First, patients are more concerned over their symptoms and functional ability rather than objective measures like expiratory airflow (FEV_1). Second, it is a unique construct that differs from physiologic measures and third, in addition to physiologic measures; the goals of therapy now include symptom relief and improvement in the quality of life. Hundreds of HRQOL instruments have been developed. There are two distinct types: Generic and Specific.

The generic HRQOL instrument is applicable to all diseases or conditions across different medical

1 Section of Pulmonary and Critical Care, Department of Medicine, UST Faculty of Medicine and Surgery; Center for Respiratory Medicine, University of Santo Tomas Hospital, Manila

interventions across a wide range of population. Examples include the Sickness Impact Profile (SIP), Nottingham health Profile (NHP) and the Short Form 36 (SF 36) questionnaires. In contrast, the specific HRQOL instrument is designed to be relevant to a particular condition or disease. Examples include the Chronic Respiratory Questionnaire (CRQ) and the St. George Respiratory Questionnaire (SGRQ); both are useful in COPD.[4,5]

The RAND-36 item HRQOL instrument is one of the most widely used instruments in the world today. It is a generic form of instrument with 36 items derived from a larger pool of questions used in the medical Outcomes Study (MOS). This instrument is distributed by the RAND Corporation and is also being distributed by the Medical Outcomes Trust as the Short-Form 36 (SF-36). Both instruments carry the same questions and construct with minor differences in scoring for the pain and general health scales. Various studies have shown that this instrument is reliable and valid in the assessment of HRQOL among individuals with different chronic illnesses such as diabetes, HIV, multiple sclerosis, sepsis and those with respiratory diseases such as asthma, idiopathic pulmonary fibrosis and COPD.[7-12] It is also a valid instrument in measuring treatment outcome in patients with COPD using bronchodilator and those undergoing pulmonary rehabilitation. This instrument has been already been translated to French, Dutch, German, Japanese, Italian, Arabic and other languages.[7,9] To date, no Filipino version of RAND 36 exists.

The use of this instrument in our country is important to assess health related quality of life and to determine outcomes of therapy or medical interventions among patients with chronic diseases. A short-form generic Filipino HRQOL instrument was developed and validated in 1993.[14] The development of a reliable and valid HRQOL is important in our setting is important in the assessment of impact of therapeutic interventions on quality of life of COPD patients especially those undergoing pulmonary rehabilitation.[15] It is the aim of this study to determine the reliability and validity of our version (Filipino) of the RAND-36 item HRQOL questionnaire among COPD patients in our institution.

METHODOLOGY

This is a hospital-based cross sectional survey

Recruitment of Patients. Patients suspected as having obstructive airway disease based on the presenting symptoms and signs with more than 20 pack year smoking history, were recruited from the Out-Patient Department and the Pulmonary Rehabilitation Unit of the University of Santo Tomas Center for Respiratory Medicine. Recruitment period was from March 2001 to August 2001.

They were asked to undergo spirometry and those whose FEV_1/FVC ratio was less than 70% and whose FEV_1 was less than 70% of predicted with no post bronchodilator reversibility or partial reversibility of less than 15% of FEV_1 were included in this study. Patients with FEV_1 between 70 to 60% of predicted were classified as having mild COPD. Those with FEV_1 between 59%-40% are considered moderate and values below 40% is labeled as having severe COPD.[1,15]

Patients who are not literate in Filipino and those who were unwilling to answer questionnaires were excluded.

Questionnaire. The English version of the RAND 36-item questionnaire was translated to Filipino in accordance to standardized methodology. The patients were asked to completely answer all the questions in the self-administered questionnaire. The RAND assesses eight health concepts or domains with multi item scales (35 items). Physical functioning (10 items), role limitations caused by physical health (4 items), role limitation caused by emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), pain (2 items), social functioning (2 items) and general health perceptions (5 items). A single item assesses change in the perceived health during the past 12 months, which does not contribute to the RAND scale scores. The pre-coded numeric response to each item is recoded and assigned a score of 0 to 100. The higher the score the more favorable is health status. The instrument does not have a single total score. Instead, the total score for each scale is averaged providing a summary score for each of the eight health concepts.[6,8,10,16]

Statistical analysis Data were analyzed using Intercooled STATA software. The means of the eight scale scores were recorded. Internal consistency reliability was analyzed using Cronbach's alpha coefficients for each of the eight health concepts. An acceptable value of 0.70 or above is recommended for each of the concepts. Item analysis was done using Item total and Inter-item correlation. A variable that has a negative correlation or a value less than 0.20 indicates that an item is subject for removal. This formula along with Cronbach's alpha coefficient is also used for construct validity of the said questionnaire.[6,17]

RESULTS

We were able to recruit 60 patients with COPD. There were 58 males and two females. Mean age is 65

Table I. Baseline characteristics

Patients	60
Male	58
Female	2
Age	
Mean	65 years
Range	38 - 84
Educational Attainment	
Elementary	20 (33%)
High School	21 (35%)
College	17 (28%)
Post-graduate	7 (3%)
Disease Severity (FEV_1 % predicted)	
Mild	38
Moderate	15
Severe	7

Table II. Distribution of patients according to time needed to complete the questionnaire

Time	Number of Patients (%)
0 – 5 minutes	2 (3)
5 – 10 minutes	19 (32)
10 – 15 minutes	21 (35)
15 – 20 minutes	18 (30)

Table III. Reliability and mean scores between the MOS 36 item and local version

Health Concepts (Domains	MOS-36 n=2471		Local Version n=60	
	Mean	Alpha	Mean	Alpha
Physical function	70.61	0.93	39.08	0.89
Role limitation (physical)	52.7	0.84	20.83	0.70
Role limitation (emotional)	65.78	0.83	28.88	0.76
Energy/ Fatigue	52.15	0.86	44.3	0.58
Emotional well-being	70.38	0.90	54.4	0.64
Pain	78.77	0.85	62.5	0.76
Social function	70.77	0.78	56.8	0.47
General health	59.66	0.78	43.6	0.62

and the range was 38 to 86 years old. Thirty-eight patients were classified as having mild COPD, 15 belong to the moderate category and 7 have severe COPD.

Thirty-three percent of the population was able to complete primary education. Thirty-five percent had or finished high school. Twenty-eight percent had tertiary education or college graduates and 3% obtained post-graduate degrees (*Table I*). Most patients were able to accomplish the questionnaire between 6 to 20 minutes. Thirty percent however took more than 20 minutes to answer the questions (*Table II*).

Scale reliability coefficients (Cronbach's Alpha) of our questionnaire were noted for each of the following concepts: Physical functioning (0.86), role limitations/physical (0.70), role limitations/emotional (0.76), energy/fatigue (0.58), emotional well-being (0.64), social functioning (0.76), pain (0.48) and general well being (0.62) (*Table III*).

Item analysis using Inter-item correlation, item-total correlation and Cronbach's alpha showed items number 26, 27, 30, and 35 as with poor correlations from the rest of the questions. This indicates the need for elimination from the questionnaire in order to increase the reliability and validity.

DISCUSSION

Reliability is the degree to which an instrument is free from random error. It estimates by examining the extent to which similar scores will be obtained with multiple replications. In other words it is synonymous to reproducibility and repeatability.[5,6,17] The results of our study showed that the internal consistency reliability of different health concepts or scales varied from low to high. Four of the eight health concepts showed reliability coefficients of greater than 0.70. The reliability coefficients obtained by the Medical Outcomes Study (MOS) administered to different sets of patients (n=2471) using the prototype 36 item HRQOL instrument were all greater than 0.75 in all concepts even reaching as far as 0.90 and 0.93 in emotional well-being and physical functioning respectively (*Table III*). However, not all studies using this type of HRQOL instrument showed high reliability coefficients in all concepts. One study among asthmatics showed that the alpha coefficient in the social function concept did not reach 0.50.[8] Another one this time with sepsis patient showed a low coefficient of 0.65 but only in one health (general health) concept.[7] The Arabic version of RAND also showed one concept (general health) with reliability below 0.60.[9] Our version had four concepts with low reliability. Coons explained that reliability estimates vary in subgroups differing in age, gender, ethnicity, education, socioeconomic status and disease severity.[5] It is also important to consider the ability and willingness of the subject to answer long self-administered instruments.[6]

We also did inter-item analysis on the concepts with low reliability coefficients and found out that some individual questions under these concepts (domains) were poorly correlated with each other influencing reliability and validity requiring the need for their

elimination from the questionnaire. An instrument with low reliability is hardly valid. Construct validity therefore was considered poor.

Perhaps the low sample population and the unequal distribution of characteristics contributed to the low reliability not to mention the influence of cultural diversity and educational status. Some items may need not be translated verbatim but rather to a simple, adaptable and applicable statement suitable for our population. Example: "pushing a vacuum cleaner" be converted to "scrubbing the floor". Much as the authors want to eliminate these items from the questionnaire, we feel that this will defeat the purpose of the study in developing a valid and reliable Filipino version of the RAND-36 HRQOL instrument. We therefore recommend that some questions on this instrument be revised even all sets in one concept (domain) with low reliability and re-administer to patients more willing to answer. It is also our recommendation that the validation of this translated version be administered to a more diverse population i.e. those with diseases other than COPD.

REFERENCES

1 Executive Summary of the Global Strategy for the Diagnosis and Management of COPD (GOLD) April 1998

2 Yusen D., what outcomes should be measured in patients with COPD, Chest 2001: 327-328

3 Bouen F., Bartleston B. et al., Quality of life be measured with a generic instrument improves the following pulmonary rehabilitation in patients with COPD, Chest 2001 119: 77-84

4 Mahler D., How should health relates quality of life be measured in patients with COPD, Chest 2000, 117: 54s-57s

5 Coons J. Samati R., A comparative review of generic quality of life instruments, Pharmacoeconomics 2000, 1: 13-35

6 Hays R., Sherbourne C., et al. Users manual for the Medical Outcomes Study (MOS) core measures of health related quality of life. MR 162 RC, RAND online publication

7 Heyward M., Hopman W. et al., Long-term health related quality of life in survivors of sepsis. Crit. Care Med. 2000, 11: 3599-3605

8 Bousquet J., Khalel J. et al, Quality of life in Asthma, Am.J. Respir. Crit. Care Med.: 1994,1: 371-375

9 Coons, J. Alabdulmhosin, S., reliability of an Arabic version of the RAND 36 health survey and its equivalence to the US-English version, Medical Care, March 1998, 36: 428-432

10 Hays, R., Morales D., et al., The Rand 36 measure of the health related quality of life, Annals of Medicine; 2001 Finnish Med. Society Duodecim

11 Martinez., Pereira C. evaluation of Short-Form 36 item questionnaire to measure health related quality of life in patients with Idiopathic Pulmonary Fibrosis, Chest 2000, 117: 1627-1632

12 Mahler D., Mackowiak J., evaluation of the Short-form 36 item Questionnaire to measure health related quality of life in patients with COPD, Chest 1995, 107: 1585-1589

13 Jones P., Bosh T., Quality of life changes in COPD patients treated with Salmeterol, Am. J. Respir Crit Care Med 1997, 155: 1283-1289

14 Espallardo N., Bes, A., Validity and Reliability of a Short-form questionnaire in the assessment of health related quality of life, concepts in out patient setting, The Filipino Family Physician, Jan.-March 1993:31:1-8

15 PCCP council on COPD, Clinical Practice Guidelines in the Diagnosis and Management of COPD, 1999

16 Hays, R. Sherbourne C. et. al., The RAND 36-Item Health Survey 1.0; Health Economics 1993, 2: 217-227

17 Glaser A., High Yield Biostatistics, Lippincott, 2nd ed. 2001

THE EFFECTS OF A COMPREHENSIVE PULMONARY REHABILITATION PROGRAM ON COPD PATIENTS

CHONA A. DE VERA MD,[1] PERCIVAL PUNZAL MD, FPCCP, [1] ABNER T. KOH MD, FPCCP, [1] MA. ENCARNITA LIMPIN MD, FPCCP, [1] TERESITA S. DE GUIA MD, FPCCP[1]

BACKGROUND COPD remains a major health problem and is expected to become a greater one in the future. Late diagnosis, the nature of the disease itself, and lack of good pharmacotherapy, combine to make the disease progressive. Pulmonary rehabilitation is one of the current approaches which offer some way of retarding the downhill course of this disease.

OBJECTIVE This study was undertaken to define the benefit of pulmonary rehabilitation in the Philippine setting

METHODOLOGY Retrospective and prospective cohort study. Patients who were subjected to pulmonary rehabilitation from January 1991 to December 2001 were evaluated for inclusion. Those who were able to complete the eight week program were assigned to Group A while the rest were assigned to Group B. Differences between the two groups using certain parameters such as treadmill workload, six-minute walked distance, and functional status as assessed by a shortness of breath questionnaire were examined.

RESULTS Data from 154 patients were analyzed out of a potential 409 who were enrolled in the program; with 109 assigned to Group A and 45 to Group B. There was a significant increase in exercise tolerance and six minute walked distance after completion of rehabilitation. Functional status as assessed by the Shortness of Breath Questionnaire likewise showed improvement post-rehabilitation. Perception of dyspnea while performing activities of daily living such as climbing the stairs, walking, eating and bathing was also reduced after rehabilitation. Fear of shortness of breath likewise improved after rehabilitation.

There was a slight but insignificant difference when the number of hospitalization per year was compared among patients who completed the program and those who dropped out. Survival analysis however showed a significant difference between the two groups, with Group A showing a better survival than Group B.

CONCLUSION This study showed a positive impact of pulmonary rehabilitation program in the long term care of patients with chronic obstructive lung disease. It reduces symptoms, increases functional ability and improves the quality of life in individuals with chronic respiratory disease. *Phil Journal Chest Diseases. Vol 11 No 1 pp 28-33*

Keywords: COPD, Pulmonary rehabilitation, QOL

INTRODUCTION

COPD is a major public health problem. It is currently the fourth leading cause of death in the world and by 2020, it is projected to rank fifth as a worldwide burden of disease.[1] Dyspnea, impaired exercise tolerance and reduced quality of life are common complaints in patients with COPD. When clinical symptoms of COPD become severe enough for patients to seek medical advice, the disease usually has entered the final decade of its 30 to 40 year course.[2] At this stage, physicians are limited in being able to reverse, to stabilize or to substantially slow down the relentless downhill course. Nevertheless, physicians are still faced with providing the best health care for these individuals.

In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report, pulmonary rehabilitation has been recommended as part of the management of patients with stable moderate to severe disease.[3] Rehabilitation for these patients is a well established and widely accepted means of enhancing standard therapy in order to alleviate symptoms and optimize function.[4-6]

The National Institute of Health (NIH) defines pulmonary rehabilitation as "a multidisciplinary continuum of services directed to persons with

1 Pulmonary Rehabilitation Unit, Division of Pulmonary and Critical Care Medicine, Philippine Heart Center

pulmonary diseases and their families, usually by an interdisciplinary team of specialists, with the goal of achieving and maintaining the individual's maximum level of independence and functioning in the community."[7]

The Pulmonary and Critical Care Division of this institution initiated the formation of a section in Pulmonary Rehabilitation in December 1990. As with all other similar programs around the world, the primary goal of the Pulmonary Rehabilitation Program is to restore the patient to the highest level of independent function. This is carried out through a structured comprehensive program including education and exercise. Patients are counseled about their illness and are encouraged to assume active roles in their own health care. Exercise programs of both upper and lower extremities are introduced as cornerstones of the program.

Numerous studies have shown the benefits derived from a pulmonary rehabilitation program, including improved exercise tolerance, improved functional status and overall improvement in the quality of life.[8-10]

This study was undertaken to evaluate the effects of pulmonary rehabilitation on COPD patients. It also sought to determine the effects of pulmonary rehabilitation on 6 minute walked distance, maximum exercise tolerance and questionnaire-rated functional status. We also wanted to determine the effect of pulmonary rehabilitation on the number of hospital confinements and survival as well as to compare the outcome of those who completed the pulmonary rehabilitation program from those who failed to complete the program.

METHODOLOGY

Study design: Retrospective and prospective cohort study

The study included all patients enrolled in the pulmonary rehabilitation program from January 1991 to December 2001. Entry criteria included (1) clinical diagnosis of COPD confirmed by history, physical examination, spirometry and chest roentgenogram: (2) stable condition for 2 weeks while receiving an acceptable medical regimen prior to entry; (3) no other significant lung disease; and (4) no unstable cardiac disease or other medical problem which would limit participation in the rehabilitation program. Baseline information included age, gender and smoking history.

Patients were grouped into two. Group A were patients who were able to finish the 8-week outpatient program while Group B consisted of patients who failed to finish the rehabilitation program.

Baseline Testing: Each patient underwent pre-rehabilitation exercise testing which included arterial blood gas analysis, spirometry, 6 minute walked distance, and incremental symptom-limited exercise testing using the treadmill.

Each patient was asked to accomplish a self-administered shortness of breath questionnaire.

ABGs Arterial blood gas samples were taken from each patient while at room air. Analysis was done using *Acid Base Laboratory 3* gas analyzer.

Spirometry Each patient was subjected to spirometry using the *Vitalograph Compact Dry* Spirometer. Both pre- and post-bronchodilator testing were recorded. Normal values used were those of Morris and co-workers for the spirometric data.[11]

6 Minute Walked Distance Each patient was asked to walk around a pre-measured track at their own pace, attempting to cover as much ground as possible in 6 minutes. Patients were allowed to stop and rest during the test but were instructed to resume walking as soon as possible. Blood pressure was monitored before and after the test while heart rate and oxygen saturation was monitored all throughout the test using *Nellcor Pulse Oximeter N100E.* Perceived breathlessness and muscle fatigue was rated using the modified Borg scale.[12]

Exercise test. Each patient performed an incremental symptom-limited exercise testing on a treadmill using a COPD protocol.[13] Arterial oxygen saturation was monitored continuously while the electrocardiogram was taken before and during the test. Blood pressure was taken at regular intervals.

The test was terminated once the patient has reached symptom-limited maximum, or the oxygen saturation fell to less than 85% or ST-T wave depression or serious arrhythmia is noted on ECG, or if BP is excessively high (systolic > 250 mmHg).

At the end of the test, patients rated the breathlessness and muscle fatigue using the modified Borg scale.[12]

Shortness of breath questionnaire Each patient was made to answer this 24-item questionnaire. A patient is asked to indicate on a 6-point scale how frequently he experiences shortness of breath (0 = 0% of the time or never, 1 = 25% of the time or sometimes, 2 = 50% or half of the time, 3 = 75% or most of the time, 4 = 100% or all of the time, and NA = not applicable or unable to do) during 21 activities of daily living that are associated with varying levels of exertion. The questionnaire

includes three additional questions about limitations caused by shortness of breath, fear of harm from overexertion and fear of shortness of breath.[14]

Exercise Training Rehabilitation sessions were scheduled two times a week for 8 weeks.

Training consisted of upper and lower body exercises. The lower body exercise involves supervised walking on a treadmill. Training was started at a level that patients can sustain for several minutes. At home, they are encouraged to continue this exercise daily at a walking pace that approximates their sustained treadmill speed. Training levels are subsequently increased during the supervised sessions, and the goal is to have them walk continuously for 30 minutes.[15]

Upper body exercise training is composed of prescribed arm exercises and upper body cycle ergometry. The arm exercises are done in three sets with six repetitions daily. Initially, they are performed without hand weights. Subsequently, light hand weights (1-2 lbs) were added as tolerated. Cycle ergometry is performed initially without resistive load for 15 minutes. The load is subsequently added during the following sessions.[15] Perceived breathlessness and muscle fatigue was rated using the modified Borg scale.

Education The education sessions consisted of lectures and discussions with the help of visual aids, slides and videotapes. The lectures are conducted by the staff in the simplest of terms. Topics covered include what is COPD, proper use of oxygen, the "hows and whys" of exercise, medications, energy-saving and breathing techniques, stress reduction, early recognition of acute symptoms and appropriate emergency measures.

Follow-up At the end of the eight week program, each patient performed the 6MWD and the incremental symptom limited exercise test using the treadmill in a manner similar to baseline. Patients were likewise made to accomplish the Shortness of Breath Questionnaire.

Patients were subsequently followed up to assess the survival status. Assessment consisted of reviewing the medical/hospital records, contacting the primary physician, the patient or the family. For patients who did not survive, cause of death were recorded and categorized into either primary pulmonary or non-pulmonary. The period of time from pulmonary rehabilitation to death was likewise recorded.

Statistical Analysis Paired *t-test* was used to determine if there are significant changes in 6MWD and maximum exercise tolerance. Wilcoxon matched pair signed ranked test was applied to functional status. Survival analysis using Kaplan-Meier was applied to the data to find out the rate of survival of patients after rehabilitation.

Table I. Patient characteristics

	Group A N = 109	Group B N = 45	p Value
Age (years)	67.8 + 8	67 + 7	0.94
Sex F M	 2 (7%) 101 (93%)	 2 (4%) 43 (96%)	
Smoking Hx (pack years)	54 ± 41	55 ±37	0.92
FEV_1, L	1.07 ± 0.45		0.010
FVC, L	2.17 ± 0.70		< 0.0001
FEV_1/FVC, %	50 ± 14		0.756
GOLD classification	Predominantly IIB	Predominantly IIB	

Table II. Pre- and post-rehabilitation assessment results of patients in Group A

	Baseline	After Rehab	Difference	p Value
Treadmill workload, mph	2.0 ± 0.68	3 ± 0.22	0.53 ± 0.605	<0.0001
Perceived breathlessness	3 ± 1.3	3 ± 1.1	0.56 ± 1.5	<0.0001
Perceived fatigue	2 ± 1.5	2 ± 1.3	0.03 ± 1.7	0.004
Six minute distance walked, m	303 ± 96	381 ± 96	77 ± 53	<0.0001
Perceived breathlessness	2 ± 1.14	2 ± 1.22	0.344 ± 1.37	<0.0001
Perceived fatigue	1 ± 1.16	1 ± 1.29	0.06 ± 1.41	<0.0001
ADL				
Dyspnea at				
Rest	1 ± 0.85	0.1 ± 0.36	0.47 ± 0.81	<0.0001
Walking	2 ± 1.28	0.5 ± 0.67	1.25 ± 1.10	<0.0001
Climbing stairs	3 ± 1.68	1 ± 1.70	1.73 ± 1.19	<0.0001
Eating	0.6 ± 1.02	0.08 ± 0.28	0.52 ± 0.85	<0.0001
Brushing teeth	0.5 ± 0.98	0.1 ± 0.80	0.37 ± 0.82	<0.0001
Shaving	0.5 ± 1.36	0.1 ± 0.8	0.4 ± 1.03	<0.0001
Bathing	2 ± 1.71	0.8 ± 1.15	1.29 ± 1.22	<0.0001
Fear of SOB	2 ± 2.09	0.8 ± 1.88	1.28 ± 1.31	<0.0001

RESULTS

A total of 409 patients were enrolled in the pulmonary rehabilitation program. Ninety-one patients were enrolled for non-COPD conditions while 318 patients fulfilled the inclusion criteria for COPD. However, records of 60 patients were lacking in data and were therefore excluded. The remaining 258 COPD patients were grouped into two, Group A were patients who completed the rehabilitation program and Group B were patients who dropped from the program. Patients who could not be followed up by telephone or by mail were likewise excluded from the study.

