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Research Article

EVALUATION OF PRE AND POST BRONCHODILATOR PULMONARY FUNCTION TEST IN FIFTY HEALTHY VOLUNTEERS

KHURANA T *, SAXENA K. N.

LOK NAYAK HOSPITAL AFFILIATED TO MAULANA AZAD MEDICAL COLLEGE, NEW DELHI, INDIA.

Corresponding Author: Dr. KHURANA T

ABSTRACT

The assessment of airway obstruction and reversibility with spirometry is established in the evaluation of Chronic Obstructive Pulmonary Disease patients (COPD). The purpose of this study was to analyze whether Salbutamol caused bronchodilatation in normal individuals and to assess its degree. This will help in analyzing the role of salbutamol in improving oxygenation even in normal patients and aid in better interpretation of degree of bronchodilatation produced in COPD patients. A prospective study was conducted in fifty volunteers with normal respiratory system who were scheduled for elective surgery for unrelated illness. The pulmonary function test were recorded before and fifteen minutes after administration of two hundred microgram of salbutamol via metered dose inhaler. Changes in Forced expiratory volume in first second (FEV_1) and Forced vital capacity (FVC) both in terms of absolute value and percentage change from the baseline value were recorded and compared using appropriate statistical tests. Mean (Standard Deviation) absolute change of FEV_1 of 0.12 (0.10) liter and percentage change of 4.75 (4.07) % was noted. An absolute increase of 0.13(0.13) liter and percentage change of 4.87 (4.48) % in mean (SD) of FVC was noted. Both the absolute and percentage change of FEV_1 and FVC are not significant according to American Thoracic society/European respiratory society guidelines but are highly significant statistically($p \leq 0.001$). As salbutamol is causing a 4.75% increase in FEV_1 and 4.87% increase in FVC in healthy individuals, it may have a role in improving oxygenation in patients with normal respiratory system under anesthesia.

Keywords: Bronchodilator test, Pulmonary function test, Salbutamol.

INTRODUCTION:

Clinically spirometry is the most frequently performed Pulmonary Function Test (PFT) for mechanical ventilatory function. Pre and post bronchodilator PFT`s are recorded to study the effect of bronchodilator therapy and analyze its role in preoperative optimization of the patient. There is marked variability in the bronchodilator used, dosage, pattern of inhalation of the drug, timing of post bronchodilator test, physiologic tests utilized and criteria for significant response [1]. In the present study the recommendations of American Thoracic Society /European Respiratory Society (ATS/ERS) 2005 have been followed. The role of Salbutamol in causing bronchodilatation in chronic obstructive pulmonary disease (COPD) patients is time tested and proven. However, there are very few studies evaluating the role of Salbutamol in patients not suffering from any respiratory disease. The purpose of this study was to analyze whether Salbutamol caused bronchodilatation in normal individuals and to assess the degree of bronchodilatation produced. This will also help in better interpretation of salbutamol induced bronchodilatation in patients with established chronic obstructive pulmonary disease. In this study we administered two hundred microgram of Salbutamol to fifty patients not suffering from any respiratory illness and recorded the change (absolute and percentage) in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).

MATERIALS AND METHODS

ETHICAL APPROVAL

This clinical study was conducted on fifty adults of either sex in the age group 20–60 years and weight 45-80 kilograms after Institutional Ethical Committee clearance. Written informed consent was obtained from all the patients. The present study methodology conformed to the standards set by the latest revision of the Declaration of Helsinki and the procedures performed were approved by our Institutional Ethics committee.

The patients were selected from those who were scheduled for elective surgery in the branches of general surgery, orthopaedics, oto-rhino-laryngology and gynaecology in our institution and came for pre anaesthesia check up.

INCLUSION CRITERIA

Healthy volunteers- American Society of Anaesthesiologists grade 1 patients.
Patients who had normal respiratory systems and had
come for elective surgery for unrelated illness.

All patients were examined and detailed history regarding cigarette smoking, occupational exposure, medication being taken by the patient were noted. The patient's age, height, weight, chest findings and chest X-ray findings were also noted.