Data from 154 patients were analyzed. One-hundred nine patients were assigned to Group A and 45 patients were assigned to Group B. Baseline characteristics of patients as well as pulmonary function tests and GOLD

Table III. Long term effects of pulmonary rehabilitation

Outcomes	Group A N = 109	Group B N = 45
Hospitalization/year	0.53 ± 1.37	0.69 ± 1.86
Survivors	48 (44%)	14 (31%)
Non-survivors	61 (56%)	31 (69%)
Pulmonary causes	48 (79%)	26 (84%
Non-pulmonary causes	13 (21%)	5 (16%)

classification are shown in *Table I*. There were no significant differences between the two groups at study entry except for the FEV_1 and FVC. Patients in both groups had a mean age of 67 years. There was also a predominance of the male gender seen in both groups. All patients had significant smoking history. Baseline pulmonary function tests showed moderate to severe obstruction with majority of the patients belonging to stage IIb of the GOLD classification. Forty-one patients in group A (38%) were on oxygen supplement while there were 20 patients in group B who were also on oxygen supplement (40 %).

Results from the exercise tests at baseline and after rehabilitation are shown in *Table II*. Baseline exercise test showed reduced maximum exercise tolerance. There was a significant increase in exercise tolerance after completion of rehabilitation. The six minute walked distance was also increased post-rehabilitation compared to the baseline. Functional status as assessed by the Shortness of Breath Questionnaire likewise showed improvement post-rehabilitation. Perception of dyspnea while performing activities of daily living such as climbing the stairs, walking, eating and bathing was also reduced after rehabilitation. Fear of shortness of breath likewise improved after rehabilitation.

There was a slight but insignificant difference when the number of hospitalization per year was compared among patients who completed the program and those who dropped out. Survival analysis however showed a significant difference between the two groups, with Group A showing a better survival than Group B. When the cause of death was evaluated, most of the patients died due to pulmonary complications. There was a significant correlation between the GOLD classification and mortality, with death increasing as the pulmonary obstruction becomes severe. This was however seen only in Group A. (*Table II*)

DISCUSSION

Numerous randomized studies have firmly established the efficacy and scientific foundation of pulmonary rehabilitation. The belief that there is little hope for improvement in patients with COPD has been refuted and pulmonary rehabilitation is no longer viewed as a last-ditch effort to manage patients with severe respiratory impairment.[16]

The results of the study clearly showed the benefits of a pulmonary rehabilitation program for patients with COPD. There was evident increase in the exercise capacity of patients after completion of the program as seen by a significant increase in workload in the treadmill as well as a significant improvement in the six minute distance walked with a reduction in the perceived breathlessness and fatigue. Both uncontrolled and controlled studies demonstrate that lower extremity exercise training improves exercise tolerance.[17-19] In addition, studies of comprehensive pulmonary rehabilitation show an improvement in dyspnea during exercise.

The possible mechanisms for improved exercise capacity and reduced severity of breathlessness are physiologic training responses that include increased skeletal muscle enzymes and reduced exercise-induced lactic acidosis. Casaburi et al[20] demonstrated physiologic training responses (an increase in peak VO_2, a decrease in exercise ventilation and an increase in lactic threshold) in a supervised, inpatient rehabilitation program in patients with mild to moderate COPD while Maltais et al[21] showed that endurance training reduced exercise-induced lactic acidosis and improved skeletal muscle oxidase acitivity in 11 patients with moderate to severe COPD. Relief of dyspnea may be due to the corresponding fall in ventilatory demand during exercise as a result of enhanced mechanical efficiency. O'Donnell et al[18] and Ramirez-Venegas et al[22] have suggested that enhanced respiratory muscle function can also contribute to improved breathlessness. Likewise, psychological factors including the development of tolerance or desensitization to dyspnea may enable

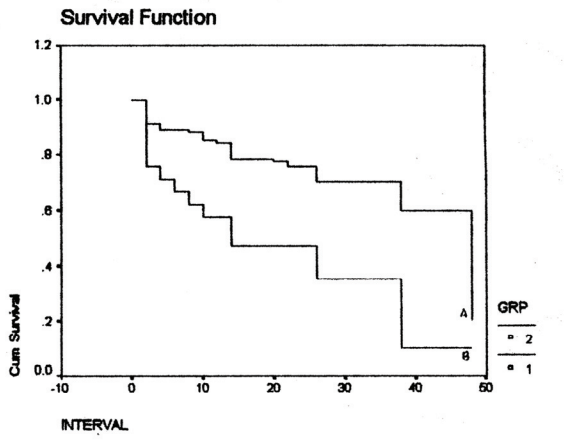

Figure 1. Survival curve of patients

patients to perform higher levels of work with reduced symptoms.

There was also an improvement in the functional status as evidenced by the reduction of dyspnea in the performance of activities of daily living. Most COPD patients become more dyspnea using their arms more than their legs, more so if they attempt to raise it to shoulder level or higher. This is thought to be due to the fact that arm and shoulder muscles become recruited as accessory muscles of ventilation during exercise at higher workloads. Patients with flattened diaphragms tend to utilize their shoulder as a kind of auxillary diaphragm.[23] When those muscles are also required to perform upper extremity work, which most activities of daily living (ADLs) require, they may not be up to the additional task of ventilatory support. Upper extremity exercise training can augment the strength and endurance of these muscles and thereby enhance inspiration and allow COPD patients to perform ADL tasks with less dyspnea.

Patient education also contributed to the over-all improvement in functional status. Patients were taught breathing strategies, specifically pursed-lip breathing and diaphragmatic breathing. Pursed-lip breathing involves a nasal inspiration followed by expiratory blowing against partially-closed lips, avoiding forceful exhalation. This strategy reduces respiratory rate, minute ventilation and carbon dioxide level and increases tidal volume, arterial oxygen pressure and oxygen saturation.[16] Diaphragmatic breathing on the other hand entails conscious expansion of the abdominal wall during inspiratory diaphragm descent. In theory, this would increase the efficiency of the diaphragm while reducing the ineffective movements of the upper rib cage during ventilation.[16] Patients were also taught principles of energy conservation and work simplification. Teaching the patients about their lungs, disease, medications and limitations possibly built the understanding and acceptance needed to alleviate their fears.

The study showed a slight difference between the two groups in terms of hospitalization per year. Although the trend was favoring a decrease in hospitalization among Group A, the results were not statistically significant. This is in contrast to results of various studies that have reported significant reductions in the number of hospitalizations and resulting cost savings in the years after pulmonary rehabilitation compared with the year before rehabilitation.

Analysis of survival showed a significant difference in the two groups, with patients in Group A showing a better survival than those in Group B. Forty four percent of those who completed the pulmonary rehabilitation were alive after 10 years compared to only 31% of those who dropped out from the program. The survival rate of 44% was similar to the figures reported in the study of Sahn et al.[2]

Several elements of pulmonary rehabilitation are known or believed to improve survival of COPD patients. Two most important factors are smoking cessation and long term oxygen therapy. At best, review of available evidence suggests that pulmonary rehabilitation may improve survival in patients with COPD. Several investigators have studied the prognosis of patients following pulmonary rehabilitation and have found that a number of severely ill patients die within the first year of the program.

CONCLUSION

The scientific basis for pulmonary rehabilitation has developed substantially over the past decade. In the Philippine setting, this study showed a positive impact of pulmonary rehabilitation program in the long term care of patients with chronic obstructive lung disease. It provides a highly effective and cost efficient means of caring for COPD patients. It reduces symptoms, increases functional ability and improves the quality of life in individuals with chronic respiratory disease, even in the face of irreversible abnormalities of lung architecture.[16] With the increasing prevalence of COPD, the benefits of pulmonary rehabilitation will impact on even more respiratory impaired patients.

Techniques and approaches may vary in different countries, but the goals will always remain the same: to return patients to the highest possible functional capacity allowed by their pulmonary handicap and overall life situation.[24]

REFERENCES

1 Philippine Consensus Report on COPD, 1999

2 Sahn SA, Nett LM, Petty TL: Ten year follow-up of a Comprehensive Rehabilitation Program for Severe COPD. Chest 77 (Suppl); 311-314, 1980.

3 Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. NHLBI/WHO workshop report

4 ACCP/AACVPR Pulmonary Rehabilitation Panel. Pulmonary Rehabilitation Joint American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation evidence-based guidelines. Chest 1997 112: 1363-96

5 Hodgkin JE, Zorn EG, Connors GL. Pulmonary Rehabilitation - guidelines to success. Boston: Butterworth Publishers, 1984

6 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152: S84-S135

7 Fishman AP, NIH Workshop Seminar. Pulmonary Rehab Research. Am J Respir Crit Care Med 1994; 825-833

8 Ries AL, Position Paper of the American Association of Cardiovascular and Pulmonary Rehabilitation: Scientific Basis of Pulmonary Rehabilitation. J Cardiopulm Rehabil 1990; 10: 418-41
9 American Thoracic Society. Standards for diagnosis and care of patients with Chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 15: 5
10 European Respiratory Society. Optional Assessment and management of COPD. Eur Respir J 1995; 8: 1398-1420
11 Morris JF, Koski A, Johnson LC. Spirometric Standards for healthy non-smoking adults. Am Rev Respir Dis 1979; 119: 831-838
12 Borg GAV. Psychophysical Basis of Perceived Exertion. Med Sci Sports Exer 1982; 14: 377-81
13 Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum Intensity Exercise training in Patients with Chronic Obstructive Pulmonary Disease. Chest 1991; 100: 618-623
14 Eakin EG, Sassi-Dambron DE, Ries AL. Reliability and Validity of Dyspnea Measures in patients with Obstructive Lung Disease. Int S Behav Med 1995; 2: 118-34
15 Punzal PA. The Philippine Perspective In: Pulmonary Rehabilitation - Guidelines to success. Hodgkin JE, Celli BR, Connors GL (eds) Third edition. Lippincott Williams and Wilkins 2000; 669-673
16 American Thoracic Society. Pulmonary Rehabilitation - 1999. Am J Respir Crit Care 1999; 159: 1666-1682
17 Ries AL, Kaplan RM, Limberg TM, et al. Effects of Pulmonary Rehabilitation on Physiologic and Psychosocial Outcomes in patients with Chronic Obstructive Pulmonary Disease. Ann Int Med 1995; 122: 823-32
18 O'Donnell DE, McGuire M, Samis L, et al. The Impact of Exercise Reconditioning on Breathlessness in Severe Chronic Airflow Limitation. Am J Respir Crit Care Med 1995; 152: 2005-13
19 Strijbos JH, Sluiter NJ, Postma DJ, et al. Objective and Subjective Performance Indicators in COPD. Eur Respir J 1989; 2:666-69
20 Casaburi R, Patessio A, Loli F, et al. Reductions in Exercise Lactic Acidosis and Ventilation as a Result of Exercise Training in Patients with Obstructive Lung Disease.Am Rev Respir Dis 1991;143: 9-18
21 Maltais F, LeBlanc P, Simard C, et al. Skeletal Muscle Adaptation to Endurance Training in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Care Med 1996; 154: 442-47
22 Ramirez-Venegas A, Ward JL, Olmstead EM, et al. The Effect of Exercise Training on Dyspnea Measures in Patients with Chronic Obstructive Pulmonary Disease. J Cardiopulm Rehab 1997; 17: 103-109
23 Celli BR, Malu BS. Dyssynchronous Breathing During Arm but not Leg Exercise in patients,with Chronic Airflow Obstruction. N Engl J Med 1986; 314: 1485-90
24 Punzal PA. Pulmonary Rehabilitation in Asia. Medical Progress 2002; 29: 9-16
25 Blanco EC, Koh A, Punzal PA, de Guia TS. Pulmonary Rehabilitation - A Multidisciplinary Program for Filipino Ratients. Phil J Chest Dis 1993; 1: 1-5

COMPARATIVE STUDY ON PATIENTS SCREENED, BOTH ENROLLED AND NOT ENROLLED AT THE UNIVERSITY OF PERPETUAL RIZAL MEDICAL CENTER - COPD REGISTRY FROM MARCH 2001 TO JUNE 2002

JOSE EDZEL V. TAMAYO, MD, FPCCP[1]

Chronic Obstructive Pulmonary Disease may be diagnosed by doing spirometry on patients presenting with its risk factors, smoking in particular, and symptoms, especially cough, phlegm and dyspnea. The UPHRMC - COPD Registry screens patients who are smokers, 40 years and above with no history of asthma or atopy, after which they undergo spirometry. Demographic and clinical profiles together with spirometric data were compared between those who were enrolled from those who were not enrolled.
Phil Journal Chest Diseases. Vol 11 No 1 pp: 34-41

Keywords: COPD, COPD registry, Spirometry

INTRODUCTION

The American Thoracic Society defined Chronic Obstructive Pulmonary Disease as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema, whereby airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.[1] The guidelines provided by the PCCP Council on COPD add, that one must exclude other causes of chronic obstructive airflow such as upper airway obstruction, bronchiectasis, asthma and cystic fibrosis.[2] Finally, the GOLD guidelines include in its definition that COPD is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[3] Despite considerable efforts by groups of well-renowned individuals who are experts in their own right, the semantics regarding COPD is still confusing.[4] As a whole, COPD is characterized by a single physiologic feature: limitation of expiratory flow, thus placing much emphasis on the use of a simple spirometry in the diagnosis of this disease including assessment of its severity, thus the importance of awareness among physicians regarding its value.

The COPD Registry at the University of Perpetual Help Rizal Medical Center was started in March 2000, in cooperation with *Boehringer Ingelheim,* providing free spirometry to patients who may be at risk for COPD. The screening criteria include: age of 40 years old and above, smoking history of more than 10 pack-years and absence of any history of bronchial asthma or any forms of atopy. Despite these screening criteria, a significant number of patients may still not be able to achieve the FEV_1/FVC ratio of less than 70% to be enrolled into the registry.

It is therefore the objective of this study to determine the profile of patients screened at the UPHR Medical Center COPD Registry from March 2001 to June 2002 and to compare the data between patients who were enrolled as against those who were not enrolled.

METHODOLOGY

The COPD Registry screens patients using three criteria: (1) 40 years old and above, (2) smokers who have smoked for at least 10 pack-years, and (3) no history of bronchial asthma. Screened patients are asked to complete a data sheet as interviewed in the vernacular by a research assistant and then undergo spirometric evaluation. Patients who are able to achieve an FEV_1/FVC ratio of less than 70% are enrolled into the registry.

Patients included in this retrospective and comparative study were those who were initially screened and thus were made to complete a data sheet and underwent spirometry, from March 2001 until June

[1] Section of Pulmonary Medicine, UPHR Medical Center

Table I. Demographic profile (%)

Parameter	Enrolled (n=59)	Not Enrolled (n=31)
Age		
40 to 49	6 (10.2)	10 (32.2)
50 to 59	12 (22.0)	14 (45.2)
60 to 69	22 (37.3)	7 (22.6)
70 to 79	17 (28.8)	0
80 to 89	1	0
Sex		
Male	53 (89.8)	29 (93.6)
Female	6 (10.2)	2 (6.4)
Residence		
Las Pinas	35 (59.3)	17 (54.8)
Cavite	15 (25.4)	9 (29.0)
Paranaque	3 (5.1)	3 (9.7)
Muntinlupa	2 (3.4)	0
Others	4 (6.8)	2 (6.5)
Civil Status		
Married	49 (83.1)	25 (80.6)
Single	3 (5.1)	6 (19.4)
Widower	6 (10.2)	0
Separated	1 (1.7)	0
Education		
College	23 (39.0)	16 (51.6)
High School	17 (28.8)	6 (19.4)
Elementary	17 (28.8)	9 (29.0)
Vocational	1 (1.7)	0
None	1 (1.7)	0

2002. Data taken include demographic information (age, gender, residence, civil status and education), exposure to fumes, type of cooking fuel, smoking history (in pack-years), acute exacerbations (past 6 months), emergency room consultations (past 6 months), hospital confinements (past 6 months), oxygen use, co-morbidities, medications used, patient symptoms (include cough, phlegm, shortness of breath, easy fatigability, wheezing), physical inspection (loss of muscle mass, barrel-chest, pursed lip breathing and use of accessory muscles) and a subjective rating by the patient of his/her overall condition using a visual analogue scale from 0 to 9. Data regarding occupation was incomplete for non-enrollees, thus it was not included. Spirometric data include the height and weight (where the body mass index was derived = height in kilograms divided by the square of the height in meters), forced vital capacity (FVC - both absolute value and percent of predicted), forced expiratory value after one second (FEV_1 - both absolute value and percent of predicted), FEV_1/FVC ratio, percent change in FEV_1 post-bronchodilator (done only in patients who were enrolled into the COPD registry) and peak expiratory flow rate (PEFR).

Patient data were then compared between those who were enrolled into the COPD registry as against those who were not enrolled but who passed the initial screening criteria, with levels of significance determined for age, smoking history, symptoms, signs, subjective overall rating, BMI, FVC, FEV_1, FEV_1/FVC ratio and PEFR using the Student *t-test*, which is a test of the difference between the means of two universes. Only the *p* values of these 10 were considered because the test requires: (1) data should be quantitative, and (2) standard deviations determined should not be markedly different (ratio of higher SD to the lower SD = less than 2), both of which were achieved.

RESULTS

A total of 90 patients passed the initial screening criteria; of these, 31 (40.4%) patients achieved FEV_1/FVC ratios of 70% and above and thus were not enrolled, whereas 59 (65.6%) patients had values of less than 70% and thus were enrolled into the COPD Registry.

Demographic data from patients who were enrolled include a male-to-female ratio of 9:1, majority (37.3%) were within the age range of 60 to 69 years old, in fact almost 90% were 50 years old and above with 81 years as the oldest, most of them resided in Las Pinas City (59.3%) and only 3 patients lived in the northern areas, 83.1% were married at the time, and 39% were college graduates or at that time were taking up college education. For the group who were not enrolled, male-to-female ratio was 9.4:0.6, almost half (45.2%) fell in the range of 50 to 59 years old with 65 as the oldest, more than half (54.8°/x) were living in Las Pinas City, 80.6% were married and 51.6% reached or finished college education. Comparing the mean age between the two groups showed a difference of 10.34 years, with standard deviations which were not markedly different and testing for significance revealed a $p > 0.0005$, thus there is a very significant difference between the two groups, with the enrolled patients significantly older.

A little more than half (52.5%) of patients who were enrolled had exposure to certain fumes, majority (79.7%) used liquefied petroleum gas (LPG) as cooking fuel, and smoking history showed a mean of 50.94 pack-years, with 27.1% smoking between 50 to 69 years duration, the longest of which was a 69 year old male with 171 pack-years. For those not enrolled, 71% claimed they had no exposure to fumes, 77.4 % also used LPG as cooking fuel, and smoking history was lesser with a mean of 41.43 pack-years, 48.4% had a duration between 30 to 49 pack years, leading the pack was a 65 year old male at 130 pack-years. Standard deviations between the two groups were almost identical, and in general, there was no significant

Table II. Exposure to environmental pollutants (%)

Environmental Pollutant	Enrolled (n=59)	Not Enrolled (n=31)
Smoking		
Mean ± SD	50.94 ± 30.45	41.43 ± 28.21
10 - 29	15 (25.4)	10 (32.3)
30 - 49	15 (25.4)	15 (48.4)
50 - 69	16 (27.1)	2 (6.4)
70 - 89	8 (13.6)	2 (6.4)
90 - 109	3 (5.1)	0
110 - 129	0	1 (3.2)
130 - 149	1 (1.7)	1 (3.2)
150 - 169	0	0
170 – 189	1 (1.7)	0
Exposure to Fumes		
Not exposed	31 (52.5)	22 (71.0)
Exposed	28 (47.5)	9 (29.0)
Cooking Fuel		
LPG	47 (79.7)	24 (77.4)
Kerosene	8 (13.6)	9 (29.0)
Charcoal	4 (6.8)	0
Electricity	4 (6.8)	1 (3.2)
Wood	3 (5.1)	0

difference between the two with a *p* value between 0.10 and 0.20.

Almost a third (28.8%) of enrolled patients had acute exacerbations (past 6 months) from at less than daily to least once a week while 18.6% claimed they had none, more than three-quarters (76.3%) had no emergency room consults (past 6 months) while 15.3% had at least one, and more than one-fourth had at least one hospital confinement (past 6 months) while 74.6% claimed they had none, and more than half had no co-morbidities (52.5%) with PTB class 4 (22%) leading the way. Cough and phlegm (each at 89.8%) expectoration were the two most commonly encountered symptoms, a little more than half (50.9%) of enrolled patients had all the five symptoms mentioned (mean at 4.05), with only 1 patient saying he was without symptoms, while 30.5% were observed to have 2 signs of COPD led by loss of muscle mass at 45.8%. For those not enrolled, most acute exacerbations (22.6%) were less than once a week to at least one exacerbation for the past 6 months, 87.1% claimed they had no ER consult (past 6 months) with the same percentage having no admissions during the same period and almost sixty percent (58.1%) had no co-morbidities with PTB class 4 and hypertension tied at 19.4% each. Top two symptoms for those not enrolled were shortness of breath (87.1%) followed by cough (83.9%), majority had 3 or 4 symptoms (each at 29%, mean was 3.19), whereas 38.7% were observed to have signs of COPD led by loss of muscle mass at 54.8%. Symptom-wise, there was a significant difference between the two groups (*p* value between 0.005 and 0.001), but differences in signs observed through physical inspection were not significant ($p < 0.50$).