EXCLUSION CRITERIA

- Any patient who complained of cough, sputum, wheezing or any symptom pertaining to the respiratory system.
- Current or ex-smoker.
- Past or present diagnosis of tuberculosis, asthma, chronic bronchitis, emphysema.
- Presence of ronchi, crepitations or any adventitious sounds in the chest.
- Abnormal chest X-ray

65 patients were evaluated. 15 patients out of them were excluded from the study.

6 patients were current or ex-smoker, 4 were asthmatic, 3 gave history of tuberculosis and 2 had productive cough.

50 selected patients were taught to perform the forced vital capacity maneuver. The whole procedure was explained and demonstrated to the patients.

A portable PFT machine - Micro Medical Microlab Spirometer (MicroLab ML 3500 , Micro Medical Ltd., PO Box 6,Rochester, Kent MEI 2AZ ENGLAND) was used for evaluation of PFT in all the patients. The procedure was performed as follows:

The patient was asked to perform spirometry in sitting position in a chair with side arms without wheels or in standing position whichever was comfortable to him. He was instructed to assume the correct posture by keeping his trunk errect, chin slightly elevated and neck stretched during the procedure and to look straight forward without bending over. The portable PFT machine was turned on and all connections were checked. Fresh mouthpiece was attached for each patient. The patient was asked to close his nose with one hand while hold the mouthpiece with the other. He was instructed to inhale maximally and to place the mouthpiece in the mouth and close his lips around it and then exhale as forcefully and as

rapidly as possible without a pause for as long as possible. The patient was motivated and made to practice this three times and then recordings were undertaken on the portable pulmonary function test machine.

The forced vital capacity maneuver was not accepted [2] if;

- The patient hesitated during the maneuver
- The patient coughed during the maneuver
- There was air leak around the mouthpiece
- The mouthpiece was obstructed by tongue, teeth or denture
- The patient took an extra breath during the procedure
- Early termination of expiration

Minimum of three acceptable curves were recorded [2]. Between the maneuvers, variability was checked as follows:

- The difference between two values the largest and the next largest FVC should be less than or equal to 0.2 liters (L)
- The difference between the largest and the next largest FEV_1 should be less than or equal to 0.2 liters (L)

If these criteria were not met the testing was continued till a total of eight tests were performed or the patient could not continue due to fatigue, dizziness, syncope. Three satisfactory curves were recorded. The sum of FEV_1 and FVC was calculated for all the three curves. The curve with the largest sum of FEV_1 and FVC was chosen as the "best curve". The value of FEV_1 and FVC were taken from the best curve as the baseline value.

The patients were taught to use a metered dose inhaler (Asthalin of Company CIPLA LTD, Plot No. L-139 Verna, Goa 403722) each puff containing salbutamol 100 microgram. The patient was instructed to take one puff of salbutamol via the metered dose inhaler, hold for as long as possible and then exhale. This maneuver was repeated after one minute. Then the patient was asked to wait for fifteen minutes after which the forced vital capacity maneuver was done and recorded. At least three acceptable recordings were undertaken and between the maneuver variability criteria applied. The sum of FEV_1 and FVC was recorded for all the three curves and the best curve was chosen. The post bronchodilator values of FEV_1 and FVC were obtained from the best curve. The patients were kept under observation for half an hour and then allowed to go if it was uneventful.

Parameters recorded

FEV_1 and FVC –baseline value (before administration of bronchodilator)
FEV_1 and FVC fifteen minutes after salbutamol inhalation –Post bronchodilator value

Statistical analysis

- Minimum, maximum, range, mean and standard deviation of both pre and postbronchodilator FEV_1 and FVC were noted.
- Paired sample test was done for (a) pre and post salbutamol FEV_1
  (b) pre and post salbutamol FVC

- Mean and standard deviation of absolute change and percentage change in FEV_1 and FVC were calculated.

RESULT

The present study was conducted on fifty patients not suffering from any respiratory illness scheduled to undergo an elective surgery in our institution. The observations on parameters studied are being presented.