Table III. Signs, symptoms and co-morbidities of patients

Parameter	Enrolled (n=59)	Not Enrolled (n=31)
Symptoms		
Cough	53 (89.8)	26 (83.9)
Phlegm	53 (89.8)	25 (80.6)
Dyspnea	51 (86.4)	27 (87.1)
Fatigue	47 (79.7)	18 (58.1)
Wheeze	35 (59.3)	9 (29.0)
No. of symptoms		
Mean ± SD	4.05 ± 1.28	3.19 ± 1.33
5	30 (50.9)	5 (16.1)
4	15 (25.4)	9 (29.0)
3	6 (10.2)	9 (29.0)
2	4 (6.8)	4 (12.9)
1	3 (5.1)	3 (9.7)
0	1 (1.7)	1 (3.2)
Signs		
Loss of muscle mass	27 (45.8)	17 (54.8)
Pursed-lip breathing	19 (32.2)	16 (51.6)
Use of accessory muscles	12 (20.3)	2 (6.4)
Barrel chest	6 (10.2)	1 (3.2)
No. of Signs		
Mean ± SD	1.31 ± 1.12	1.29 ± 0.86
4	2 (3.4)	0
3	6 (10.2)	2 (6.4)
2	18 (30.5)	11 (35.5)
1	15 (25.4)	12 (38.7)
0	15 (25.4)	6 (29.0)
AEs past 6 mons		
Daily	11 (18.6)	0
1x/week < daily	17 (28.8)	6 (19.4)
< 1x/week	15 (25.4)	7 (22.6)
None	11 (18.6)	18 (58.1)
ER visit past 6 mons		
Frequent	1 (1.7)	0
4	1 (1.7)	0
3	1 (1.7)	0
2	2 (3.4)	1 (3.2)
1	9 (15.3)	3 (9.7)
0	45 (76.3)	27 (87.1)
Admission past 6 mons		
3	1 (1.7)	0
2	3 (5.1)	0
1	11 (18.6)	4 (12.9)
0	44 (74.6)	27 (87.1)
Co-morbidities		
None	31 (52.5)	18 (58.1)
PTB Class 4	13 922.0)	6 (19.4)
Hypertension	8 (13.6)	6 (19.4)
DM Type 2	6 (10.2)	1 (3.2)
Ischemic Heart Disease	3 (5.1)	0
Arthritis	3 (5.1)	0
Peptic Ulcer Disease	1 (1.7)	0

Sixty-one percent of those enrolled used between one and three medications for their lung problem most (25.4%) of whom used a combination anti-cholinergic plus short-acting beta-2 agonist inhaler device, 8.5% were using oxygen supplementation (as needed or

Table IV. Treatment and subjective self-assessment

	Enrolled (n=59)	Not Enrolled (n=31)
Medications		
SABA + AC	15 (25.4)	1 (3.2)
SABA	9 (15.3)	3 (9.7)
ICS	8 (13.6)	1 (3.2)
LABA	6 (10.2)	1 (3.2)
Theophylline	6 (10.2)	2 (6.4)
Mucolytics	6 (10.2)	1 (3.2)
Procaterol	1 (1.7)	0
No. of medications		
3	4 (6.8)	1 (3.2)
2	15 (25.4)	1 (3.2)
1	17 (28.8)	5 (16.1)
None	23 (39.0)	24 (77.4)
Oxygen Use		
At night	1 91.7)	0
As needed	4 (6.8)	0
None	54 (91.5)	31 (100)
Subjective assessment		
Mean $\pm$ SD	6.4 $\pm$ 0.61	7.29 $\pm$ 0.90
9	2 (3.4)	1 (3.2)
8	10 (16.9)	14 (48.4)
7	18 (30.5)	7 (22.6)
6	13 (22.0)	8 (25.8)
5	11 (18.6)	0
4	2 (3.4)	0

maintenance), and majority (30.5%) rated themselves 7 (0 to 9 scale; mean at 6.4). Whereas, 77.4% of those not enrolled had no medications at all (9.7% used only short-acting beta-2 agonist), none of them were on oxygen supplementation, and 48.4% had their rating pegged at 8 (mean at 7.29). There was very significant difference between the two groups with regards to subjective overall rating ($p > 0.0005$).

Spirometric data for those enrolled include an FVC percent of predicted mean at 82.68%. Most (55.9%) of them had values of more than or equal to 80%, FEV_1 mean value (% of predicted) was 55.64%; majority (37.3%) were between 40 to 59%, FEV_1/FVC ratio had a mean value of 54.67%, most of which was between 60 to 69%, and PEFR with mean at 318.32, one-third of which was between 201 to 400 liters per minute. Majority (42.4%) of these patients had BMIs between 15 and 19. As opposed to those not enrolled, an FVC percent of predicted mean at 98.52% most (83.9%) of them also had values of more than or equal to 80%, FEV_1 mean value (% of predicted) of 94.81% majority (83.9%) were also more than or equal to 80%, unfortunately no percentage change in post-bronchodilator FEV_1 was determined for these patients, thus it was not included in this study, FEV_1/FVC ratio had a mean value of 78.87% most of which was between 70 to 79%, and PEFR with a mean value of 653.35, 41.9% of which were between

Table V. BMI and spirometric data

	Enrolled (n=59)	Not Enrolled (n=31)
BMI (kg/m^2)		
Mean $\pm$ SD	22.57 $\pm$ 4.88	22.58 $\pm$ 3.27
15 – 19	25. (42.4)	9 (29.0)
10 – 24	21 (35.6)	13 (41.9)
25 – 29	7 (11.9)	8 (25.8)
30 – 34	5 (8.5)	1 (3.2)
35 – 39	1 (1.7)	0
FEV_1 (% predicted)		
Mean $\pm$ SD	55.64 $\pm$ 19.79	94.81 $\pm$ 16.35
$\geq$ 80	9 (15.3)	26 (83.9)
60 – 79	14 (23.7)	5 (16.1)
40 – 59	22 (37.3)	0
< 40	14 (23.7)	0
FVC (% predicted)		
$\geq$ 80	33 (55.9)	26 (83.9)
60 – 79	20 (33.9)	5 (16.1)
40 – 59	6 (10.2)	0
< 40	0	0
FEV_1/FVC (%)		
Mean $\pm$ SD	54.67 $\pm$ 12.1	78.87 $\pm$ 7.55
100 – 109	0	1 (3.2)
90 – 99	0	2 (6.4)
80 – 89	0	7 (22.6)
70 – 79	0	21 (67.7)
60 – 69	22 (37.3)	0
50 – 59	11 (18.6)	0
40 – 49	15 (25.4)	0
30 – 39	10 (16.9)	0
< 30	1 (1.7)	0
PEFR (lpm)		
Mean $\pm$ SD	318.32 $\pm$ 145.94	653.35 $\pm$ 169.99
0 – 200	19 (32.2)	0
201 – 400	20 (33.9)	3 (9.7)
401 – 600	16 (27.1)	8 (25.8)
601 – 800	4 (6.8)	13 (41.9)
801 – 1000	0	6 (19.4)
1001 - 1200	0	1 (3.2)

601 to 800 liters per minute. Their BMIs were mostly (41.9%) between 20 and 24. All spirometric data when compared between the two groups were significantly different ($p > 0.0005$) except for the BMI ($p < 0.50$), which also had almost the same mean values.

DISCUSSION

The topic of spirometry screening for COPD was revised in a consensus statement from the National Lung Health Education Program 2000, which recommends widespread use of office spirometry by primary care physicians for smokers over 45 years old.[1]

One of the screening criteria we used was age, set at 40 years old and above.[2] Although COPD commonly appears in the fifth decade of life, as in this study where more than 90% of those enrolled were 50 years old or more, the FEV_1 even among non-smokers without

respiratory disease declines by 25 to 30 ml. per year beginning at about 35 years old, thus stressing the need to catch these patients at a much earlier stage.[5] In this study there is a 10-year difference between the mean ages of both groups, with those enrolled being much older, revealing a statistically significant difference. However, age cannot be separated from the number of years of cigarette smoking, but is clearly a risk factor for more rapid decline of lung function.[6]

The second criterion is a smoking history of 10 pack-years, although COPD patients usually have a smoking history of more than 20 pack-years.[7] We are lenient with this criterion; we just require our patients to be smokers, whether past or present without considering initially if they satisfy the mentioned value, since patients usually underreport their smoking history. Smokers are not a reliable source of information about their own smoke inhalaltion.[8] After spirometry, especially if the results reveal some form of airway obstruction then we query them much further and convince them to give their true and as much as possible an accurate smoking history. Cigarette smoking is overwhelmingly the most important etiologic agent in the development of COPD.[9] Data from longitudinal, cross-sectional, and case control studies show that, compared with non-smokers, cigarette smokers have higher death rates, higher prevalence and incidence of COPD.[10] The latest surveys in the Philippines indicate that one out of every three adult Filipinos currently smoke, another 13% count themselves as ex-smokers, while these smokers affect at least 60% of all households in our country resulting in more than 12,000 deaths secondary to COPD in 1996.[11,12] Although tobacco smoking accounts for an estimated 80 to 90% of the risk of developing COPD, only about 15% of cigarette smokers develop COPD.[13] Burrows concluded that smoking habit has only some relation to the number of cigarettes smoked per day and cumulative pack-years, and that the relationship between amount of smoking and risk of COPD is quite unpredictable on an individual basis.[8,14] This was reflected in our study, where although there was an almost 10 pack-year difference between the two groups, wherein those enrolled having higher numbers, but it was not statistically significant.

The absence of bronchial asthma or atopy is the third criterion although serum IgE levels were not taken. However, the Dutch hypothesis, ascribes the role of allergy and airway hyperresponsiveness as a susceptibility to COPD.[15] There seems to be two different contexts; in one, COPD develops out of an asthmatic predisposition and it is not uncommon that we see asthmatic patients who smoke, in the other, airway hyperresponsiveness does not predispose to COPD, but rather its consequence.[8]

Despite these three criteria, less than two-thirds of those who satisfied them had FEV_1/FVC values of less than 70% and were thus enrolled into the COPD registry, although patients who passed the criteria but were not enrolled will be followed up every six months with repeat spirometry.

Several authors have conflicting views on the effect of gender to the risk of developing COPD. Barnes insists that gender does not appear to be important and there is no evidence that men or women are more susceptible to the effects of cigarette smoking.[7] Pride and Burrows say that after standardization for smoking, males are more at risk than females.[14] In an epidemiologic, multi-center, population-based study conducted in seven areas in Spain composed of 4,035 individuals, men and women aged 40 to 69 years old were selected randomly.[16] Out of these, 1,023 were smokers, 15% of whom were diagnosed to have COPD and men had a higher probability of developing this disease. In our study around 90% are males in both groups. WHO predicts faster increases in tobacco consumption by women in the following decades, in 1987 only 8% of adult Filipinos smoked, in 1999 the National Nutrition Survey says that smoking prevalence among Filipinos have more than doubled to 18%.[11] For the same exposure to smoking, evidence is mounting in favor of a female predisposition to the effects of smoking and several studies have found that women develop COPD more frequently.[9,17,18]

In this study, there was not much difference between the two groups in terms of the area of residence, civil status and educational attainment, unfortunately the actual socioeconomic status was not determined, which does have significance as a risk factor in the development COPD as reflected in studies and guidelines previously mentioned.

Noxious particles and gases do play the largest etiologic role in this disease, as what was previously discussed regarding cigarette smoking. Although most of those who were enrolled were more exposed to fumes (47.5% versus 29%) and cooking fuels which produce smoke (charcoal and wood - 11.9% versus none) the role of environmental pollution particularly sulphur dioxide and particulates should be emphasized since almost all these patients live in urban areas. An epidemiologic study done by the UP College of Public Health (supported by WHO) in 1990 to 1991, showed the prevalence of COPD among commuters was 14.8% and among jeepney drivers a staggering 32.5%.[19] Although data in this study regarding occupation was incomplete

among those not enrolled, for those who were enrolled more than two-thirds have work-related exposure to smoke (drivers topping the list with 10.2%), solvents, fibers and dust, the latter appearing to be significant with the risk relating to the intensity of exposure.[20] In all studies, however, smoking effects are generally much greater than environmental and occupational effects.[21]

Cough is the most frequent symptom reported by patients with COPD, it is usually productive and occurs most often in the early morning especially those with chronic bronchitis, but it is commonly dyspnea that causes patients to seek medical attention.[10,22] This is also the time when patients usually have lost a considerable amount of their lung volume, with FEV_1 values of less than 50% of predicted, a history of heavy smoking, often more than 25 pack-years.[7] Cough, expectoration of phlegm and dyspnea were the most common symptoms in this study, more than 80% in all three for both groups. In terms of the number of symptoms, those who were enrolled on the average have four symptoms, while those not enrolled had a mean value of three, the difference of which was statistically significant.

Looking for signs of COPD is a crude and insensitive means of detecting airflow obstruction and one cannot differentiate the possible diagnoses.[2] In mild disease, there may be no abnormal signs and as it becomes more severe, patients demonstrate more apparent clinical signs.[7] For both groups in this study, loss of muscle mass and pursed-lip breathing were the most common physical sign, with the former being the highest. With regards to the number of signs, the difference between the two groups has statistical significance.

The hallmarks of an exacerbation of COPD include increased cough, purulent sputum, increased dyspnea and on occasion perceptible wheezing.[10] Although the influence of acute exacerbations on the progression of COPD has not been established, it has recently been reported that exacerbations can further aggravate the symptoms and result in complications, hospitalizations and a negative impact on health-related quality of life.[23,24] With disease progression, the intervals between acute exacerbations grow shorter.[25] Acute exacerbations for the past six months among those not enrolled in our COPD Registry were fewer; majority (58.1%) of whom had none, whereas many (28.8%) of those who were enrolled had one at least once a week to less than daily. But there was not much difference between the two groups with regards to emergency room visits and hospital admissions the past six months. In terms of co-morbidities, majority in both groups had none, but the top co-morbidity is pulmonary tuberculosis class 4 in both groups, but the diagnoses were based on history, without the benefit of sputum examination or chest radiography. The most common trigger of an acute exacerbation of COPD is a superimposed pulmonary diagnosis.[9] Whereas the most common and serious extra-pulmonary trigger of COPD is cardiovascular disease, which is the second most common co-morbidity in our study in both groups in the form of hypertension.

Less than 16% among those not enrolled used an inhaler device using short or long-acting beta-2 agonist with or without an anti-cholinergic, whereas only a little more than 50% of enrolled patients do, even though more 95% of them in both groups were symptomatic, with almost 90% complaining of some form of difficulty of breathing. To add, 39% of those not enrolled and 77.4% among those enrolled did not use any medication at all. Although no documentation of the reasons were done, those mentioned include cost, social stigma, denial and/or just plain and simple stubbornness on the part of the patient, all of which definitely has an impact on quality of life, morbidity and mortality. Compliance can be very poor and should be seen as a significant barrier to improving clinical outcomes for those with COPD, in fact in the lung health study, patient compliance with bronchodilator therapy by self-report at one-year follow-up was slightly over 60%[26] but their population was composed of largely non-symptomatic patients, as opposed to ours. Although much has been said of the benefits of long-term oxygen therapy in COPD patients in terms of survival, increasing exercise capacity and endurance,[27,28] all of those not enrolled and more than 90% of those enrolled did not use supplemental oxygen, reasons mentioned for medications also apply.

A visual analogue scale (0 to 9) was used to determine patients' subjective assessment of their overall condition at the time of examination. Patients not enrolled had better scores than those enrolled and the difference was statistically significant.

No parameter is specific to nutritional status, but the health professional can compare the patient's current weight to a healthy weight that is based on current guidelines for height and weight such as the body-mass index (BMI) which is well correlated with body fat.[9] In a recent population-based study of subjects with COPD followed up for an average of 17 years, underweight (BMI of less than 20 kg/m^2) was an independent risk factor for COPD-related mortality and all-cause mortality. In our study, the mean BMI values for both groups had no significant difference, but 42.4% of those enrolled had BMIs between 15 to 19, compared with only 29% for those not enrolled.

Spirometry should be performed in all patients in whom the diagnosis of COPD is being considered, with an FEV_1/FVC ratio (Tiffenau index) of less than 70% as an early sign of airflow limitation and using FEV_1 values to best assess the severity of airway obstruction especially among moderate to severe disease.[2,3,30]

All spirometry results of patients enrolled in the COPD Registry had lower values compared to those not enrolled and all were statistically significant with the following levels of significance in descending order: FEV_1/FVC: t_{calc} = 10.1322 ($p>0.0005$); PEFR: t_{calc} = 9.7718 ($p>0.0005$); FEV_1: t_{calc} = 9.4485 ($p>0.0005$); FVC: t_{calc} = 4.0391 ($p>0.0005$). Since the FEV_1/FVC ratio was used as the single criteria whether to enroll patients or not into the registry, thus it ended up with the highest level of significance. But what was surprising was the peak expiratory flow rate (PEFR) values. The use of PEFR measurements was said to have no utility in managing COPD, but its advocates have recently adopted it in their quest for indirect measurements that might obviate the need for spirometry.[9] In COPD, there is a poor relationship between PEF and FEV_1, and it is impossible to predict FEV_1 from PEF and vice-versa.[31] However, these two values were not compared head-to-head in this study. As what was previously mentioned, FEV_1 is the most useful test to assess severity and progression of COPD. FVC is initially normal but is reduced as the disease progresses.[7] Post-bronchodilator FEV_1 was determined for those enrolled; the mean value was 14.7% with a standard deviation of 16.5%. Thirty-two patients (54.2%) had a change of 15% and above, while 25 (42.4%) had a change of less than 15%. An acute response in FEV_1 is neither sufficiently sensitive nor specific to differentiate asthma from COPD.[32] A significant increase in FEV_1 after an inhaled beta-adrenergic agonist has been observed in up to one-third of COPD patients during single testing sessions and up to two-thirds during serial testing and the percentage of individuals improving at least 15% increases with increasing severity of the disease.[33]

CONCLUSION

Majority (65.6%) of the patients screened at the UPHR Medical Center COPD Registry from March 2001 to June 2002 were enrolled. Both those who were enrolled and those who were not, had close percentage values with regards to: male as the predominant gender, residence in urban areas, married civil status, college and high school levels in educational attainment, LPG as the major cooking fuel, top three symptoms of cough, phlegm and dyspnea, loss of muscle mass as the number one physical sign, emergency room visits and admissions for the past six months, oxygen supplementation, and majority had no co-morbidities, with the top two listed as pulmonary tuberculosis class 4 followed by hypertension.

Higher percentages were appreciated for those enrolled in terms of being exposed to fumes, acute exacerbations for the past six months, and number of medications (short acting beta-2 agonist + anti-cholinergic versus predominantly short acting beta-2 agonist by those not enrolled).

Significant difference between the two groups regarding: age (older for those enrolled), number of symptoms (more for those enrolled), patients' subjective self-assessment of overall condition (higher score for those not enrolled), FEV_1/FVC ratio, FEV_1, FVC and PEFR (with all spirometric values lower for those enrolled). Smoking history, BMI and the number of physical signs were not that much between the two groups when computed for their levels of statistical significance.

REFERENCES

1 Ferguson, Gary T., et al, Office Spirometry for Lung Health Assessment in Adults: A Consensus Statement from the National Lung Health Education Program, CHEST, 117-1146-1161, 2000.

2 Clinical Practice Guidelines in the Diagnosis and Management of Chronic Obstructive Pulmonary Disease (COPD), Report of the Council on COPD-Philippine College of Chest Physicians, 1999.

3 Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, NHLBI/WHO Workshop Report, April 1998.

4 Rennard, Stephen I., COPD: Overview of Definitions, Epidemiology, and Factors Influencing Its Development, CHEST, 113:2355-2415, 1998.

5 American Thoracic Society Guidelines: Diagnosis and Care of Patients with COPD, I, ATS Board of Directors, March 1995.

6 Burrows, B., Airway Obstructive Diseases: Pathogenetic Mechanisms and Natural Histories of the Disorders, Medical Clinics of North America, 74:547, 1990.

7 Barnes, Peter J., Managing Chronic Obstructive Pulmonary Disease, 2002.

8 Fishman, Alfred P., Pulmonary Diseases and Disorders, 3rd edition, 1998.

9 Bourbeau, Jean, et al, Comprehensive Management of Chronic Obstructive Pulmonary Disease, BC Decker Inc., 2002.

10 Murray, John F. and Nadel, Jay A., Textbook of Respiratory Medicine; Std edition, 2000.

11 A White Paper on Tobacco and Smoking, Philippine Senate Committee on Health and Demography, 1999.

12 Health Indicators: Mortality: Ten Leading Causes, 1996, Department of Health Website, www.doh.gov.ph, 2002.

13 US Surgeon General, The Health Consequence of Smoking: Chronic Obstructive Lung Disease, DHHS Publication No. 84-50205, US Department of Health and Human Services, Washington D.C., 1984.

14 Pride and Burrows, Development of Impaired Lung Function: Natural History and Risk Factors in Chronic Obstructive Pulmonary Disease, 1995.

15 American Thoracic Society: Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease, American Journal of Respiratory and Critical Care Medicine, 152:577-5121, 1995.