There were 31 males (62%) and 19 females (38%). In the 50 patients studied mean age was 32 years, mean height was 163.22 centimeters and mean weight was 58.36 kilograms. The mean [standard deviation (SD)] of baseline FEV_1 recorded was 2.61 L (0.67 L). It increased to 2.72 L (0.70 L) post salbutamol therapy. Mean absolute change of 0.12 L (0.10 L) and percentage change of 4.75% (4.07%) was noted. The ATS/ERS Task force 2005 has endorsed the criteria that increase in FEV_1 > 12% above the baseline value and 200 ml absolute change or increase in FVC > 12% above the baseline value and 200 ml absolute change during a single testing session as 'significant bronchodilatation' [1]. Both the absolute and percentage change of FEV_1 may not be significant according to ATS/ERS guidelines but are highly significant statistically ($p \leq 0.001$).

Table- 1 FEV_1 response to bronchodilatation

	Pre-BD FEV_1, L	Post-BD FEV_1, L	Absolute Change, L	Percentage change, %
MIN	1.38	1.45	-0.07	-3.91
MAX	4.12	4.26	0.40	14.65
RANGE	2.74	2.81	0.47	18.56
MEAN	2.61	2.72	0.12	4.75
STD DEVIATION	0.67	0.70	0.10	4.07

BD – bronchodilator, L- litre

In 1 patient out of 50, a decrease in FEV_1 was noted post bronchodilator therapy, leading to a negative value for minimum absolute and percentage change.

In the 50 patients studied mean (SD) of baseline FVC recorded was 2.71 L (0.72 L) which increased to 2.84 L (0.75 L) post salbutamol therapy. An absolute increase of 0.13 L (0.13L) and percentage change of 4.87% (4.48%) was noted. Both the absolute and percentage change of FVC are not significant accordingly to ATS/ERS guidelines but are highly significant statistically ($p \leq 0.001$). In 3 patient's negative value for minimum absolute and percentage change of FVC were noted.

Table-2 FVC response to bronchodilatation

	Pre-BD FVC, L	Post-BD FVC, L	Absolute Change, L	Percentage change, %
MIN	1.38	1.45	-0.06	-1.65
MAX	4. 2	4.27	0.47	16.42
RANGE	2.82	2.82	0.53	18.07
MEAN	2.71	2.84	0.13	4.87
STD DEVIATION	0.72	0.75	0.13	4.48

DISCUSSION

Spirometry performed pre and post administration of a bronchodilator is used in assessment of patients with COPD. Bronchodilatation response refers to the change in airway caliber as a result of inhaled bronchodilating medication that causes improvement in flow or volume variables detectable by pulmonary function tests. Salbutamol was used in the present study to assess whether it causes bronchodilatation in healthy individuals and to analyze the degree of bronchodilatation produced. It is a highly selective $ß_2$ adrenergic receptor agonist. It acts specifically on the smooth muscle of bronchiole and causes bronchodilatation. The undesirable $ß_1$ cardiac sympathomimetic effects are less prominent especially if given by aerosol therapy.

Bronchial responsiveness to bronchodilator medication is an integrated physiological response involving airway epithelium, nerves, mediators and bronchial smooth muscles. The bronchiolar musculature is under the control of sympathetic, parasympathetic and local factors like histamine, slow reactive substance of anaphylaxis, Substance P, vasoactive intestinal peptide. Direct control of sympathetic nerve fibers is weak but bronchial tree is very much exposed to circulating epinephrine and nor epinephrine released into the blood by

sympathetic stimulation of the adrenal medullae. Epinephrine because of its greater stimulation of ß receptors causes dilatation of the bronchial tree. Parasympathetic nerve fibers secrete acetylcholine and when activated cause mild to moderate constriction of the bronchioles. Trigger factors for parasympathetic stimulation are irritation of the epithelial membrane of the respiratory passageways by noxious gases, dust, cigarette smoke or bronchial infection.

Initially there were no uniform guidelines to the performance of spirometry and to interpretation of its results. In an attempt to foster research a joint task force was formed between the American Thoracic Society and European respiratory Society in 2005 to develop uniform standards in pulmonary function testing. In the present study, the procedure of performing spirometry has been in accordance with the joint ATS/ERS 2005 standards on spirometry.

The ATS/ERS recommendations are that short acting drug like salbutamol should be used. Four separate doses of hundred microgram via metered dose inhaler using a spacer are advised for COPD patients. For subjects with no previous exposure to ß adrenergic agents two hundred micrograms is recommended[3]. In the present study two hundred micrograms of salbutamol has been used for healthy volunteers as we were concerned about public safety and ethical issues. The time to repeat spirometry following bronchodilator administration should reflect the time for onset of action of the drug used.