16 Jimenez-Ruiz, Carlos A etal, Smoking Characteristics: Differences in Attitudes and Dependence Between Healthy Smokers and Smokers with COPD, CHEST, 119:1365-1370,2001.
17 Xu, X. et al, Gender Difference in Smoking Effects on Adult Pulmonary Function, European Respiratory Journal, 7:477-483, 1994.
18 Chen, Y. et al, Increased Susceptibility to Lung Dysfunction in Female Smokers, American Review of Respiratory Diseases, 143:1224-1230, 1991.
19 Vehicle Emissions Reduction: Health Data, Asian Development Bank Webpage, www.adb.org 2002.
20 Burge, P., Occupation and Chronic Obstructive Pulmonary Disease (COPD), European Respiratory Journal, 7:1032-1034, 1994.
21 Becklake, MR, Occupational Exposures: Evidence for a Causal Association with Chronic Obstructive Pulmonary Disease, American Review of Respiratory Diseases, 140: S85-891, 1989.
22 Petty, TL, Definitions in Chronic Obstructive Pulmonary Disease, Clinical Chest Medicine, 11:363-373, 1990.
23 Osman, IM, etal, Quality of Life and Hospital Re-admission in Patients with Chronic Obstructive Pulmonary Disease, THORAX, 62:67-71, 1997.
24 Seemungal, TA, etal, Effects of Exacerbation on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease, American Journal of Respiratory and Critical Care Medicine, 157:1418-22, 1998.
25 American Thoracic Society Guidelines: Diagnosis and Care of Patients with COPD, II, ATS Board of Directors, March 1995.
26 Anthonisen, NR, etal, Effects of Smoking Intervention and the Use of an Inhaled Bronchodilator on the Rate of Decline of FEV1: The Lung Health Study, Journal of the American Medical Association, 272:1497-505, 1994.
27 Nocturnal Oxygen Therapy Trial Group: Continuous or Nocturnal Oxygen Therapy in Chronic Obstructive Lung Disease: A Clinical Trial, Annals of Internal Medicine, 93:391-398, 1980.
28 Medical Research Council Working Party: Long Term Domiciliary Oxygen Therapy in Chronic Hypoxic Cor Pulmonary Complicating Chronic Bronchitis and Emphysema, The Lancet, 1:681-686, 1981.
29 Landbo, C, et al, Prognostic Value of Nutritional Status in Chronic Obstructive Pulmonary Disease, American Journal of Respiratory and Critical Care Medicine, 160:1856-61, 1999.
30 Quanjer, PH, et al, Lung Volumes and Forced Expiratory Flows, European Respiratory Journal, 6(Spp116):5AO, 1993.
31 British Thoracic Society: Guidelines for the Management of Chronic Obstructive Pulmonary Disease, The COPD Guideline Group of the Standards of Care Committee of the BTS, THORAX, 52 Suppl: S 16-28.
32 Stubbing, DG, etal, Some physical Signs in Patients with Chronic Obstructive Airflow, American Review of Respiratory Diseases, 125:549-552, 1989.
33 Anthonisen, NR and Wright, EC, Bronchodilator Response in Chronic Obstructive Pulmonary Disease, American Review of Respiratory Diseases, 133:814, 1986.

POTENTIAL ASSOCIATION OF EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH PERIODONTAL DISEASE

RUBEN A. ONG JR., MD,[1] TITO C. ATIENZA, MD, FPCCP[1]

BACKGROUND: Chronic obstructive pulmonary disease (COPD) now rises as a national health problem not only because of rising morbidity and mortality but also because of issues related to health care costs. Several studies have been undertaken to address these issues. One approach was to determine factors that increase the frequency of exacerbation among COPD patients and control it. Periodontal disease was one of the potential factors affecting COPD exacerbation based on the analysis done on the National Health and Nutrition Examination Survey III conducted in the United States.

METHODS: This is a cross-sectional, prospective study done at Ward 17 of Veterans Memorial Medical Center from January 2002 to August 2002. Nineteen subjects were included in this study and all were diagnosed to have COPD based on history and physical examination and confirmed by spirometry. Subjects were at least 45 years of age and with at least six natural teeth. Excluded in the study are those with bronchogenic CA, tuberculosis, pleural effusion and pneumothorax, diabetes mellitus and bronchiectasis. The subjects then underwent dental examination, where number of natural teeth, dental caries and mean attachment loss and gingival bleeding were noted. Frequency of exacerbation of COPD, Emergency ward and OPD consult and hospital admission related to exacerbation of COPD were recorded.

RESULTS: The mean age of all the subjects was 72.7 $\pm$ 8.6. There was an equal gender distribution among the subjects. Majority of the subjects belong to the low-income bracket and attained minimal level of education. There was almost equal distribution of subjects with $\leq$ 6 and > 6 times per year episodes of exacerbations of COPD. There were more subjects who frequently consult at the emergency ward (78.9%) and re-admitted at the hospital (78.9%). In contrast, there was almost equal distribution of subjects with $\leq$ 6 and > 6 times per year visits at the OPD because of exacerbations of COPD. The mean number of natural teeth among the subjects was 17.4 $\pm$ 5.7 with a mean percentage of dental caries of 31.5 $\pm$ 5.7. Most subjects had < 20% gingival bleeding (84.2%) however there were more subjects with $\geq$1.5 mm mean attachment loss (84.2%). There was no significant relationship noted between the frequencies of exacerbation, consult at emergency ward, OPD consult and hospital admission with percentage of dental caries, mean attachment loss and gingival bleeding.

CONCLUSION: There is no relationship between frequencies of exacerbation of COPD with Periodontal disease. *Phil Journal Chest Diseases. Vol 11 No 1 pp: 42-47*

COPD, periodontal disease, exacerbations

INTRODUCTION

One route of respiratory infections is through aspiration or inhalation of fine droplets containing microbiological agent from the mouth and throat into the lungs. Studies have shown that that bacteria found in the throat, as well as bacteria found in the mouth, can be drawn into the lower respiratory tract. This can cause infections or worsen existing rung conditions. Patients with respiratory diseases, such as chronic obstructive pulmonary disease, usually have reduced pulmonary protective mechanisms, leading to delayed clearance of microbiologic pathogens in the lungs and hence increase susceptibility to recurrent pulmonary infections.l

Researchers have found that bacteria that grow in the oral cavity can be aspirated into the lung to cause respiratory diseases such as pneumonia, especially in people with periodontal disease. This discovery led researchers to believe that these respiratory bacteria can travel from the oral cavity into the lungs to cause infection.

Chronic obstructive pulmonary diseases (COPD) cause persistent obstruction of the airways. The main

[1] Department of Pulmonary Medicine, Veterans Memorial Medical Center

cause of this disease is thought to be long-term smoking. Pulmonary irritants like smoke or air pollution can also cause airway destruction and narrowing. Further damage to the tissue and working function of the lungs can be prevented, but already damaged tissue cannot be restored - untreated or undetected COPD can result in irreversible damage. Researchers believe that through the aspiration process, bacteria can cause frequent bouts of infection in patients with COPD. Studies are now being planned to determine to what extent oral hygiene and periodontal disease may be associated with more frequents bouts of respiratory disease in COPD patients.

In an effort to improve the quality of life of patients with COPD at Veteran's Memorial Medical Center, the department of Pulmonary Medicine has undertaken several projects that include Pulmonary Rehabilitation and Education for COPD patients. Knowledge emerging from studies on association of dental health with respiratory infections will prove clinically important in optimizing treatment and rehabilitation of COPD patients.

If there would be an association between frequency of exacerbation of COPD with periodontal health, these would now put a new light on care of COPD patients to include dental education and intervention.

Recently, there has been a resurgence of interest in the interaction between oral conditions and a number of prevalent systemic diseases.[1] Among these interactions is that between oral infections such as periodontitis and respiratory disease. Respiratory diseases are responsible for significant morbidity and mortality in human populations. These diseases are widely prevalent and exact an extensive toll on human health and the cost of health care. One of these respiratory diseases is chronic obstructive pulmonary disease (COPD).

In 1998, according to the World Health Organization, 40% of all deaths in developing countries are secondary to non-infectious causes (COPD included) and that this 40% accounts for 67% of all COPD deaths wordwide.[2]

COPD is defined as a disease characterized by presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway reactivity and may be partially reversible.[3] This definition excludes other causes of chronic airflow obstruction such as upper airway obstruction, bronchiectasis, asthma and cystic fibrosis.[4] One of the most useful test to diagnose COPD is spirometry. The presence of airway obstruction as measured by spirometry is recognized as a reduction in FEV_1 to vital capacity (VC) or forced vital capacity (FVC).[5]

Known risk factors for COPD include history of prolonged cigarette smoking and genetic conditions such as the presence of defective alpha 1-antitypsin gene, variant alpha-1 antichymotrypsin, alpha-2 macroglobulin, vitamin D-binding protein, and blood group antigen genes.[6] Other environmental risk factors include chronic exposure to toxic atmospheric pollutants (e.g., second hand smoke).

One of the major complications of COPD is the occurrence of "exacerbations," or episodes in which there are objective signs that bronchitis has worsened as evidenced by increased sputum production showing a change in color and/or consistency. Increased cough, dyspnea, chest tightness, and fatigue may also accompany an exacerbation.

However, the factors responsible for the initiation of exacerbation are not completely known, although they are thought to be provoked in part by bacterial infection.[7] The organism most closely associated with exacerbation are non-typeable *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. It should be pointed out that the frequency of exacerbation in COPD patients varies from individual to individual and the frequency of exacerbation is not related to lung disuse. Although viral infections, fluid overload, and allergy have been suggested to enhance risk for exacerbation, no studies have yet proven the role of these factors in the disease process.[8]

It is therefore our objective to determine potential associations between frequency of exacerbation of chronic obstructive pulmonary disease patients with periodontal disease. We also want to determine the association of the level of oral health status which includes the measure of attachment level, and gingival bleeding of COPD patients with frequency of exacerbation of COPD patients. Specifically, we will determine the frequency of exacerbation of COPD patients; the number of previous hospital admissions of patients for treatment of exacerbation of COPD; and the number of outpatient consult of patients for treatment of exacerbation of COPD.

METHODOLOGY

Study Design: This -was a cross-sectional, prospective study of a potential association of exacerbations of Chronic obstructive pulmonary disease with periodontal disease

Study Population: Included in the study were all patients diagnosed to have chronic obstructive

Table I. Demographic characteristics of subjects (%)

Age (Mean ± SD)	72.7 ± 8.6
Gender	
Male	10 (52.6)
Female	9 (47.4)
Education (years)	
≤ 7	12 (63.2)
8 – 11	4 (21.1)
≥ 12	3 (15.8)
Household Income	
No income	8 (42.1)
≤ 90,000/year	9 (47.4)
> 90,000/year	2 (10.5)
Smoking (pack years)	
None	9 (47.4)
< 20	1 (5.3)
≥ 20	9 (47.4)
Alcohol intake	
None	6 (31.6)
Occasional	12 (63.2)
Regular	1 (5.3)

Table II. Frequency of exacerbations of COPD

Frequency of exacerbations	
≤ 6 times a year	9 (47.4)
> 6 times a year	10 (52.6)
Frequency of consult at Emergency Ward because of COPD exacerbations	
≤ 6 times a year	15 (78.9)
> 6 times a year	4 (21.1)
Frequency of consult at out patient department or private doctor because of COPD exacerbations	
≤ 6 times a year	10 (52.6)
> 6 times a year	9 (47.6)
Frequency of hospital admission because of COPD exacerbations	
≤ 6 times a year	15 (78.9)
> 6 times a year	4 (21.1)

pulmonary disease, admitted at Ward 17 from January 2002 to August 2002 who are at least 45 years of age and with six natural teeth. Chronic obstructive pulmonary disease (COPD) was diagnosed based on history and physical examinations of the subjects and confirmed by spirometric study based on criteria set by the Global Initiative far Chronic Obstructive Lung Diseases work group.

There were initially at least 80 patients considered, however after screening only 19 patients qualified for the study.

Inclusion Criteria: Age > 45 yrs.; All patient diagnosed with Chronic obstructive pulmonary disease should have undergone at least one pulmonary function test at Veteran's Memorial Medical Center with official result suggesting a chronic obstructive pulmonary disease; and at least have 6 natural teeth.

Exclusion Criteria: Patients with bronchogenic cancer, untreated, moderate to far-advance pulmonary tuberculosis; with pleural effusion or pneumothorax not related to COPD (i.e. cancer, tuberculosis, CHF, etc.); and patients with Diabetes Mellitus; bronchiectasis, and chronic sinusitis

The subjects were interviewed and data on gender, smoking history, alcohol consumption, frequency of COPD exacerbation, hospital admission and outpatient consult for exacerbation of COPD were collected. Exacerbation of COPD was defined to the subjects as symptoms of increased breathlessness, often accompanied by increased cough, and sputum production.

An assigned dentist supervised by Dr. Pastora Rene C. Aurelio of the Department of Dental Medicine determined the periodontal health, which was measured around the teeth of one upper quadrant and one lower quadrant randomly selected at the beginning of each examination. The buccal and medial-buccal surfaces of each tooth were measured for gingival bleeding, gingival recession and probing depth. Periodontal disease was measured by determination of:

a. Attachment level, was obtained by subtracting the distance from the free gingival margin (FGM) to the cemento-enamel junction (CEJ) of each tooth, from the distance from the FGM to the bottom of the sulcus. Mean attachment loss (MAL) was computed and dichotomized as those with <1.5 mm MAL, and > 1.5 mm MAL. Patients with greater than 1.5 mm MAL are considered to have some degree of periodontal attachment loss.

b. Gingival bleeding (GB) was dichotomized as 2 categories: GB < 20% of sites that bled on probing, and GB ± 20% of sites that bled on probing.

Statistics: Student *t test* was used to evaluate and compare the means of the parameters under study. Fisher exact probability test were used to determine the association of periodontal health with frequency of COPD exacerbation, hospital admission and outpatient consult for exacerbation of COPD. A p value of ≤ 0.05 was considered significant.

RESULTS

The demographic data of the subjects are summarized in *Table I*. The mean age of all the subjects was 72.7 ± 8.6 years. There was an equal gender distribution among the subjects. Majority of the subjects belong to the low-income bracket and attained

Table III. Dental health of subjects (%)

Natural teeth (Mean ± SD)	17.4 ± 5.7
Percentage of dental carries	31.5 ± 29
Mean attachment loss	
< 1.5 mm	3 (15.8)
≥ 1.5 mm	16 (84.2)
Gingival bleeding	
< 20% of sites	16 (84.2)
≥ 20% of sites	3 (15.8)

Table IV. Relationship between COPD exacerbations and percentage of dental carries

	% of Dental Carries (Mean + SD)	*p* Value
Frequency of exacerbations		0.428
≤ 6 times a year	28.6 + 19.7	
> 6 times a year	34 + 36.3	
Frequency of consult at ER		0.428
≤ 6 times a year	34.3 + 30.5	
> 6 times a year	20.9 + 22.7	
Frequency of OPD consult		0.8
≤ 6 times a year	33.1 + 27.6	
> 6 times a year	29.6 + 31.9	
Frequency of hospital admission		0.377
≤ 6 times a year	34.6 + 30.2	
> 6 times a year	19.8 + 23.5	

minimal level of education. This finding might be important to consider in relation to maintenance of dental hygiene if a relationship between periodontal health and exacerbations of COPD is established in this study. There was also almost equal distribution of smoker and non- smoker in the subjects. Most of the subjects were occasional alcoholic beverage drinkers.

The subjects' frequency of exacerbations of COPD in relation to their consult at the OPD, emergency room and hospital admissions are tabulated in *Table II*. There was almost equal distribution of subjects with ≥ 6 times per year episodes of exacerbations of COPD. There were more subjects who frequently consult at the emergency ward (78.9%) and re-admitted at the hospital (78.9%). In contrast, there was almost equal distribution of subjects with ≥ 6 times per year visits at the OPD because of exacerbations of COPD.

Oral health parameters of the subjects are compared in *Table III*. The mean number of natural teeth among the subjects was 17.4 ± 5.7 with a mean percentage of dental caries of 31.5 + 5.7. Most subjects (84.2%)had less than 20% gingival bleeding; however there were more subjects with ± 1.5 mm mean attachment loss (84.2%).

Table IV showed that there was no significant relationship noted between the frequencies of exacerbation, consult at emergency ward, OPD consult and hospital admission with percentage of dental caries.

Table V. Relationship between COPD exacerbations and mean attachment loss

	Mean Attachment Loss			p Value
	≤ 1.5 mm	1.5 mm	TOTAL	
Frequency of exacerbations				0.21
≤ 6 times a year	0	9	9	
> 6 times a year	3	7	10	
TOTAL	3	16	19	
Frequency of consult at ER				0.53
≤ 6 times a year	2	13	15	
> 6 times a year	1	3	4	
TOTAL	3	16	19	
Frequency of OPD consult				0.53
≤ 6 times a year	2	8	10	
> 6 times a year	1	8	9	
TOTAL	3	16	19	
Frequency of hospital admission				0.53
≤ 6 times a year	2	13	15	
> 6 times a year	1	3	4	
TOTAL	3	16	19	

Table VI. Relationship between COPD exacerbations and gingival bleeding

	Gingival Bleeding			p Value
	≤ 20%	> 20%	TOTAL	
Frequency of exacerbations				0.58
≤ 6 times a year	7	2	9	
> 6 times a year	9	1	10	
TOTAL	16	3	19	
Frequency of consult at ER				1.0
≤ 6 times a year	12	3	15	
> 6 times a year	4	0	4	
TOTAL	16	3	19	
Frequency of OPD consult				0.58
≤ 6 times a year	9	1	10	
> 6 times a year	7	2	9	
TOTAL	16	3	19	
Frequency of hospital admission				1.0
≤ 6 times a year	12	3	15	
> 6 times a year	4	0	4	
TOTAL	16	3	19	

Table V shows no significant relationship noted with the frequencies of exacerbation, consult at emergency ward, OPD consult and hospital admission to mean attachment loss.

Table VI showed that there was no significant relationship noted between the frequencies of exacerbation, consult at emergency ward, OPD consult and hospital admission with gingival bleeding

DISCUSSION

Chronic obstructive pulmonary disease has ranked 7th among the ten leading causes of mortality with a rate of 14.4 per 100,000 according to Philippine Health Statistics. COPD take its toll primarily at the older ages; in a US data more than 95% of all deaths from COPD in 1985 occurred in persons over the age of 55 years. Men and Women have similar mortality rates for COPD before age 55 years, but men have appreciably higher rates thereafter. With improvement in cardiovascular prevention and treatment, COPD now rises as a national health problem not only because of rising morbidity and mortality but issues of health care costs.

Several studies have been undertaken to address the issues of morbidity and curbing the cost of maintenance care of COPD patients. One approach was to determine factors that increases the frequency of exacerbation among COPD patients. Peridontal health was one potential culprit as cited by Dr. Scannapicco in several of his researches.[9,11]

In this study, it can be noticed that majority of the patients have > 1.5 mm mean attachment loss; although statistical analysis shows that this parameter was not related to frequencies of exacerbation of COPD. It is possible that mean attachment loss is related to COPD per se as suggested in the National Health and Nutrition Examination Survey III conducted in the United States.[15] Another prospective epidemiologic study would be needed to establish such relationship. In addition the same survey noted no potential relationship between worsening gingival bleeding and dental caries to risk of having COFD similar to the observation in this study.[11]

The main finding in this study was that no relationship was established between the dental health parameters with frequencies of COPD exacerbations. Although several authors proposed that poor oral health can cause respiratory infections, the mechanisms remained obscured.[10,12]. These mechanisms include: 1) aspiration of oral pathogens such as *P. gingivatis*, *A. actinomycetemcomitans,* etc. into the lung; 2) periodontal disease-associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens,[16] 3) periodontal disease-associated enzymes may destroy salivary pellicles on pathogenic bacteria; and 4) cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens.[9,16]

It cannot be denied that the relatively small number of subjects in this research could have influenced the outcome of this study. Two main reasons for this is first, the peculiarity of subject population at Veterans Memorial Medical Center, it was observed that a lot of patients have no more teeth. Many would explain that they rather have it removed so that a more complete false teeth set could be fitted on them. Secondly it was observed that many of the patients admitted at Ward 17 at the time of the study have concurrent medical problems that are part of exclusion criteria namely, diabetes mellitus, malignancy, bronchiectasis and parapneumonic effusions.

CONCLUSION AND RECOMMENDATIONS

This study has shown that there is no significant relationship between frequency of COPD exacerbation, emergency consultation, OPD consultation and hospital admission because of exacerbation of COPD with periodontal health parameters like dental caries, gingival bleeding and mean attachment loss.

Considering the size of the subject group in this study, validation studies with bigger population groups could be done. Also there is a need to conduct prospective studies regarding the role of periodontal disease with disease progression. Further investigation regarding the role of oral bacteria in COPD would also be interesting.

REFERENCES

1 The American Academy of Periodontology. Periodontal disease as a potential risk factor for systemic diseases (position paper). J. Periodontal 1998;69:841-850

2 The World Health Report 1998 -Life in the 21st Century - a vision for all by the World Health Orgarazation.

3 American Thoracic Society. Medical Section of the American Lung Association. Standards for the diagnosis and are of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225-44

4 Burrows B. Differential diagnosis of chronic obstructive pulmonary disease. Chest 1990; 97 (Suppl 2):16S-18S

5 Petty TL Chronic obstructive pulmonary disease: can we do better? Chest 1990; 97 (Suppl 2):2S-5S

6 Sanford AJ, Weir TD, Pare PLC. Genetic risk factors for chronic obstructive pulmonary disease. Eur Resp J 1997;10:1380-1391.

7 Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;146:1067-1083.

8 Ingram RH. Chronic bronchitis, emphysema, and airways obstruction. Harrison's Principles of Internal Medicine. Mac Graw-Hill: New York, 2001:1491-1499

9 Scanrapieco FA. Role of oral bacteria in respiratory infection. J. Periodontol 1999;70:793-802

10 Garrouste-Orgeas M Chevret S, Arlet G, et al. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am J Resp Crit Care Med 1997;156:1647-1655

11 Scannapieco FA, Ho AW. Potential associations between chronic respiratory disease and Periodontal disease: Analysis of National Health and Nutrition Examination Survey III. J. P Periodontol 2001;72:50-56

12 Fourrier F, Duvivier B, Boutigny H, Roussel-Delvallez M, Chopin C. Colonization of dental plaque: A source of nosocomial infections in intensive care unit patients. Crit. Care Med 1998;26:301-308

13 Travis J, Pike R, et al. The role of Proteoiytic Enzymes in the Development of Pulmonary Emphysema and Periodontal Disease. Am J Respir Crit. Care Med 1994;150:S143-S146
14 Stokley RA., The role of Proteinases in the Pathogenesis of Chronic Bronchitis. Am J Respir Crit Care Med 1994;150:S 109-S109-S113
15 U.S. Department of Health and Human Services, National Center for Health Statistics/Centers for Disease Control and Prevention. NHANES III Reference Manuals and Reports. 1996.
16 Johanson WG, Higuchi JH, Chaudhuri TR, Woods DE. Bacterial adherence to epithelial cells in bacillary colonization of the respiratory tract. Am *Rev Resp Dis* 1980;121:55-63.

USE OF BILEVEL POSITIVE AIRWAY PRESSURE (BIPAP) FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ACUTE HYPERCAPNEIC RESPIRATORY FAILURE

JESUS N. EGARGO, MD,[1] N. FRANCISCO, MD, FPCCP, [1] S. NAVAL, MD, FPCCP, [1] V. BALANAG, MD, FPCCP[1]

Study Objectives The primary objective of this study was to determine the success rate in the use of BiPAP for COPD in ARF and to compare our results with foreign literature. Secondary objectives were to identify patient characteristics that can predict the successful use of BiPAP and to determine complications with the use of BiPAP.
Design Observational prospective cohort study.
Setting Tertiary specialty hospital
Patients 12 patients meeting a predetermined definition of acute hypercapneic respiratory failure upon admission or during hospitalization refractory to conventional treatment.
Methods Non-invasive pressure ventilation was administered using a BiPAP ventilatory assist system. Inspiratory and expiratory pressures were titrated to patient comfort. Once stable settings had been achieved for 8 hours, patient was liberated from BiPAP machine.
Measurements and Results The primary outcome measure was the need for intubation and mechanical ventilation. Secondary outcomes included systolic and diastolic blood pressure, heart rate, and respiratory rate, arterial blood gases, length of stay, complication and mortality. Three patients (25%) needed intubation, however no statistically significant difference was noted when one compared those who were successfully managed by BiPAP alone to those who required intubation. Average IPAP at 24 hours was 8 ± 2 cm H_2O. The EPAP was set at the lowest setting 3 ± 0.4 cm H_2O. The average duration of BiPAP use was 27 ± 5 hours. Binomial test showed that our failure rate was comparable with foreign literature (31%) with a *p* value of > 0.46. No complications were noted and no mortality was recorded. The length of hospital stay was significantly shorter for BiPAP patients as compared to intubated patients.
Conclusions NPPV therapy with BiPAP in selected COPD patients with ARF was associated with significantly reduced need for intubation and conventional mechanical ventilation. Our success rate of 75% was comparable with foreign literature. It is well tolerated and has a number of favorable benefits in patients with ARF including the avoidance of intubation. *Phil Journal Chest Diseases Vol 11 No 1 pp: 48-52*

Keywords: COPD, Respiratory failure, mechanical ventilation

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) patients presenting with acute respiratory failure frequently require some form of assisted ventilation. In the past, intubation and mechanical ventilation were the treatment of choice; however this form of management can be associated with various adverse outcomes, including infectious (e.g. nosocomial pneumonia, sinusitis) and non-infectious (e.g. barotrauma, oral and laryngeal trauma and muscle weakness complications).[1] Noninvasive methods of ventilatory assistance have become a popular alternative to intubation and mechanical ventilation in selected COPD patients with acute respiratory failure. The potential advantages of this approach are obvious: airway defense mechanisms, speech, and swallowing functions are left intact, trauma to the larynx and trachea are avoided, and patient comfort may be improved. However, the noninvasive delivery of positive pressure ventilation also has potential limitations including the lack of direct access to the airway for removal of secretions, discomfort and facial trauma related to the mask, need for patient cooperation, and the potential for abrupt respiratory deterioration if the mask becomes dislodged or patient breathing becomes asynchronous with the ventilator.[2]

[1] Department of Pulmonary Medicine, Lung Center of the Philippines

Two recent prospective randomized studies strongly suggest the use of noninvasive mechanical ventilation in patients with severe exacerbations of COPD. Both studies show that the noninvasive ventilation group had significantly lower rates of complication, reduced need for endotracheal intubation, shorter hospital stay and lower mortality than those receiving standard treatment.

Literature review however showed that application of BiPAP has undergone limited prospective investigation, in fact no such study has been conducted in our setting. In view of this limitation, we conducted an observational prospective cohort study to determine the success rate in the use of BiPAP ventilation and to compare our results with foreign literature. We would like also to identify patient characteristics that can predict the successful use of bilevel pressure ventilation, to determine complications associated with the use of BiPAP as well as mortality and length of hospital stay. We would like also to compare our results with foreign literature with the same BiPAP protocol in terms of intubation or failure rate.

METHODS

Patients: The study was performed between September 2001 and May 2002. COPD patients with acute hypercapneic respiratory failure upon admission or during hospitalization refractory to conventional treatment were eligible to enter the study.

Acute hypercapneic respiratory failure as evidence by pH < 7.35, $paCO_2$ > 45 mmHg and a respiratory rate greater than 24 breaths/min.. Patients should be alert, responsive and hemodynamically stable. Patients were excluded if they had any of the following: an immediate indication for intubation; hypotension defined as BP < 90 mmHg; presence of ventricular tachycardia and other fatal arrhythmias; upper airway obstruction or facial trauma; inability to clear secretions from airways; those with severe nasal congestion; inability to cooperate with fitting and wearing of mask; and presence of pneumothorax or chest trauma. Informed consent was obtained for each patient or next of kin prior to enrollment.

Study Design: This is an observational prospective cohort study.

This present study followed the BiPAP protocol used in Kramer's study in 1995 which served as the historical control with which our results were compared and analyzed.

BiPAP delivery system: Once enrolled, the patient was first fitted with a tight-fitting nasal mask. Non-invasive pressure ventilation was administered using a BiPAP ventilatory assist system (*KnightStar 335* respiratory support system), a pressure limited device that cycles between adjustable inspiratory and expiratory pressures using either patient flow-triggered or time-triggered modes.

The initial inspiratory positive airway pressure (IPAP) was set at 8 cm H_2O and the expiratory pressure (EPAP) was set initially at the lowest possible setting approximately 3 cm H_2O. Supplemental oxygen was blended in via a mask port to maintain oxygen saturation greater than or equal to 90%. The patient was then encouraged to coordinate their breathing with the ventilator.

Subsequent adjustment of IPAP was made if arterial blood gases still showed persisting respiratory acidosis (pH < 7.35) or there was clinical evidence of continued respiratory distress. If the patient could not tolerate the nasal mask or excessive air leak, an oronasal face mask was used.

The patient was kept on BiPAP for as long as tolerated, aiming for at least 8 hours a day. In addition the patient received all standard therapy considered indicated by their attending physicians. The mask was removed intermittently during meals.

Discontinuation of BiPAP: Once clinical stability had been achieved, patient successfully treated with BiPAP was liberated from the machine no sooner than 8 hours. Clinical stability was defined as a reduction in respiratory rate (< 24 breaths/min), a heart rate of 110 beats/min a compensated pH of > 7.35 and adequate oxygenation > 90% with an oxygen flow rate of no more than 3 L/min. When BiPAP was discontinued, oxygen was provided via a nasal cannula or face mask. If patients remain stable, BiPAP was not reinstituted. If there was fatigue as evidenced by increased dyspnea and tachypnea, or had a detrioration in ABG, BiPAP was restarted at the prior setting and then was weaned gradually. Patients who were able to tolerate 24 hours of oxygen/nasal cannula were considered successfully weaned from BiPAP.

Outcome measures: The primary outcome to be measured was the need for intubation and mechanical ventilation. Intubation was necessary if progressive clinical deterioration occurred after entry into the study as manifested by worsening mental status, dyspnea or tachypnea, development of hypotension, a rise in $PaCO_2$ > 5 - 10 mmHg or a fall in pH of 0.5 to 1.0.

Secondary outcome measures included heart rate and respiratory rate, and arterial blood gases, as well as length of stay, complication and mortality.

Table I. Baseline patients' characteristics

Characteristics	Successful on BiPAP (n=9)	Intubated Patients (n=3)
Systolic BP	131.1 ± 17.6	143.3 ± 15.2
Diastolic BP	83.3 ± 10	93.3 ± 5.77
Heart Rate	98.2 ± 10.5	110.3 ± 0.57
Respiratory Rate	27.7 ± 4.9	31.3 ± 1.15
pH	7.28 ± 0.03	7.25 ± 0.05
pCO_2	66.2 ± 10.5	68.4 ± 2.26
pO_2	75.08 ± 25.5	72.1 ± 8.82

Table II. Patients' characteristics at four hours on BiPAP

Characteristics	Successful on BiPAP (n=9)	Intubated Patients (n=3)
Systolic BP	126.6 ± 7.07	133.3 ± 5.7
Diastolic BP	80.0 ± 5.0	90.0 ± 10.0
Heart Rate	91.8 ± 7.4	109.3 ± 8.14
Respiratory Rate	22.5 ± 2.78	28.0 ± 2.64
pH	7.36 ± 0.05	7.28 ± 0.05
pCO_2	54.7 ± 9.81	66.56 ± 3.48
pO_2	80.7 ± 20.6	68.1 ± 2.67

Statistical analysis: Non parametric test was used to analyze baseline variables as well as secondary outcomes.

The binomial test was used to analyze results in comparison with historical control. A *p* value of 0.05 was considered as statistically significant.

RESULTS

A total of 12 patients were enrolled in the study. All patients were male with a mean age of 71 ± 5 years. Three patients (25%) needed intubation during the course of non-invasive ventilation. Analysis showed however, that there was no statistically significant difference noted in any variables mentioned when one compared the successfully managed with BiPAP patients and those intubated patients.

Baseline characteristics are shown in *Table I*. The baseline mean systolic and diastolic blood pressure, cardiac rate and respiratory rate were much lower in successfully treated BiPAP patients compared to those patients who were eventually intubated. The mean baseline pH was lower in non-responders with higher pCO_2 although this may not be statistically significant. Initially, coaching was necessary to encourage patients to relax and synchronize with the ventilator; however, after several hours most of them were synchronizing well and appeared comfortable. Most patients however did not tolerate the initial 8 cm H_2O IPAP compared to historical control, most of our patients tolerated only lower levels initially with a IPAP average of 6 ± 1 cm H_2O. Subsequently, upward adjustments were made as tolerated in attempts to lower $PaCO_2$. Average IPAP at 24 hours was 8 ± 2 cmH_2O. The EPAP was set at the lowest setting remaining at 3 ± 0.4 cm H_2O for the duration of the study. The average duration of BiPAP use was 27 ± 5 hours. At four hours BiPAP, patients who were eventually intubated still showed much lower pH, and still with unacceptable elevation of pCO_2.

Binomial test also showed that our failure rate was comparable with foreign literature (31%) with a *p* value of > 0.46.

Like those in most studies on the use of bilevel pressure ventilation for acute respiratory failure, our successful BiPAP patients experienced a significantly greater decline in heart rate and respiratory rate within the first hour; however, no statistically significant difference in vital signs was seen between those successfully managed with BiPAP alone and those who required intubation afterwards.

Likewise patient receiving BiPAP had significant improvements in $paCO_2$, pH, and pCO2 within 1 hour of initiation of treatment. These rapid improvements occurring with BiPAP use are most likely related to the higher inspiratory rather than expiratory pressures, enabling BiPAP to actively assist inspiration, augmenting tidal volume and decrease the work of breathing.

Complications such as nasal ulceration, pneumothorax, hypotension and myocardial infarction were not seen among the 12 patients on BiPAP, and no mortality recorded during the entire study period. The length of hospital stay was significantly shorter for BiPAP patients as compared to intubated patients, with a mean of 5.7 days and 19.37 days, respectively.

DISCUSSION

Noninvasive positive pressure ventilation is a safe and effective means of ventilatory support for many patients with ARF. It is generally well tolerated and with reduced complications.

Bilevel PAP ventilation is a non invasive positive pressure ventilation with the application of positive airway pressure that varies in magnitude during inspiration and expiration, similar in concept to the pressure support ventilation, however it differs in terminology, where in the expiratory pressure with BiPAP is equivalent to the PEEP, and the inspiratory pressure is equivalent to the sum of PEEP and the pressure support level.[3]

Bilevel positive airway pressure can be given effectively by nasal or by face mask hooked to a mechanical ventilator. In our prospective observational study, four patients who were initially on nasal mask were shifted to face mask due to persistent air leak. The application of bilevel pressure ventilation delivered by face mask or nasal mask to patients with acute exacerbations of COPD, has been shown to reduce the inspiratory workload of breathing and the magnitude of inspiratory efforts, leading to improvement in gas exchange.

Several published studies support the use of bilevel pressure ventilation as a treatment for acute exacerbation of COPD. These controlled trials have shown an improvement in gas exchange, a decrease in hospital stay, and a lower in-hospital mortality rate. Ambrosio et al retrospectively reviewed their experience with bilevel pressure ventilation in patients with COPD. After an analysis of multiple variables, the baseline pH remained the best predictor of success (sensitivity = 97%, specificity = 71%).[3]

Although, it is difficult to predict which patients will be successfully treated with bilevel pressure ventilation, patients with preserved neurologic status who are cooperative and capable of protecting their airway should be offered a trial. In multiple studies, bilevel pressure ventilation has been shown to decrease the complications associated with ARF, primarily by avoiding intubation and mechanical ventilation.

Our finding that NPPV reduced the need for intubation is compatible with the findings of most other studies on the use of bilevel pressure ventilation in acute respiratory failure. Brochard and coworkers found that one of 13 patients with COPD exacerbations required intubation when treated with NPPV as compared with 11 of 13 historically matched control patients.[7] Benhamou and coworkers reported avoidance of intubation in 60-70% of patients with acute respiratory failure deemed to require immediate intubation, the major limitations however of all these studies were they have a relatively small sample size.

Several limitations of this study should be noted. First, as with other studies, we examined a relatively small number of patients, increasing the likelihood of statistical errors.. Second, we cannot exclude the possibility that bias contributed to our findings. Third, we did not dictate how conventional medical therapy was to be administered. Finally, we did not directly monitor respiratory muscle function; perhaps more sophisticated monitoring of respiratory muscle function would have allowed us to better determine the lack of efficacy of NPPV, and the need for tracheal intubation.

CONCLUSION

In summary, we found that NPPV therapy with BiPAP in selected COPD patients with ARF was associated with a significantly reduced need for intubation and conventional mechanical ventilation, our success rate of 75% was comparable with foreign literature. Furthermore, there were no complications and mortality associated with BiPAP treatment, but we were unable to determine factors that would successfully predict the use of BiPAP.

Although we were unable to determine predictors of success at the time of presentation, our study supports an interventional trial of bilevel pressure ventilation in patients with ARF, because patients who were successfully treated with BiPAP ventilation had shorter hospital stay and reduced ventilator times.

Any patient with ARF who is capable of cooperating with the respiratory therapist should be offered a trial of BiPAP ventilation. The failure to improve after 4-8 hours on stable BiPAP ventilation setting should be an indication for the discontinuation of BiPAP ventilation and the initiation of conventional mechanical ventilation.

Our results demonstrated that BiPAP ventilation is well tolerated and can be used safely with few complications and has a number of favorable actions in patient with ARF including the avoidance of intubation. These findings support the use of NPPV as initial therapy in patients with acute exacerbations of COPD meeting our entry criteria.

LIMITATIONS

Several limitations of this study should be noted. First as with other studies, we examined a relatively small number of patients, increasing the likelihood of statistical errors, secondly, we did not dictate how conventional medical therapy was to be administered and finally we did not directly monitor respiratory muscle function, perhaps more sophisticated monitoring of respiratory muscle function would have allowed us to better determine the lack of efficacy of NPPV, and the need for tracheal intubation.

Our results demonstrated that BiPAP ventilation is well tolerated and can be used safely with few complications and has a number of favorable actions in patient with ARF including the avoidance of intubation and mechanical ventilation.

RECOMMENDATIONS

A prospective randomized trial comparing those patients on BiPAP and those patients on conventional medical treatment should have been done to definitely conclude the beneficial effect of noninvasive mechanical

ventilation on patients with acute respiratory failure. Although we were unable to determine predictors of success at the time of presentation, our study still supports an interventional trial of bilevel pressure ventilation in patients with ARF.

Any patient therefore with ARF who is capable of cooperating with the respiratory therapist showed be offered a trial of BiPAP ventilation. Failure to improve after 4-8 hours on stable BiPAP ventilation setting should be an indication for the discontinuation of BiPAP ventilation and the initiation of conventional mechanical ventilation.

REFERENCES

1 Kramer, Naomi et al. Randomized, Prospective Trial of Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure, Am. J. Resp. Crit. Care, 1995, 151; 1799-1806.

2 Martin, Thomas et al. A Randomized, prospective Evaluation of Noninvasive Ventilation for Acute Respiratory Failure, Am J: Resp. Crit. Care, 2000, 161; 807-813.

3 Mehta, Sangeeta et al. Randomized, Prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema, Crit. Care Med. 1997 25; 4, 620-628.

4 Poponick, Janet et al. Use of a Ventilatory Support System (BiPAP) for Acute Respiratory Failure in the Emergency Department, Chest 1999, 116,166-170.

5 Wood, Kelly et al. The use of Noninvasive Positive Pressure Ventilation in the Emergency Department, Chest 1998, 113, 1339-1346.

6 Francisco, Norberto et al. Continuous Positive Airway pressure for COPD patients in Acute Hypercapneic respiratory failure, Scientific proceedings, 1994, 75-84.

7 Brochard, L. et al. Noninvasive ventilation for acute exacerbations of COPD, NEJM 333; 817-822.

8 Wysocki, M. et al. Noninvasive pressure support ventilation in patients with acute respiratory failure, Chest 107; 761-768.

9 Antonelli, M. et al. A comparison of noninvasive positive pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure, NEJM, 339; 429-435.

10 Criner, G. et al. Efficacy of of a new full face mask for non invasive positive pressure ventilation, Chest, 106; 1109-1115.

KNOWLEDGE, ATTITUDES AND PRACTICES OF PULMONOLOGISTS AND CARDIOLOGISTS ON SMOKING AND SMOKING CESSATION

ETHEL ANONUEVO, MD, FPCCP,[1] MANUEL JORGE, MD, FPCCP, [1] RHODERICK IAN REYES, MD[1]

BACKGROUND: The World Health Organization (WHO) has recommended that tobacco-smoking surveys be conducted among health professionals primarily to determine how their smoking behavior might affect their role as models and educators for appropriate health behavior. There are still no reports in the literature on the prevalence of smoking among physicians in the Philippines.

OBJECTIVES: It is the aim of this study to determine the knowledge, attitudes and practices on smoking and smoking cessation of Cardiologists and Pulmonologists practicing in the Medical Centers within the Metro Manila Area. We also aim to determine the prevalence of cigarette smoking among this group of physicians and to determine the influence of the personal smoking habits of each to their practice towards smoking cessation.

MATERIALS AND METHODS: Members of the Philippine College of Chest Physicians and the Philippine Heart Association with clinic practice within the Metro Manila area where targeted for inclusion in the survey. All physicians included in the survey were sent a letter containing a request for them to answer the questionnaire; an accompanying explanation regarding the objectives of the survey; and the 40-item modified Global Health Professional Survey. The chi square and unpaired T test were used for statistical analyses and a p value of < 0.05 was regarded as statistically significant.

RESULTS: A total of 650 survey forms were distributed and 154 (23.7%) were returned which were included in the analysis. There were 95 pulmonologists (61.7%) and 59 (38.3%) cardiologists with a mean age of 55.6 years and a range of 31 to 70 years. Sixty-three percent of the responders were male and 37% were female.

The over all prevalence of physicians who smoke in the study population was 5.8% (9) and the prevalence among cardiologists and pulmonologists were 5% and 6.3%, respectively. When stratified for age, the prevalence of smoking was highest among physicians over 60 years old. Majority of the physicians (98%) agree that smoking is harmful to health and that physicians should set a good example by not smoking. Majority of the physicians surveyed have positive attitudes towards policies that would ensure a smoke-free environment.

Pulmonologists and cardiologists routinely ask about the smoking habits of their patients, however, only 25% of cardiologists and 31% of pulmonologists routinely advise their patients to quit smoking. Most physicians primarily employ opportunistic advice and counseling to encourage their patients to quit.

CONCLUSIONS and RECOMMENDATIONS: The Pulmonologists and Cardiologists surveyed have a similar and adequate knowledge about the hazards of smoking and they recognize their role as "exemplars" to their patients and the community. Moreover, physicians who smoke are no different when compared with physicians who are non-smokers in their knowledge, attitudes and practices towards smoking and smoking cessation. The prevalence of smoking among cardiologists and pulmonologists in the Metro Manila area is lower than the smoking prevalence among adult Filipinos. *Phil Journal Chest Diseases. Vol 11 No 1 pp: 53-57*

Key words: Physician, smoking, attitudes

INTRODUCTION

Cigarette smoking is considered a worldwide major public health problem. It has been identified as the single most important cause of preventable death in industrialized countries. The World Health Organization (WHO) reports that there are about 4 million people dying from smoking related disease daily and this is expected to rise to 10 million deaths per day by the year 2020

1 Section of Pulmonary Medicine, Department of Medicine Philippine General Hospital

Table I. Demographic data of the respondents

	All N=154 (%)	Cardiologists N=59 (%)	Pulmonologists N=95 (%)
Age (Mean ± SEM)	55.62 ± 9.97	52.63 ± 10.94	57.47 ± 8.89
Gender			
Male	97 (63)	43 (72.9)	54 (56.8)
Female	57 (37)	16 (27.1)	41 (43.1)

Table II. Smoking profile of the respondents

	All N=154 (%)	Cardiologists N=59 (%)	Pulmonologists N=95 (%)
Prevalence of current smokers	9 (5.8)	3 (5)	6 (6.3)
Prevalence of Non-smokers	145 (94.2)	56 (95)	89 (93.7)
Prevalence of Former smokers	46 (29.9)	25 (42)	21 (22.1)
Prevalence of Never smokers	99 (64.3)	31 (52.5)	68 (71.6)
Onset of smoking (mean age, yrs)			
Former smokers	17.8	17.7	17.8
Current smokers	21.2	26.0	18.2
Cigarette consumption of current smokers (mean no. of sticks/day)	4.6	3.0	5.4
Mean age stopped smoking by former smokers	28.7	27.5	30.1

The role of the physician in curbing this epidemic was outlined in the joint statement of the American College of Physicians, American Thoracic Society, Asia Pacific Society of Respirology, Canadian Thoracic Society, European Respiratory Society and the International Union Against Tuberculosis and Lung Disease wherein physicians were exhorted to be exemplars to their patients and communities; and act as role models by not smoking and by creating a smoke free environment in their office.[2] The WHO has recommended that tobacco-smoking surveys be conducted among health professionals primarily to determine how their smoking behavior might affect their role as models and educators for appropriate health behavior.[3] There are still no reports in the literature on the prevalence of smoking among physicians in the Philippines.

It is therefore the aim of this study to determine the knowledge, attitudes and practices on smoking and smoking cessation of Cardiologists and Pulmonologists practicing in the Medical Centers within the Metro Manila Area. We also aim to determine the prevalence of cigarette smoking among this group of physicians and to determine the influence of the personal smoking habits of each to their practice towards smoking cessation.