A number of possible indices have been evaluated in search of a good measure of bronchodilation. By far the most commonly used measurement to express the bronchodilator response is FEV_1 [4]. ATS/ERS 2005 recommendations are increase in $FEV_1 > 12\%$ above the baseline value and 200 ml absolute change or increase in FVC > 12% and 200 ml absolute change during a single testing session as significant bronchodilatation. In the present study we recorded a mean absolute change of 0.12 L (0.10 L) and percentage change of 4.75% (4.07%) in FEV_1 post salbutamol therapy. In 1 patient out of 50 a decrease in FEV_1 was noted. We also noted a mean absolute change of 0.13 L (0.13 L) and percentage change of 4.87% (4.48%) in FVC post salbutamol therapy. In another 3 patients, a decrease in FVC was noted. Both the absolute and percentage change of FEV_1 and FVC are not significant according to ATS/ERS guidelines but are highly significant statistically ($p \leq 0.001$). The negative response was seen post salbutamol therapy may be because salbutamol was not administered correctly by these patients. There are many factors which affect the delivery of drug to the distal airways when given by metered dose inhaler. They are size of the particle, inspiratory flow rate, tidal volume, breath holding time, airway diameter [5] .More than 50% of patients using inhalers do not use proper technique and thus deposit too small a fraction of the inhaled drug into the lungs.

As salbutamol is causing a 4.75% increase in FEV_1 and 4.87% increase in FVC in healthy individuals, it may have a role in improving oxygenation in patients under anaesthesia. This requires further discussion. If salbutamol causes x% increase in FEV_1 in COPD patients and 4.75% increase in healthy individuals, then maybe actual effective increase in FEV_1 in COPD patients is (x-4.75)%. It is just another way of interpretation and analysis of results. Further studies and analysis will be required to throw more light on this topic.

Studies on bronchodilation response have been conducted on various samples with differing bronchodilating medications, dosages and delivery methods. Watanabe et al in 1974 investigated 75 subjects aged 20-81 years. They were classified as 'normal' based on subjects' self reported status. Bronchodilatation testing was undertaken with isoetharine 350

microgram, phenylephrine 70 microgram and thienyldiamine 30 microgram. Average FEV_1 changed from 3.61 liters to 3.69 liters which is +2.5% (SD 3.9%). FVC remained unchanged in light of the mean value of 0.2% (SD 2.5%).

Dales et al in 1988 studied a population sample of 1982 adults. Bronchodilatation testing was performed using 500 microgram of terbutaline sulfate and change in FEV_1 of 57 (128) ml or 1.8% (4%) from the baseline was noted.

Table-3 enlists the studies where bronchodilatation testing has been done using salbutamol in various doses in normal healthy subjects

	Drug used(microgram)	Number of Subjects	Change in FEV_1(%)
Holmes [6] et al 1978	Salbutamol 200	5	4
Houghton [7] et al 2004	Salbutamol 100 200 800	12	 4.1 3.8 4.7

Various population studies have been done to develop post bronchodilator reference values. Some of them are listed below.

Table-4 enlists the studies where bronchodilatation testing has been done in reference population to develop post bronchodilator reference values.

	Drug used(microgram)	Number of Subjects	Change in FEV_1
Lehmann [8] S et al 2006	Salbutamol 400	3506	2.4
Perez-Padilla [9] R et al 2007	Salbutamol 200	887	3

Johannessen et al evaluated FEV_1 and FVC in 515 healthy never smokers in the age group 26-82 years before and after 300 microgram of salbutamol [10]. They have reported an improvement that is not constant across age. Older subjects have lower reversibility than younger subjects. Even healthy subjects experience improvement in lung function after reversibility testing. The reason for change in FEV_1 and FVC in healthy individuals is not clear. Maybe a deep inspiration preceeding the forceful expiration during a FVC maneuver itself may induce bronchospasm [4] which is getting corrected by salbutamol inhalation. May be it is possible that the normal state of the bronchi is that of partial bronchodilatation which has the capacity to further dilate in response to the beta action of salbutamol. The factors contributing to this state of incomplete bronchodilatation at rest warrants further studies.

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