MATERIALS AND METHODS

Members of the Philippine College of Chest Physicians and the Philippine Head Association with clinic practice within the Metro Manila area where targeted for inclusion in the survey. The lists of physicians were collected from the official directory of both organizations with the permission of the officials of the respective organizations. All physicians included in the survey were sent a letter, either by mail or by courier, which contained a request for them to answer the questionnaire; an accompanying explanation regarding the objectives of the survey; and the 40-item modified Global Health Professional Survey. The identities of all respondents were kept confidential.

The questionnaire utilized in this study is a modified version of the 40-item Global Health Professional Survey obtained from the WHO Western Pacific Regional Office, United Nations Avenue, Manila. Permission was requested from and granted by the WHO for us to modify some parts of the questionnaire for use in this study. The questionnaire focused on demography, smoking status, use of other tobacco products and knowledge and attitudes on smoking and smoking cessation practices. The chi square and unpaired t test were used for statistical analyses and a p value of < 0.05 was regarded as statistically significant.

RESULTS

A total of 650 survey forms were distributed and 154 (23.7%) were returned which were included in the analysis. There were 95 pulmonologists (61.7%) and 59 (38.3%) cardiologists with a mean age of 55.6 years and a range of 31 to 70 years. Sixty-three percent of the responders were male and 37% were female (*Table I*).

The over all prevalence of physicians who smoke in the study population was 5.8% (9) and the prevalence among cardiologists and pulmonologists were 5% and 6.3%, respectively. All of the current smokers are male. *Table II* summarizes the prevalence of smoking among the respondents. When stratified for age, the prevalence of smoking was highest among physicians over 60 years

Table III. Physicians' knowledge and attitudes

	Cardiologists N=59 (%)	Pulmonologists N=95 (%)
Agree that smoking is harmful	58 (98)	93 (98)
Agree that breathing in other people's smoke (passive smoking) is harmful	56 (95)	92 (97)
Agree that neonatal death is associated with passive smoking	51 *86)	82 (86)
Agree that physicians should set a good example by not smoking	58 (98)	93 (98)
Agree that physicians should be role models	58 (98)	93 (98)
Agree that patient's chances to quite increased if his HP advises him to quite	51 (86)	88 (93)
Agree that physicians should speak to lay groups about smoking	54 (92)	90 (95)
Agree that current knowledge and skills are sufficient to counsel patients	49 (83)	79 (83)
Agree that physicians should get specific training on cessation techniques	50 (85)	91 (96)

Table IV. Attitudes towards tobacco control

	Cardiologists N=59 (%)	Pulmonologists N=95 (%)
Agree that tobacco sales should be banned to children and adolescents	58 (98)	93 (98)
Agree that sales of cigarette by the stick should be prohibited	51 (86)	79 (83)
Agree that tax of tobacco products should be increased sharply	55 (93)	88 (93)
Agree that health warnings on cigarette packages should be in BIG print	57 (97)	93 (98)
Agree that there should be complete ban on advertising of tobacco	47 (80)	79 (83)
Agree that sports sponsorship by tobacco industry should be allowed	5 (8)	16 (17)
Agree that smoking in enclosed public places should be prohibited	59 (100)	92 (97)
Agree that hospitals and health care centers should be completely smoke free	58 (98)	92 (97)

Table V. Clinical practice on smoking cessation

	Cardiologists N=59 (%)	Pulmonologists N=95 (%)
Do you routinely ask about your patients smoking habits?	54 (91)	90 (94)
Do you routinely advice your patient to quite smoking	15 (25)	30 (32)
What smoking cessation techniques do you employ among your patients?		
A. None	1 (2)	1 (1)
B. Advice/counseling	44 (74)	83 (87)
C. Nicotine replacement	14 (24)	23 (24)
D. Cessation group	4 (7)	18 919)
E. Cut down gradually	22 (37)	31 (32)
F. Set date of quitting	13 (22)	32 (34)
G. Other pharmacologic interventions	7 (12)	5 (5)

old who comprise 66.7% of all smokers. The age at which the smoking habit was taken among current smokers and former smokers were 18.2 and 17.8 years, respectively. Physicians who are current smokers consume a mean of 5.4 cigarette sticks per day. Among the current smokers, 89% (8) had attempted to quit smoking and 44% (4) claim that they are ready to quit. Former smokers got rid of the habit at a mean age of 28.9 years or after a mean of 10.9 years after they started smoking.

Majority of the physicians (98%) agree that smoking is harmful to health and that physicians should set a good example by not smoking. A similar result was noted regarding their opinion on the association of passive smoking to neonatal death. *Table III* summarizes the knowledge and attitudes of the respondents on smoking. *Table IV* summarizes the physicians' views on tobacco control showing that most of them agree on the banning of tobacco sales to children and adolescents, prohibition of smoking in enclosed spaces, that hospitals be made completely smoke free and other aspects of tobacco control such as the use of signage and advertising.

Pulmonologists routinely ask about the smoking habits of their patients more than cardiologists, but the difference is not statistically significant ($p > 0.05$). Only 25% of cardiologists and 31 % of pulmonologists routinely advise their patients to quit smoking (*Table V*). Most physicians primarily employ opportunistic advice and counseling to encourage their patients to quit and a significantly higher proportion of pulmonologists than cardiolologists use it as their main smoking cessation technique ($p=0.04$). Only 24% of the physicians use nicotine replacement therapy and less than 10% are

familiar with the drug *Buproprion*. There was no significant difference between the two groups with regards to the use of other smoking cessation techniques. On analysis of the other aspects of the questionnaire, no statistically significant differences were observed between smokers and non-smokers or between cardiologists and pulmonologists.

DISCUSSION

The 5.8% smoking prevalence rate among physicians included in the survey is lower than that of the general adult population (19 years old and above) of the Philippines which has an estimated prevalence smoking rate of 33%.[4] This finding is consistent with previous studies in the US[5] and Japan[6] indicating that physicians are less likely to smoke than the general population. However, it can be noted that a considerable number are former smokers, 22.1 % and 42% among pulmonologists and cardiologists, respectively. Noteworthy is the concentration of smokers in the age group above 60 years and a much lesser prevalence among the younger physicians which is consistent with surveys done abroad.[5] This decline in smoking among younger physicians and the decreasing prevalence of smoking is the result of an increase both in quitting behavior and the increasing number of nonsmokers who enter the medical profession. Other factors that may have contributed to the lower prevalence of smoking among physicians are the higher level of education, self-selection of nonsmokers for careers in health occupations and social pressures from colleagues and organizations. This is important in keeping with their role as tutors of the people in matters of health. Physicians are important models and educators for appropriate health behavior and cigarette smoking by persons in these occupations undermines both of these roles.[5]

Our study demonstrates that there is a general agreement among the physicians in several areas related to policies that would deter the practice of smoking. First, 93% of the physicians agree that tax on tobacco products should be raised, 84% recommend prohibition on sales of cigarette by the stick while 82% conforms to complete ban on tobacco advertising. Furthermore, all believe that since smoking is harmful to health, it must be curbed early on and selling to children and adolescents should be prohibited. Majority of the physicians surveyed have positive attitudes towards policies that would ensure a smoke-free environment.

Most cardiologist and pulmonologists routinely ask their patients about their smoking habits, however, only a few routinely advice their patients to quit the habit. There may be poor knowledge of the fact that a simple five-minute advice from a physician will double the spontaneous quit rate from 2% to 4%.[7] Among the smoking cessation techniques, most physicians would prefer to advice/counsel their patients and very few would offer Nicotine replacement therapy (NRT) or advice their patients to join a cessation group. Overall, the use of pharmacologic adjuncts is very low even if they are available in the market which is in contrast to present guidelines which suggest that pharmacologic adjuncts (NRT or *Bupropion*) be offered to smokers whenever appropriate.[6,7] This may be due to the lack of knowledge or unfamiliarity of the physicians with these agents. This lack of knowledge is also suggested by the agreement of the majority that further training on the techniques and methods of smoking cessation is necessary.

Our results do not show a very significant difference in the knowledge, attitudes and practice on smoking and smoking cessation between physicians who smoke and those who do not smoke. This is in contradistinction to other studies[6] which have shown that non-smoking physicians carry out smoking cessation guidance more actively and have stricter views on smoking than do physicians who smoke.

CONCLUSIONS and RECOMMENDATIONS

The Pulmonologists and Cardiologists surveyed have an adequate knowledge about the hazards of smoking and they recognize their role as “exemplars” to their patients and the community. Furthermore, they are aware that public policy regarding sales, advertising and use of tobacco products can be an effective instrument for the promotion of public health. Our study did not show any significant difference between the cardiologist and pulmonologists in any aspect of the questionnaire. Moreover, physicians who smoke are no different when compared with physicians who are non-smokers on their knowledge, attitudes and on their practices towards smoking and smoking cessation. The prevalence of smoking among cardiologists and pulmonologists in the Metro Manila area is lower than the prevalence among adult Filipinos in the general population.

We acknowledge the possibility of bias in our findings as the smokers in this group of physicians targeted for survey may consist of the majority who refused to answer or failed to return the questionnaire. Since this is the first survey of its kind in the Philippines, we recommend that a more extensive survey be conducted aiming for a better retrieval rate.

ACKNOWLEDGMENT

This survey was conducted with the support of GlaxoSmithkline, Philippines.

REFERENCES

1 World Health Organization. Tobacco Free Initiative. 2000
2 Smoking and Health: Physician Responsibility. A Statement of the Joint Committee on Smoking and Health. Eur Respir J, 1995; 8:1808-1811.
3 Working Group on Tobacco and Health. Guidelines for the Conduct of Tobacco-Smoking Surveys Among Health Professionals. World Health Organization Regional Office for Western Pacific; 1987:3-19.
4 Dans A, Canizares L, Fajutrao L, et al. The Economic Impact of Smoking in the Philippines. Phil J Int Med; 37 (6): 261-268.
5 Nelson D, Giovino G, Ernont S, Brackbill R, et al. Trends in Cigarette Smoking Among US Physicians and Nurses. JAMA; 271 (16): 1273-1275. 6.
6 Ohida T, Sakurai H, Mochizuki Y, et al. Smoking Prevalence and Attitudes toward Smoking Among Japanese Physicians. JAMA; 285 (20): 2643-2648.
7 West R, McNeill A, Raw M. Smoking Cessation Guidelines for Health Professionals: An Update. Thorax 2000; 55: 987-999.

EXERCISE TOLERANCE AND QUALITY OF LIFE IMPROVEMENT FOLLOWING AEROBIC AND STRENGTH TRAINING EXERCISE IN PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

OGEE MER PANLAQUI, MD,[1] TERESITA AQUINO MD, FPCCP, [1] CELESTINO DALISAY MD, FPCP, FPCCP[1]

BACKGROUND: Chronic obstructive pulmonary disease is a progressive disease characterized by airflow limitation and poor airway reversibility. Patients with such disease suffer not only from cardio-pulmonary complications but also develop renal, hormonal and peripheral muscle dysfunction. Advance COPD patients are wasted with loss of protein and muscle mass. Essential in the treatment modality of patients with such debilitating disease is pulmonary rehabilitation and exercise is one of its components. Aerobic exercise prescription among COPD patients was found to improve patient's dyspnea tolerance measured by a six minute walk test. Combining this exercise modality with strength training exercise may not only prevent muscle mass atrophy but also improve patient's well being through a quality of life study.

OBJECTIVE: To determine the efficacy of aerobic combined with strength training exercise in the improvement of exercise tolerance and quality of life of mild and moderate COPD patients.

MATERIALS AND METHODS: The study is an experimental study design. Subjects included were (1) physician diagnosed COPD based on smoking history, cough of 3 months in 2 consecutive years. (2) pulmonary function test compatible with COPD (i.e. FEV_1/FVC ratio of less than 70% and bronchodilator response less than 15%) or showing irreversible bronchial obstruction. (3) stable patients at the time of entry. (4) patients having exercise limitation manifested as shortness of breath or general fatigue. Exclusion criteria are patients having clinical evidence of cardiovascular or neuromuscular disease.

RESULTS: Nine patients were able to complete the program. Pre-training lung function studies and anthropometric measurement were obtained showing mild to moderate airflow obstruction with adequate oxygenation, normal resting carbon dioxide level and body mass index. Post-training, there was an increase in the circumference of the upper and lower extremities using stationary bicycle, treadmill and ergocycle. Only the increase in the right arm and left thigh circumference were significant with a mean difference of 1.3 cm $\pm$ 0.32 cm and 1.14 cm $\pm$ 0.28, respectively. There was marginal improvement in lung function post-training which is not significant. The six-minute walk test was obtained pre and post training which improve to 631 m $\pm$ 148 with a significant mean difference of 218 meters. The Mahler's Baseline Dyspnea Index was obtained showing significant improvement in patient's performance of activities of daily living.

CONCLUSION: Aerobic combined with strength training exercise significantly improved patients exercise capacity and tolerance as shown by the change in the six minute walking distance test and increase in the upper arm extremity circumference. No improvement was seen in the pulmonary function test which is an anticipated finding. The greatest benefit in the combined modality of aerobic and strength training exercise was the improvement in the baseline dyspnea index of patients during and after the exercise program.
Phil Jour Chest Diseases. Vol 11 No 1 pp: 58-64

Keywords: Pulmonary Rehabilitation, Exercise tolerance, COPD

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a disease characterized by the presence of airflow obstruction is generally progressive, may be accompanied by airway hyperactivity and may be partially reversible. The presence of non-specific entity of chronic productive cough, breathlessness on exertion and physiologic evidence of airflow limitation and poor reversibility are some of its distinctive features.[1]

Aside from the symptomatology of cough of 3 months over 2 consecutive years and dyspnea, patients suffering from COPD are identified by the presence of an abnormal lung function such as the reduction of the forced expiratory volume (FEV_1). The annual loss of FEV_1 among susceptible individuals who develop COPD

[1] Department of Pulmonary Diseases, Veterans Memorial Medical Center

is between 50 and 100 ml per year. Hence, majority of patients usually experience exertional dyspnea when FEV_1 falls below 40% of the predicted and have dyspnea at rest when the FEV_1 < 25% of the predicted.[2] In addition to dyspnea at rest, CO_2 retention and cor pulmonale occur when the FEV_1 falls below 25% of the predicted.

Patients with chronic obstructive pulmonary disease suffer not only from cardio-pulmonary complications but also develop renal, hormonal and peripheral muscle dysfunction. The rapid energy expenditures during exacerbation of the disease coupled with poor nutritional and caloric intake lead to cachexia and reduction of body mass index. Advance COPD patients are wasted with loss of protein and muscle mass. The skeletal muscle bulk is lost with proportional reductions in strength. Proximal limb girdle muscles of the upper and lower extremities are particularly affected, contributing to dyspnea with activities of daily living. These changes occur in parallel with FEV_1 and independently of glucocorticoid use, which can also cause myopathy and muscle weakness.[2] In addition, Bernard et al. showed that there exist a preferential distribution of muscle weakness in the lower limb as compared to the upper limb, the shoulder girdle, pectoralis major and the latissimus dorsi muscle groups. This uneven muscle weakness distribution and the loss of muscle mass is in proportion to the reduction in strength suggesting that the muscle contractile apparatus is preserved. The preferential loss in lower limb muscle mass and strength and their relationship with FEV_1 percentage of predicted suggest that muscle disconditioning and disuse atrophy are important factors in explaining peripheral skeletal muscle dysfunction in COPD. [3]

Patients with chronic obstructive pulmonary disease (COPD) demonstrate widely variable exercise capacities. Until recently, it was felt that the FEV_1 provides a good expression of the mechanical changes by which COPD affects exercise tolerance.[4] It was therefore assumed that patients with low FEV_1 would not be able to tolerate limited exercise even a six minute walking distance (6MWD). There are various theories to such response and one of which is the patient's loss muscle mass and consequent to this is muscle atrophy due to disuse. The fear of a COPD patient to experience exacerbation of dyspnea with exercise is well founded. To allay such fears, aerobic exercise became one of the components of pulmonary rehabilitation. Strength training exercise on the other hand had been part of muscle mass growth in normal subjects. The use of strength exercise modality for 8 weeks as shown by Simpson et al.[5] as mode of intervention in peripheral muscle function of patients suffering from chronic airflow limitation was helpful in improving their exercise capacity, dyspnea tolerance and quality of life.

Our general objective for this study was to determine the efficacy of aerobic combined with strength training exercise in the improvement of exercise tolerance and the quality of life of mild and moderate COPD patients. Specific objectives were: To describe the demographic characteristics and lung function status of COPD patients; To asses the efficacy of aerobic combined with strength training exercise in the improvement of peripheral muscle mass and prevention of muscle atrophy pre and post training; To determine the improvement in exercise tolerance following the institution of aerobic combined with strength training exercise using 6 minute walking distance as parameter and To determine weather exercise training modalities improve the quality of life of patients with COPD using the Mahler's Dyspnea Index.

METHODS

Subjects and Materials. The study was conducted at the Pulmonary Rehabilitation Unit of the Veterans Memorial Medical Center (VMMC). Subjects included were (1) physician diagnosed COPD based on smoking history, cough of 3 months in 2 consecutive years (2) pulmonary function test compatible with COPD (i.e. FEV_1/FVC ratio of less than 70% and bronchodilator response less than 15%) or showing irreversible bronchial obstruction. (3) stable patients at the time of entry (4) patients having exercise limitation manifested as shortness of breath or general fatigue. Exclusion criteria are patients having clinical evidence of cardiovascular of neuromuscular diseases. The research protocol was submitted for scrutiny by the research ethics committee and a written consent was obtained from each participant.

Methodology. This is a prospective experimental study of COPD patients who met the inclusion criteria. Enrolled subjects were interviewed using the Mahler's Baseline Dyspnea Reference Index which assessed the patient's perception of dyspnea with regards to activities of daily living, the magnitude of task that the patient can perform and the magnitude of effort. The patient was graded from 0 to 4 i.e. their perception of dyspnea from severe to no perception at all. Patients underwent anthropometric measurements, arterial blood gas, and pulmonary function tests before and after the exercise program. In addition, proper nutrition was advised with the assistance of a qualified nutritionist and dietician.

Exercise Training. The study group underwent a 12 wk training program consisting of two weekly sessions for one hour with 10 minutes of deep breathing and

Table I. Patient characteristics

Age (years)	71 ± 7
Sex (M:F)	7 : 2
Smoking	
Average	24 ± 19
Pack years	79 ± 58
FEV_1 (L)	1.19 ± 0.32
FEV_1 (% predicted)	60 ± 15
FVC (L)	1.76 ± 0.55
FVC (% predicted)	68 ± 17
FEV_1/FVC	69.7 ± 14
PaO_2 (mmHg)	83.31 ± 8
$PaCO_2$ (mmHg)	33.2 ± 6.8

Table II. Anthropometric measurements

Height (m)	1.62 ± 0.054
Weight (kg)	54 ± 7.5
BMI (kg/m^2)	20.45 ± 2.83
Arm (cm)	
Right	23.5 ± 1.8
Left	23.7 ± 2.0
Leg (cm)	
Right	31.3 ± 4.03
Left	32.5 ± 4.16
Thigh (cm)	
Right	38.9 ± 3.1
Left	38.1 ± 3.79

Table III. Patient maintenance medications

Beta-2 Agonist	
Oral	7 (66.7%)
Inhaled	1 (11.1%)
Both	2 (22.2%)
Anticholinergic	4 (44.4%)
Theophylline	2 (22.2%)
Steroids	
Oral	6 (66.6%)
Inhaled	3 (33.3%)

relaxation period. During the relaxation period, subjects were instructed to do breathing exercises consisting of diaphragmatic and pursed lip breathing.

Aerobic Training. The aerobic training consisted of leg exercise on a calibrated stationary bicycle for 20 mins and another 20 mins for treadmill exercise on each of the two weekly sessions. The subjects were encouraged to reach a peak work rate of 80% from the baseline as the target training intensity exercise. During the exercise the investigator monitored and supervised the subjects. Vital signs were monitored and causes of early termination of the exercise were duly noted such as generalized fatigue, muscle cramps, chest pain, progressive dyspnea and signs of respiratory distress. Supplemental oxygen was available in case of exercise induced oxygen desaturation.

Strength Training. In addition to the aerobic exercise, the subjects underwent 20 minutes of cycle ergometer for the upper extremities. The cycle ergometer was equipped with a calibrated resistance workload from 0 to 10 and in each patient visit the resistance was increased until a maximum workload was achieved.

Evaluation. At the end of the 12 wk exercise training program patients were evaluated based on the following parameters:

Pulmonary function tests. Standard pulmonary function test like spirometry was conducted before and at the end of the exercise program. Likewise oxygen saturation were taken during and after the exercise using a pulse oximeter. Any patient manifesting with exercise induced oxygen desaturation will be given supplemental oxygen.

Anthropometric Measurements. Anthropometric measurements were taken and the body mass index computed prior to the exercise program and also at the end of the 12 wk aerobic combined strength training exercise using a caliper. These measurements were taken by a respiratory therapist. A six minute walking distance test was done before and after the exercise program which was conducted in the hall of the hospital. The subjects were asked to walk as long as they could for 6 minutes with the assistance of investigator and the distance was measured. There were three trials and the best of the three were taken and analyzed.

A health related quality of life assessment was part of the outcome measure using the Mahler's Baseline Dyspnea Index (BDI) which was conducted by the investigator pre and post training exercise. The BDI measured three components that influenced dyspnea, namely functional impairment, (the degree to which activities of daily living are impaired), and lastly magnitude effort (the overall effort exerted to perform activities) and the magnitude of task that provokes breathing difficulty.[6]

Data and Statistical Analysis. The statistical package SPSS was used in obtaining the mean values ± SD. The average training exercise was obtained by dividing the total work performed over the duration of the exercise program. Using the paired t-test and Wilcoxon Test the effects of pre and post training changes were compared. A value of $p<0.05$ was considered statistically significant.

RESULTS

Patient recruitment began by poster and leaflet information drive including patient education regarding the benefits of pulmonary exercise rehabilitation among

Table IV. Mean training exercise achieved during training sessions for the whole 12 week program

	Mean	± SD
Bicycle Exercise		
Speed (km/hr)	26.80833	5.966419
Mets	9.131	1.514862
HR	101.5137	17.09021
SBP	121.1407	5.566734
DBP	74.87037	3.568592
Treadmill Exercise		
Speed (km/hr)	4.310324	1.126473
Calories	13.15799	3.279256
Distance (km)	1.64125	0.285029
HR	106.0743	8.294883
SBP	122.712	4.697042
DBP	74.44074	1.849983
Ergocycle		
Workload (kg)	3.355185	1.072895

Table V. Physiologic and anthropometric parameters before and after exercise

	Before Exercise	After Exercise	Mean Difference	p Value
Weight (kg)	54.47 ± 7.5	53.9 ± 6.45	0.53 ± 1.93	0.431
BMI (kg/m^2)	20.45 ± 2.83	20.29 ± 2.4	0.16 ± 0.61	0.462
Arm (cm)				
Right	23.5 ± 1.8	24.89 ± 1.55	1.3 ± 0.32	0.003*
Left	23.7 ± 2.0	25.98 ± 2.4	2.2 ± 1.25	0.112
Leg (cm)				
Right	31.3 ± 4.03	33.12 ± 4.9	1.8 ± 1.19	0.166
Left	32.59 ± 4.16	31.84 ± 5.4	0.74 ± 0.94	0.450
Thigh (cm)				
Right	38.9 ± 3.1	38.35 ± 4.31	0.58 ± 1.1	0.611
Left	38.7 ± 3.79	39.24 ± 4.21	1.14 ± 0.28	0.004*
FEV_1 (L)	1.19 ± 0.32	1.24 ± 0.35	0.25 ± 0.003	0.125
FEV_1 (% predicted)	60 ± 15	65 ± 18	4.8 ± 2.99	0.146
FVC (L)	1.76 ± 0.55	1.8 ± 0.56	0.004	0.872
FVC (% predicted)	68 ± 17	74 ± 18	5.2 ± 3.94	0.222
FEV_1/FVC	69.7 ± 14	74.5 ± 16	4.9 ± 2.55	0.086
PaO_2 (mmHg)	83.31 ± 8	86 ± 5.6	2.4 ± 1.47	0.143
$PaCO_2$ (mmHg)	33.2 ± 6.8	38.213 ± 4.0	5.8 ± 2.621	0.060
pH	7.42 ± 0.315	7.435 ± 0.268	0.014 ± 0.0012	0.300
HCO_3	24.44 ± 1.7	21.54 ± 2.8	2.9 ± 0.916	0.016*
6MW	412 ± 135	631 ± 148	218 ± 65.12	0.000

COPD patients. Initially there were sixteen patients who qualified however, four patients were excluded due to COPD exacerbations requiring hospitalizations, two complained of joint pains at the start of the program and one subject underwent biliary surgery.

Nine patients remained and were able to complete the program. Baseline characteristics of the subjects are presented in *Table I*. On the average the mean age is 71 ± 7 years, with seven males and two females. Out of the nine patients, seven were previous smokers with average daily consumption of 24 ± 19 sticks per day or a computed 79 pack years of smoking history. Pre-training lung function studies were obtained showing mild to moderate airflow obstruction with adequate oxygenation and normal resting carbon dioxide level.

Anthropometric measurements revealed normal body mass index. The arm, leg and thigh circumference were obtained expressed in Mean ± SD values in *Table II*.

Medications of the patients consisted of beta-2 agonists in oral and inhaler form, theophylline, inhaled anticholinergic and steroids in oral and inhaled form. *Table III* shows that among the nine patients, six (66.7%) are taking oral beta-2 agonist, only one is taking inhaled beta-2 agonist and two subjects are taking both. Four patients are taking inhaled anticholinergics, two out of the nine are on oral theophylline, and six of the nine patients are on inhaled steroids while the remaining three are on oral form of steroids.

The mean exercise training achieved by the patients during the whole duration of the 12 week program is shown in *Table IV*. Patients obtained a mean speed in the bicycle exercise of 26.8 ± 5.96 with maximum metabolic energy expenditure of 9.13 ± 1.5. Likewise the mean walking speed of the subjects in the treadmill was 4.31 km/hr ± 1.12 and within the allotted 20 minutes exercise the maximum distance achieved was 1.64 km ± 0.28 and calories spent was 13.15 kcal ± 3.3. Strength training for the upper extremity using the ergocycle was achieved by the subjects with a maximum workload of 3.35 kg ± 1.07. Vital signs of the patients were obtained while undergoing the exercise program and maximum heart rate was 101 bpm ± 17 and 106 bpm ± 8 for the bicycle and treadmill exercise respectively. No episode of hypotension or oxygen desaturation noted on the whole duration of the exercise program.

The effect of the exercise training on muscle and lung function is shown in *Table V*. There were increases in the circumference of the upper and lower extremities after exercise using the stationary bicycle, treadmill and arm cycle. However, only the increase in right arm circumference and left thigh circumference were significant with a mean difference of 1.3 cm ± 0.32 cm and 1.14 cm ± 0.28 respectively. The pulmonary function of the patients were obtained pre and post training showing marginal improvement in lung function which is not significant. With regards to the tolerance of the patients to exercise training, the six minute walk test was obtained pre and post training. Before the exercise

Table VI. Mahler's Dyspnea Index scoring pre- and post-training

	Pre-Training	Post-Training	p Value
Functional Impairment			
0	3 (33.3%)	0	
1	2 (22.2%)	0	
2	3 (33.3%)	3 (33.3%)	
3	1 (11.1%)	4 (44.4%)	
4	0	2 (22.2%)	
TOTAL	9	9	0.007*
Magnitude of Task			
0	3 (33.3%)	0	
1	3 (33.3%)	0	
2	2 (22.2%)	0	
3	1 (11.1%)	7 (77.8%)	
4	0	2 (22.2%)	
TOTAL	9	9	0.007*
Magnitude of Effort			
0	1 (11.1%)	0	
1	6 (66.7%)	0	
2	1 (11.1%)	1 (11.1%)	
3	1 (11.1%)	7 (77.8%)	
4	0	1 (11.1%)	
TOTAL	9		0.006*

started the mean distance achieved by the patients within the allotted six minutes was 412 meters $\pm$ 135. After the 12 week duration, the six minute walk test improved to 631 m $\pm$ 148 with a significant mean difference of 218 meters.

The effects of the exercise training in the dyspnea perception and quality of life of the patients was obtained using Mahler's Baseline Dyspnea Index (*Table VI*). Pre-training the dyspnea index of the subjects showed that majority of them perceived dyspnea even before they start their usual activities. Thirty-three percent answered that they are very severely functionally impaired with regards to their usual activities while five of them belong to the moderate to severely impaired. Likewise, six of the subjects belong to grade 0 to 1 in terms of their magnitude of task i.e. they become short of breath at rest or lying down or even walking on the level, washing or standing. With regards to their magnitude of effort, six of the nine belong to grade 1 wherein they become short of breath with little effort. Post training, the dyspnea score of the patients improved significantly with none of them belonging to grade 0 to 1.

DISCUSSION

Exercise training is the foundation of pulmonary rehabilitation but it is just of the components of an effective pulmonary rehabilitation program for patients suffering from chronic lung disease. Although exercise has to date not resulted in measurable effects on the underlying respiratory impairment, its positive effects on dyspnea underscores the importance of physical reconditioning as a co-morbid factor in advance lung disease.[7]

This study sought to evaluate the benefits of aerobic combined with strength training exercise in a patient suffering from chronic lung disease in terms of exercise tolerance and change in the perception of dyspnea that gravely affects his activity of daily living. The results showed that with a twice weekly session in a 12 week program, there was an increase in the upper arm, leg and thigh circumference after exercise. Further, there was a significant increase in the right arm circumference and left thigh circumference. In this regard, strength training exercise using an incremental resistive workload of a cycle ergometer is beneficial in strengthening the upper extremities. Vogiatzis et al demonstrated significant physiologic training response such as reduction in minute ventilation, carbon dioxide output, ventilatory equivalent for oxygen and increase in oxygen uptake following incremental symptom limited cycle ergometer testing irrespective of the degree of ventilatory obstructive defect.[8] Although such physiologic parameters were not obtained in this study due to limited available equipment to measure such parameters. It is worthwhile mentioning that aside from the physical changes that occurs with exercise training, there are physio-biochemical changes that likewise occur.

Including the upper extremities strength training in the exercise program among COPD patients greatly increase their exercise tolerance and decrease dyspnea perception.[7-9,11]

It can be observed that there's significant muscle atrophy in the upper extremities among COPD patients because of muscle disuse and wastage during exacerbations. Arm training prevents muscle atrophy and improves the ventilatory contribution of those muscles by increasing shoulder girdle muscle strength. Hence, strength and endurance training of the upper extremities improves arm function in patients with COPD. Arm exercises are safe and should be included in rehabilitation program for patients with COPD.[10]

There was significant marginal improvement in the lung function of the patients after the 12 week exercise program. The lack of change of lung function of patients undergoing pulmonary rehabilitation is a consistent finding. Most previous studies have also failed to show significant changes in lung function.[2,6,8,9,11-13]

The six minute walk test is a widely accepted test in determining exercise tolerance in patients with advanced lung disease. The test was performed before and after the

exercise program in a hallway measuring 50 meters. In this study, there was significant improvement in the ability of the patients to walk the 50 meters within six minutes. This means that the exercise capacity of the patients increased significantly and the level of perception of dyspnea decreased as they walk within six minutes in the hallway after the institution of the 12 week exercise program. Such findings were also seen in other related studies using six minute walk test as a parameter of exercise tolerance.[14-17] Further, Berry et al showed that there was a significant increase in the 6-minute walk distance among patients with mild, moderate and severe stage of chronic obstructive lung disease.[18] Supporting the information that with exercise rehabilitation regardless of stage, patients with COPD could obtain optimal benefit.

Salient in the evaluation of the benefits of exercise program was the change or improvement in the perception of dyspnea in performing the activities of daily living post exercise among COPD patients. Such evaluation is labeled as the quality of life improvement. In this study, there was a significant change in the grading of patients from moderate grade of their functional impairment at all in performing their activities of daily living. In terms of the magnitude of task that the patients perform, there was also significant improvement in grading from moderate task such as walking uphill into doing extraordinary activity such as carrying heavy loads. Lastly, the magnitude of effort also improved wherein patients would experience shortness of breath with moderate effort to no shortness of breath at all with ordinary effort.

The Baseline Dyspnea Index used in this study is just one of the validated questionnaires that deal with measurement of dyspnea with regards to the targeted activities of daily living. In all published clinical trials, comprehensive pulmonary rehabilitation programs resulted in improvement in dyspnea during and after exercise and with activities of daily living [2,19-21] Therefore improvement in the quality of life of patients with pulmonary disease is an important goal of pulmonary rehabilitation.[6]

CONCLUSION AND RECOMMENDATIONS

Aerobic combined with strength training exercise significantly improved patients exercise capacity and tolerance as shown by the change in the six minute walking distance test and increase in the upper arm extremity circumference. No improvement was seen in the pulmonary function test which is an anticipated finding. The greatest benefit in the combined modality of aerobic and strength training exercise was the improvement in the baseline dyspnea index of patients during and after the exercise program. This benefit can be translated in terms of assuring patients that they could perform daily activities and could even be of help to their households which is a significant reversal from their dependency for care.

Exercise training is just one of the components of pulmonary rehabilitation among chronic lung patients, other components are nutrition, education and psycho-behavioral intervention. The multidisciplinary approach is essential to achieve an effective and successful pulmonary rehabilitation. It is beyond the scope of this study to support through evidence such approach but it is worth mentioning.

In this regard, we put forward the following recommendations: Study on the long term benefits of exercise training, education and nutrition intervention among COPD patients in our institution. How should such programs be structured to produce long term benefits? In this study, patient requirements and follow-up were difficult due to transportation difficulties of patients in going to the hospital as well as the lack of financial help that the institution can offer to do such a study. Alternative would be to confine patients undergoing the exercise program although such inpatient study is costly on the part of the hospital. A prospective study could be done comparing the benefits of once weekly exercise with home exercise program with a twice or three times per week exercise program.

REFERENCES

1 Fishman, A. Pulmonary Diseases and Disorders, Third Edition, vol. 1.683-696, 1998

2 Bernard, S. Aerobic and Strength Training in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory Critical Care Medicine. vol. 159.896-901,1999

3 Bernard S. et al. Peripheral Muscle Weakness in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory Critical Care Medicine. vol. 158.629-634. 1998

4 Bauerle, O. et al. Mechanism by which COPD Affects Exercise Tolerance. American Journal of Respiratory Critical Care Medicine. vol. 157.57-68,1998

5 Simpson, K. et al. Randomised Controlled Trial of Weightlifting Exercise in Patients with Chronic Airflow Limitation. Thorax 47:70-75.1992

6 Ries AL and Carlin BW. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Guidelines. Journal of Cardiopulmonary Rehabilitation 17:6 1997

7 American Thoracic Society. Pulmonary Rehabilitation 1999. American Journal of Respiratory and Critical Care Medicine. 159:5. 1999

8 Vogiatzis I, et al. Physiologic Response to Moderate Exercise Workloads in a Pulmonary Rehabilitation Program in Patients with Varying Degrees of Airflow Obstruction. Chest 116. 1200-1207.199

9 Reis AL. Position Paper of the American Association of Cardiovascular and Pulmonary Rehabilitation: Scientific Basis of Pulmonary Rehabilitation. Journal of Cardiopulmonary Rehabilitation. 10:418-41.1990

10 Reis AL, et al. Effects on Pulmonary Rehabilitation on Physiologic and Psychological Outcomes in Patients with Chronic Obstructive Pulmonary Disease. Annals of Internal Medicine. 122:823-832. 1995
11 O'Hara WJ, Lasachuk BP, Matheson P, et al. Weight Training and backpacking in Chronic Obstructive Pulmonary Disease. Respiratory Care 29:1202-1210. 1984
12 Troosters T, Gossenlink R. Decramer M. Short and Long-term Efforts of Outpatient Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease, A Randomized Trial. The American Journal of Medicine. 109:3.207-212. 2000
13 Guell R., et al. Long-term Effect of Outpatient Rehabilitation of COPD, A Randomized Trial. Chest 117:976-983. 2000
14 Scherer, YK, Schmieder LE. The Effect of Pulmonary Rehabilitation Promgram on Self-efficacy, Perception of Dyapnea and Physical Endurance. Heart and Lung. The Journal of Acute and Critical Care. 26:1. 15-22. 1997
15 Damien S et al. Comparison of Hallway and Treadmill Six-minute Walk Tests. American Journal of Respiratory and Critical Care Medicine. 160:5. 1540-1543. 1999.
16 Finnerty JP et al. The Effectiveness of Outpatient Pulmonary Rehabilitation in Chronic Lung Disease. A Randomized Controlled Trial. Chest. 119. 1705-1710. 2001
17 Wedzicha JA et al. The Prediction of Benefit from Pulmonary Rehabilitation: Setting, Training, Intensity and the Effect of Selection by Disability. Thorax. 54 Suppl. 2, S3-S7. 1999
18 Berry MJ et al. Exercise Rehabilitation and Chronic Obstructive Pulmonary Disease Stage. Journal of Cardiopulmonary Rehabilitation. 169: vol. 20 (2). 2000
19 Fuschs CD et al. Quality of life and Exercise Tolerance in Chronic Obstructive Pulmonary Disease: Effect of a Short and Intensive Inpatient Rehabilitation Program. 78:4. 330-335. 1999
20 Benzo R et al. Effect of Pulmonary Rehabilitation on Quality of Life in Patients with COPD. The Use of SF-36 Summary Scores as Outcome Measures. Journal of Cardiopulmonary Rehabilitation. 20:4. 231-234. 2000
21 de Torres JP. Et al. Power of Outcome Measurements to Detect Clinically Significant Changes in Pulmonary Rehabilitation of Patients with COPD. Chest 121. 1092-1098. 2002

Special Article

POLYMORPHISMS OF THE BETA 2 ADRENERGIC RECEPTORS AND ASTHMA

MA. THERESA T. SARMIENTO-PINLAC, MD[1]

The β2 adrenoceptor gene is highly polymorphic in the human population, with 19 reported single nucleotide polymorphisms (SNPs). Of the 9 SNPs occurring in its coding block, four result in missense polymorphisms (Arg16Gly, Gln27Glu, Val34Met, and Thr164Ile). The Gly16 allele is associated with increased receptor downregulation, nocturnal asthma, greater asthma severity, and decreased response to beta-2 agonists. The Glu 27 allele appears to protect against receptor downregulation and is associated with less reactive airways. The Ile164 allele is associated with a decreased agonist-binding affinity of the receptor while the Met34 allele appears to have normal receptor function.

Because the genetic variation in the beta 2-adrenoceptor is common, it is potentially relevant to the clinician. These variants may be the first genetic loci that will provide for individualized therapy in asthma.
Phil Journal Chest Diseases. Vol 11 No 1 pp: 65-70

Keywords: Beta-2 agonist, Beta-2 receptor, Bronchial asthma

INTRODUCTION

The human β2 adrenoceptor is a member of the 7-transmembrane family of receptors[1,2] expressed in many cell types throughout the body such as neutrophils, eosinophils, alveolar macrophages and airway epithelial cells.[2] It is the most common adrenergic receptor in the lung[3] and is widely distributed in the respiratory tract, particularly in airway smooth muscle.[1]

Documented effects of the activation of the β2 adrenoceptor in the human lung include smooth muscle relaxation, inhibition of acetylcholine release from cholinergic terminals, stimulation of serous and mucous cell secretion, increases in ciliary beat frequency, promotion of water movement into the airway lumen, increase in bronchial blood flow, reduction in venular permeability, and inhibition of mediator release from some, but not all, inflammatory cells.[4]

Being G-protein-coupled receptors,[5] intracellular signaling following β2 adrenoceptor activation is largely affected through a trimeric Gs protein coupled to adenylate cyclase. This leads to the production of cyclic AMP which induces airway relaxation through phosphorylation of muscle regulatory proteins and attenuation of cellular Ca^{+2} concentrations.[1]

Drugs that work by activating β2 adrenoceptors are known as β2 adrenoceptor agonists. These drugs, which include salbutamol, are the most widely prescribed rescue agents in the treatment of asthma.[6-8] They activate the β2 adrenoceptors on the surface of bronchial cells thereby causing the smooth muscles of the respiratory system to relax.

However, not all asthma sufferers respond well to such β2 adrenoceptor agonists. A marked heterogeneity in the response to β-agonists has been observed in the treatment of asthma.[9]

It had been hypothesized that the observed differences in response may be due to polymorphisms in the gene that encodes the β2 adrenoceptor. A genetic variation in the receptor can alter signal transduction which, in turn, could lead to an altered response to beta agonists in asthma.[9]

The gene that encodes for the β2 adrenoceptor is located on chromosome 5q31-33. It is an intron-less single gene that codes for a polypeptide of 413 amino acids.[10] The cloning and characterization of this gene have opened new insights into the structure, function, and regulation of the β2 adrenoceptor.[11]

The β2 adrenoceptor gene is highly polymorphic in the human population.[2] Nine polymorphisms in the coding region and 10 polymorphisms in the 5' promoter region have been reported.[10]

[1] Associate Professor, Department of Biochemistry and Molecular Biology, UP College of Medicine

The 9 different point mutations in the coding region were found in nucleic acid residues 46, 79, 100, 252, 491, 523, 1053, 1098, and 1239. Of these 9 single nucleotide polymorphisms, 4 were found to cause changes in the encoded amino acids.[12] These missense mutations are: 1. the substitution of guanine (G) for adenine (A) at nucleotide position 46 that leads to the substitution of glycine (Gly) for arginine (Arg) at amino acid position 16 (A46G leads to Arg16Gly) 2. the substitution of guanine (G) for cytosine (C) at nucleotide position 79 that leads to the substitution of glutamic acid (Glu) for glutamine (Gln) at amino acid position 27 (C79G leads to Gln27Glu) 3. the substitution of adenine (A) for guanine (G) at nucleotide position 100 that leads to the substitution of methionine (Met) for valine (Val) at amino acid position 34 (G100A leads to Val34Met) and 4. the substitution of thymine (T) for cytosine (C) at nucleotide position 491 that leads to the substitution of isoleucine (Ile) for threonine (Thr) at amino acid position 164 (C491T leads toThr164Ile).[13]

The arginine16 to glycine (Arg16→Gly) and glutamine 27 to glutamic acid (Gln27→Glu) are the most frequent polymorphisms found in the general population[12] and their allele frequencies show significant differences due to ethnic background. Among Caucasians, Blacks, and Asians, the allele frequencies of Gly16 are 0.61, 0.50, and 0.40, respectively while the allele frequencies of Glu27 are 0.43, 0.27, and 0.20, respectively.[14] The threonine 164 to isoleucine (Thr164→Ile) and valine 34 to methionie (Val34→Met) are both rare, representing 5% and <1% of those assessed, respectively.[13]

The functional consequences of the four β2 adrenoceptor missense polymorphisms arising from the single nucleotide polymorphisms of the β2 adrenoceptor gene were studied by site-directed mutagenesis and recombinant expression in cells.[15,16] The ability of the different mutated receptors to bind agonists was the initial focus of investigation.

Studies revealed that receptors with Gly16, Glu27 or Met34 mutations displayed normal agonist binding and functional coupling to Gs, resulting in the stimulation of adenylyl cyclase activity.[13,15,17] However, the Ile164 receptor displayed substantial dysfunction.[13]

The Ile164 receptor exhibited a lower binding affinity for isoproterenol, salbutamol, metaproterenol, terbutaline, formaterol and salmeterol.[18] It failed to exhibit detectable high affinity binding, suggesting an impairment in the formation of the agonist-receptor-Gs complex. Consistent with this finding, functional coupling to Gs as determined in adenylyl cyclase assays was significantly (approximately 50%) depressed under both basal and agonist-stimulated conditions. β2 adrenoceptor sequestration, which is also triggered by agonist binding, was also found to be approximately 65% reduced in the Ile 164 polymorphism.[16]

The decreased agonist-binding affinity of the Ile164 receptor may be explained by the location of the mutated amino acid in relation to the ligand-binding pocket of the 7 transmembrane spanning domains of this receptor. Site-directed mutagenesis has identified Asp 113 and Ser 204/207 within the third and fourth membrane domains as the active site of the beta2-receptor, critical for beta2-agonist binding and activity.[1] Agonists bind in a pocket formed by transmembrane spanning domains 3, 5 and 6, where key contact points initiate receptor activation.[19] The relatively uncommon polymorphism of substituting isoleucine for threonine at amino acid 164 is a mutation that occurs in the 4th transmembrane spanning domain within the proposed ligand binding pocket of the β2 adrenoceptor. It is adjacent to Ser 165 which has been predicted to interact with the carbon hydroxyl group of adrenergic ligands.[16] Thus, a change in the amino acid 164 from threonine to isoleucine alters the environment for proper ligand/agonist binding.

While the binding of agonists brings about receptor stimulation that leads to intracellular signaling, sustained stimulation of several G-protein-coupled receptors is known to lead to a reduction in the signaling efficacy.[20] This almost universal phenomenon[21] is named agonist-induced or agonist-promoted desensitization.[20]

Agonist-induced desensitization of G-protein-coupled receptors results in partial uncoupling of receptor from cognate G-protein, a process that provides for rapid adaptation to the signaling environment.[22]

With the beta-adrenergic receptors, desensitization is defined as the loss of receptor activity due to over-stimulation by beta-mimetic drugs. This has been demonstrated in experimental studies using cell cultures, isolated organs and in vivo models.[23] It is characterized by a decreased efficacy of β adrenergic agonists to stimulate the adenylyl cyclase activity.[20]

The desensitization of beta-adrenergic receptors generally evolves in two steps. The first step involves the uncoupling between the receptor and adenylate cyclase,[23] which may be brought about by the uncoupling of the receptor from the cognate G-protein.[22] Studies performed on cellular models have shown that this can be related to phosphorylation of the receptor by a cAMP-dependent protein kinase.[19,23] The second step is a decrease of the number (or down-regulation) of receptors. This has been shown to correspond to the incorporation of the β receptor in cytoplasmic vesicles.[23]

Studies of bronchial β2 adrenoceptor, mostly performed on isolated organs, have shown that β mimetic drugs can induce desensitization of β receptors.[23] Thus, aside from looking at agonist binding, in vitro studies of β2 adrenoceptor polymorphisms have concentrated on desensitization and downregulation as functional endpoints.[24]

Polymorphisms affecting amino acid 16 and 27 of the β2 adrenoceptor were shown to affect agonist-promoted downregulation of this receptor.[25] Compared to cells with the wild type β2 adrenoceptor, cells with the Arg16→Gly mutated receptor displayed an increased agonist-promoted downregulation of receptor expression while cells with the Gln27→Glu mutated receptor was found to be completely resistant to downregulation.[15,17]

For cells expressing Glu27 β2 adrenoceptor, the resistance to downregulation resulted in a significant attenuation of agonist-promoted functional desensitization.[17,26] On the other hand, the Ile164 receptor had been observed to undergo greater desensitization compared with wild type β2 adrenoceptor. A general model is thus proposed whereby up to 10 levels of signaling by G-protein-coupled receptors can be present based on the influences of desensitization and genetic variation on coupling.[22]

Since in vitro studies have shown that the β2 adrenoceptor polymorphisms affect receptor function,[3] studies investigating the clinical relevance of these polymorphisms have also been undertaken. Given the importance of the β2 adrenoceptor in modulating lung function, studies have been carried out to determine if polymorphic forms may play roles in establishing bronchial hyperreactivity, promoting asthmatic phenotypes, or influencing the response to acute or chronic beta-agonist therapy.[13]

Bronchial hyperresponsiveness (BHR) is a hallmark of asthma and represents a strong risk factor for the disease. However, because not all asthmatics have it and it can also be observed in normal subjects, BHR is believed to have a genetic predisposition.[27] Because of its involvement in the regulation of airway tone, the β2 adrenoceptor is considered a candidate for bronchial hyperresponsiveness associated with asthma.[28] The potential relations between bronchial hyperresponsiveness and the β2 adrenoceptor polymorphisms have thus been examined.

No individual polymorphism was found to be associated with bronchial hyperreactivity.[28] Neither the polymorphism affecting amino acid 16 nor that affecting amino acid 27 showed evidence of linkage to qualitative measures of bronchial hyperresponsiveness and asthma or to quantitative measures of serum IgE and airway reactivity.[29] Study results indicate that asthma, allergy, and methacholine airway hyperresponsiveness were not linked to any polymorphism of the β2 adrenoceptor gene.[30]

However, there is evidence that bronchial hyperresponsiveness is influenced by certain β2 adrenoceptor haplotypes. The β2 adrenoceptor haplotype with a Gly at position 16 and Gln at position 27 (Gly16/Gln27) was found to be associated with BHR, with the association persisting even after correction for potentially confounding variables such as specific and total IgE levels.[27] This observation suggests that β2 adrenoceptor gene can confer genetic susceptibility to BHR. On the other hand, the Gly16/Gln27/Th164 haplotype was significantly underrepresented in the asthma case group of another study, indicating a protective effect of this haplotype with regard to BHR.[28]

It must be noted that an association with BHR or with any other symptom of asthma does not necessarily translate to an association with the diagnosis of asthma. For instance, results of one study revealed that although the polymorphism at position 27 was associated with decreased airway responsiveness in its study population, and the polymorphism at position 16 was associated with increased wheeze during respiratory infection, neither was associated with physician-diagnosed asthma.[31]

Since it has long been hypothesized that a defective β2 adrenoceptor may be a pathogenic factor in bronchial asthma,[12] studies investigating the association between the β2 adrenoceptor polymorphisms and asthma itself have been done.

An initial American study that sequenced genomic DNA from normal individuals and those with asthma showed no difference in the frequencies of the β2 adrenoceptor polymorphisms in the 2 groups, indicating that a mutation of the β2 adrenoceptor is unlikely to be a major cause of asthma.[12]

Similarly, the genetic distribution of β2 adrenoceptor polymorphisms in severe Israeli asthmatics was found to be not different from that of non-asthmatic Israelis.[32] There was also no significant difference in the allele frequency of asthmatics compared to healthy groups in the people of the Han nationality of northern China.[33] Likewise, a study among the Japanese did not find any associations between any alleles of the β2 adrenoceptor polymorphisms and asthma.[34] Results of a study in New Zealand also showed no significant association between polymorphisms at amino acid 27 and 16 and asthma.[35] All these results, as well as results of other studies[29-31,36]

indicate that β2 adrenoceptor polymorphism does not contribute substantially to susceptibility to asthma.[34]

However, in a recent study involving 907 Mexican *Mestizos*, a significant inverse association was found between subjects with Glu27 allele and Gly16-Glu27 haplotype and asthma.[37] In this population therefore, a variation in the β2 adrenoceptor gene seems to be associated in the pathogenesis of asthma.

In addition to the association of the β2 adrenoceptor polymorphisms with asthma, their association with nocturnal asthma and asthma severity had also been investigated.

A study initially revealed that the β2 adrenoceptor of nocturnal asthmatics but not that of normal subjects or non-nocturnal asthmatics undergoes downregulation overnight.[38] A subsequent study[39] investigating the possible role of the β2 adrenoceptor polymorphisms on this observation revealed that there was an overrepresentation of the Gly16 allele in nocturnal asthma (significant at $p = 0.007$) with an odds ratio of having nocturnal asthma and the Gly16 polymorphism being 3.8. In contrast, there was no such overrepresentation of alleles at loci 27 or 164.[13]

In the above study, nocturnal asthmatics were defined as those who demonstrated 5 consecutive bedtime-to-morning decrements of 20% or more in PEFR. When patients were segregated based on history of frequent nocturnal asthma rather than the PEFR criteria, the odds ratio for having the Gly 16 polymorphism and nocturnal asthma by history was found to be 33.[13] A similarly high value was revealed by another study which showed that the odds ratio of having the Gly16 polymorphism in corticosteroid-dependent nocturnal asthma was 25.5.[16] Such association between nocturnal asthma and the Gly 16 allele had also been noted in still another recent study.[37]

Aside from an apparent association with the nocturnal asthma phenotype, the Gly16 polymorphism had also been found to be significantly associated with asthma severity.[33,35,40] One study showed that the percentage of the Gly/Gly genotype was significantly higher in moderate to severe asthma than in mild asthma (33.3 and 14.0%, respectively, $p < 0.05$)[40] while another study revealed that the odds ratios (95% CI) for the Gly16 allele were 1.56 (1.02-2.40, $p = 0.04$) and 0. 98 (0.61-1.57, $p = 0.92$) for the severe and mild asthma groups, respectively and the corresponding odds ratios (95% CI) for Gly16 homozygotes were 1.91 (0.82-4.41, $p = 0.13$) and 0.82 (0.35-1.92, $p = 0.65$) for the severe and mild asthma groups, respectively.[35]

Although no significant association between polymorphism at amino acid 27 and asthma severity had been found,[35] the Gly16/Gln27 haplotype (which undergoes enhanced downregulation *in vitro* was found to be substantially more prevalent in moderate asthmatics than in mild asthmatics.[14] This is consistent with the result of the earlier mentioned study[27] which found an association of this haplotype with bronchial hyperresponsiveness. No polymorphism or haplotype was found to be associated with fatal or near-fatal asthma.[14]

Taken together, the above findings suggest that although the β2 adrenoceptor polymorphisms may not be associated with the development of asthma per se, they are important modifiers of the clinical characteristics of bronchial asthma.[40]

One clinical aspect of bronchial asthma that may also be subject to modification by the β2 adrenoceptor polymorphisms is the response to beta agonist therapy. Thus, the possible role of the β2 adrenoceptor polymorphisms in the observed variability of response to beta-agonist therapy had also been investigated.

Results of several studies have shown that β2 adrenoceptor polymorphisms play an important role in the airway responsiveness to β2-agonists.[7,41-45] Asthmatics homozygous for Gly16 showed significantly lower airway responsiveness to inhaled salbutamol than those heterozygous for Arg/Gly16 or homozygous for Arg16.[43] Arg16 homozygotes had a higher salbutamol-evoked FEV_1 and a more rapid response compared with the cohort of carriers of the Gly variant.[44] The Gly 16 allele was also found to be carried by all subjects who have a poor FEV_1 vs salbutamol concentration relationship.[45] In addition, a study involving 269 children revealed that when compared to homozygotes for Gly-16, homozygotes for Arg-16 were 5.3 times (95% confidence interval 1.6-17.7) and heterozygotes for Arg/Gly16 were 2.3 times (1.3-4.2) more likely to respond to salbutamol, respectively. Similar trends were observed for asthmatic and non-asthmatic children, and results were independent of baseline lung function, ethnic origin, and previous use of anti-asthma medication.[7]

All the above findings show that the Gly 16 polymorphism significantly decreases the response to acute salbutamol therapy. However, a similar finding was not obtained in a study involving 166 asthmatic Chinese children. This study noted no significant association between the Arg-Gly 16 polymorphism and the airway responsiveness to β2 agonists in childhood asthma cases.[46]

Concerning GlnGlu27 polymorphism, no significant association was found between this polymorphism and the airway responsiveness to β2 agonists.[37,46]

In addition to their effect on the response to acute beta-agonist therapy, the β2 adrenoceptor polymorphisms had also been investigated for their possible effect on the response to prolonged beta-agonist therapy.

Studies have indicated a relationship between the polymorphism at codon 16 of the β2 adrenoceptor gene and the response to recurrent β agonist therapy.[6] Asthma patients with the homozygous Gly form was significantly more prone to bronchodilator desensitization than those with Arg 16.[47] After regular inhaled salbutamol, a significant decrease of FEV_1 and a significant increase of airway responsiveness were observed in patients with Gly 16/Gly.[40]

Thus, the Gly 16 polymorphism seems to affect the response to both acute and prolonged β-agonist therapy. These results may explain some of the observed variability in the response to therapeutic doses of beta2-agonists like salbutamol.[7] It had therefore been recommended that future pharmacodynamic studies of β2 agonists should include determination of the β2 adrenoceptor genotype.[44]

Because the genetic variation in the beta 2-adrenoceptor is common, it is potentially relevant to the clinician.[24] To date, clinical studies suggest that these β2 adrenoceptor polymorphisms act as disease modifiers in asthma. They may alter asthmatic phenotype and the response to β agonist therapy, making these variants the first of undoubtedly several genetic loci that will ultimately be found to provide for individualized therapy in asthma.[48] Also, the possibility that they also contribute to the actual development of asthma is still under study. More recently, a small number of frequently occurring, functionally relevant β2 adrenoceptor haplotype pairs have been confirmed. These combinations of alleles may be more important in determining genotype/phenotype relationships than individual SNPs, and may explain why earlier investigations have yielded contrasting results. Future studies will be required to clarify the effects of β2 adrenoceptor haplotypes both in vitro and in vivo.[49]

REFERENCES

1. Johnson M. The beta-adrenoceptor. Am J Respir Crit Care Med 1998;158(5 Pt 3):S146-53.
2. Weglarz L, Grzanka A, Kierot J, Wilckzok T. Polymorphism of beta 2-adrenergic receptors. Wiad Lek 2003; 56(5-6):283-8.
3. Hall IP. Pharmacogenetics of asthma. Eur Respir J 2000; 15(3):449-51.
4. Bai TR. Beta 2 adrenergic receptors in asthma : a current perspective. Lung 1992; 170(3) :125-41.
5. Liggett SB. Pharmacogenetics of beta-1- and beta-2- adrenergic receptors. Pharmacology 2000;61(3):167-173.
6. Yu H, Merchant B, Scheffel C, Yandava C, Drazen JM, Huff J. Automated detection of single nucleotide polymorphism in beta-2-adrenergic gene using LCx(R)). Clin Chim Acta 2001;308(1-2):17-24.
7. Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R. Association between genetic polymorphism of the beta-2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J Clin Invest 1997; 100(12)3184-8.
8. Katsunuma T, Fujita K, Mak JC, Barnes PJ, Ueno K, Iikura Y. Beta-adrenergic agonists and bronchial hyperreactivity: role of beta2-adrenergic and tachykinin neurokinin-2 receptors. J Allergy Clin Immunol. 2000l;106(1 Pt 2):S104-8.
9. Small KM, Brown KM, Theiss CT, Seman CA, Weiss ST, Ligett SB. An Ile to Met polymorphism in the catalytic domain of adenylyl cyclase type 9 confers reduced beta-adrenergic receptor stimulation. Pharmacogenetics 2003;13(9):535-41.
10. Munakata M. [Beta 2-Adrenergic receptor gene polymorphisms] Nippon Rinsho. 2001;59(10):1889-93.
11. Pelaia G, Marsico SA. Regulation of beta 2-adrenergic receptors and the implications for bronchial asthma: an update. Monaldi Arch Chest Dis. 1994;49(2):125-30.
12. Reihsaus E, Innis M, MacIntyre N, Liggett SB. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. Am J Respir Cell Mol Biol. 1993;8(3):334-9.
13. Liggett SB. Polymorphisms of the beta2-adrenergic receptor and asthma. Am J Respir Crit Care Med. 1997;156(4 Pt 2):S156-62.
14. Weir TD, Mallek N, Sandford AJ, Bai TR, Awadh N, Fitzgerald JM, Cockcroft D, James A, Liggett SB, Pare PD. beta2-Adrenergic receptor haplotypes in mild, moderate and fatal/near fatal asthma. Am J Respir Crit Care Med. 1998;158(3):787-91
15. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry. 1994;33(32):9414-9.
16. Green SA, Cole G, Jacinto M, Innis M, Liggett SB. A polymorphism of the human beta 2-adrenergic receptor within the fourth transmembrane domain alters ligand binding and functional properties of the receptor. J Biol Chem. 1993;268(31):23116-21.
17. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol. 1995;13(1):25-33.
18. Green SA, Rathz DA, Schuster AJ, Liggett SB. The Ile164 beta(2)-adrenoceptor polymorphism alters salmeterol exosite binding and conventional agonist coupling to G(s). Eur J Pharmacol. 2001;421(3):141-7.
19. Liggett SB. Molecular and genetic basis of beta2-adrenergic receptor function. J Allergy Clin Immunol. 1999;104(2 Pt 2):S42-6.
20. Chidiac P, Nouet S, Bouvier M. Agonist-induced modulation of inverse agonist efficacy at the beta 2-adrenergic receptor. Mol Pharmacol. 1996;50(3):662-9.
21. Dolen WK. The beta-2 adrenergic receptor and its agonists. Allergy Proc. 1994;15(6):283-90.
22. Rathz DA, Gregory KN, Fang Y, Brown KM, Liggett SB.Hierarchy of polymorphic variation and desensitization permutations relative to beta 1- and beta 2-adrenergic receptor signaling. J Biol Chem. 2003;278(12):10784-9.
23. Cros G. [Mechanisms of desensitization of beta-adrenergic receptors] Bull Eur Physiopathol Respir. 1985;21(5):35s-43s.
24. Taylor DR, Kennedy MA. Beta-adrenergic receptor polymorphisms and drug responses in asthma. Pharmacogenomics. 2002;3(2):173-84.
25. McGraw DW, Liggett SB. Coding block and 5 leader cistron polymorphisms of the beta2-adrenergic receptor. Clin Exp Allergy. 1999;29 Suppl 4:43-5.
26. Hall IP, Wheatley A, Wilding P, Liggett SB. Association of Glu 27 beta 2-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. Lancet. 1995;345(8959):1213-4.

27. D'amato M, Vitiani LR, Petrelli G, Ferrigno L, di Pietro A, Trezza R, Matricardi PM. Association of persistent bronchial hyperresponsiveness with beta2-adrenoceptor (ADRB2) haplotypes. A population study. Am J Respir Crit Care Med. 1998;158(6):1968-73
28. Ulbrecht M, Hergeth MT, Wjst M, Heinrich J, Bickeboller H, Wichmann HE, Weiss EH. Association of beta(2)-adrenoreceptor variants with bronchial hyperresponsiveness. Am J Respir Crit Care Med. 2000;161(2 Pt 1):469-74.
29. Summerhill E, Leavitt SA, Gidley H, Parry R, Solway J, Ober C. beta(2)-adrenergic receptor Arg16/Arg16 genotype is associated with reduced lung function, but not with asthma, in the Hutterites. Am J Respir Crit Care Med. 2000;162(2 Pt 1):599-602.
30. Emala CW, McQuitty CK, Eleff SM, Hopkins-Price P, Lawyer C, Hoh J, Ott J, Levine MA, Hirshman CA. Asthma, allergy, and airway hyperresponsiveness are not linked to the beta(2)-adrenoceptor gene. Chest. 2002 Mar;121(3):722-31.
31. Ramsay CE, Hayden CM, Tiller KJ, Burton PR, Goldblatt J, Lesouef PN. Polymorphisms in the beta2-adrenoreceptor gene are associated with decreased airway responsiveness. Clin Exp Allergy. 1999;29(9):1195-203.
32. Shachor J, Chana Z, Varsano S, Erlich T, Goldman E, Dror Y, Yakovy I, Navon R. Genetic polymorphisms of the beta-2 adrenergic receptor in Israelis with severe asthma compared to non-asthmatic Israelis. Isr Med Assoc J. 2003;5(11):821-4.
33. Gao G, Wang S, Zhang J. [Study on beta 2 adrenergic receptor genetic polymorphisms in asthmatics in the people of the Han nationality of northern China] Zhonghua Jie He He Hu Xi Za Zhi. 2000;23(2):93-7.
34. Migita O, Noguchi E, Jian Z, Shibasaki M, Migita T, Ichikawa K, Matsui A, Arinami T. ADRB2 Polymorphisms and Asthma Susceptibility: Transmission Disequilibrium Test and Meta-Analysis. Int Arch Allergy Immunol. 2004;134(2):150-7.
35. Holloway JW, Dunbar PR, Riley GA, Sawyer GM, Fitzharris PF, Pearce N, Le Gros GS, Beasley R. Association of beta2-adrenergic receptor polymorphisms with severe asthma. Clin Exp Allergy. 2000;30(8):1097-103.
36. Dewar JC, Wilkinson J, Wheatley A, Thomas NS, Doull I, Morton N, Lio P, Harvey JF, Liggett SB, Holgate ST, Hall IP. The glutamine 27 beta2-adrenoceptor polymorphism is associated with elevated IgE levels in asthmatic families. J Allergy Clin Immunol. 1997;100(2):261-5.
37. Santillan AA, Camargo CA Jr, Ramirez-Rivera A, Delgado-Enciso I, Rojas-Martinez A, Cantu-Diaz F, Barrera-Saldana HA. Association between beta2-adrenoceptor polymorphisms and asthma diagnosis among Mexican adults. J Allergy Clin Immunol. 2003;112(6):1095-100.
Szefler SJ, Ando R, Cicutto LC, Surs W, Hill MR, Martin RJ. Plasma histamine, epinephrine, cortisol, and leukocyte beta-adrenergic receptors in nocturnal asthma. Clin Pharmacol Ther 1991;49:59-68
38. Turki J, Pak J, Green SA, Martin RJ, Liggett SB. Genetic polymorphisms of the beta 2-adrenergic receptor in nocturnal and nonnocturnal asthma. Evidence that Gly16 correlates with the nocturnal phenotype. J Clin Invest. 1995;95(4):1635-41.
39. Sato R. [The role of beta 2-adrenoceptor gene polymorphisms in asthma] Hokkaido Igaku Zasshi. 2000;75(2):81-94.
40. Joos L, Sandford AJ. Genotype predictors of response to asthma medications. Curr Opin Pulm Med.2002;8(1):9-15.
41. He JQ, Joos L, Sandford AJ. Recent developments in the genetics of asthma. Pharmacogenomics. 2001;2(4):329-39.
42. Kotani Y, Nishimura Y, Maeda H, Yokoyama M. Beta2-adrenergic receptor polymorphisms affect airway responsiveness to salbutamol in asthmatics. J Asthma. 1999;36(7):583-90.
43. Lima JJ, Thomason DB, Mohamed MH, Eberle LV, Self TH, Johnson JA. Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther. 1999;65(5):519-25.
44. Lima JJ, Mohamed MH, Self TH, Eberle LV, Johnson JA. Importance of beta(2)adrenergic receptor genotype, gender and race on albuterol-evoked bronchodilation in asthmatics. Pulm Pharmacol Ther. 2000;13(3):127-34.
45. Fu J, Chen H, Hu L, Zhang H, Ma Y, Chen Y. [Association between the genetic polymorphisms of beta2-adrenergic receptor gene and the asthma susceptibility and clinical phenotypes in a Chinese population] Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2002;19(1):41-5.
46. Tan S, Hall IP, Dewar J, Dow E, Lipworth B. Association between beta 2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics.Lancet. 1997;350(9083):995-9.
47. Liggett SB. The pharmacogenetics of beta2-adrenergic receptors: relevance to asthma. J Allergy Clin Immunol. 2000;105(2 Pt 2):S487-92.
48. Taylor DR, Kennedy MA. Genetic variation of the beta(2)-adrenoceptor: its functional and clinical importance in bronchial asthma. Am J Pharmacogenomics. 2001;1(3):165-74