

Study the Pulmonary Hypertension among Heavy Smokers Young Adult Males before the Clinical Evidences of Chronic Lung Disease

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Abstract

Background: Smoking is a well-known risk factor for development of COPD. Prevalence of smoking is high. Its effect on the pulmonary pressure before the development of COPD still needs to be explored on human model.

Aim of the study: The aim of the study is to evaluate the pulmonary hypertension in young heavy smokers adult population prior to the development of the clinical and the abnormal pulmonary function test.

Material and Methods: The study was carried out at Al Sader Najaf Teaching Hospital during the period April 2015 to April 2016 where 93 Smokers who smoke at least 2 packets/day for minimal two years period were included in the study with 93 non-smokers used as a control group. The age of the smokers group and non-smokers group was less than 40 year with mean age 25 ± 4.1 for smokers and 24.9 ± 3 for non-smokers. BMI for all was >30 . All had their pulmonary function test with the clinical examination to exclude any evidences of the chronic lung disease. Transthoracic Echocardiography and Doppler study was done for the smokers and non-smokers groups to evaluate the Maximum tricuspid valve velocity, the Mean pulmonary pressure gradient and the Pulmonary artery pressure.

Results: Mean tricuspid maximum velocity (TGmax) for smokers was 0.9 ± 0.1 and for non-smokers 0.60 ± 0.20 (p value less than 0.001). The mean pulmonary pressure gradient for smokers was 3.4 ± 1.0 and for non-smokers 1.5 ± 0.8 with p value less than 0.001. The mean pulmonary artery pressure for smokers group was 12.2 ± 1.6 and for non-smokers group 7.0 ± 1.2 with p value less than 0.001.

Conclusion: There is an increase in the pulmonary arterial pressure among the heavy smokers young adults when was compared with the non-smokers young adults.

Keywords: Smoking; Pulmonary hypertension

Introduction

Smoking is a known risk factor for COPD [1]. Pulmonary hypertension can be defined as a pathophysiological or abnormal hemodynamic condition with pulmonary arterial pressure ≥ 25 mmHg [2] and when associated the pulmonary lung diseases it can predict the severity as well as the mortality for the patients awaiting the lung transplantation [3]. The long term mortality in patients with pulmonary hypertension still high and largely related to right heart failure [4]. Smoking can induce remodelling in intravascular pulmonary artery and it was found that smoking can be a triggering factor for the alteration in pulmonary vasculature and not necessarily secondarily to the hypoxia caused by the chronic lung disease [5]. Recent studies that were done on animal model clearly demonstrated that pulmonary hypertension occurs even before the development of emphysematous lung changes [6]. The prevalence of the smoking although showed drop in many developed countries still we find the prevalence in developing countries had increased and it was estimated to be 33% in male smokers in Iraq (2012) while it was 30.84% in 2009

and that of 2006 was 29% according to the world bank of smoking which included all types of smoking for people <15 years [7].

Material and Methods

Design of the study

This is a retrospective cohort study. Two groups of subjects were included in the study (smokers and non-smokers) their age <40 years. The smokers subjects had duration of smoking >2 years. Both groups were studied by Echocardiography Doppler method for evaluation the pulmonary arterial pressure.

Ethics consideration

Permission and agreement with informed consent forms were taken from all participants who were included in the study after explanation the method and the aim of the study and with the agreement of the hospital administration.

Inclusion criteria

Young age population <40 years, BMI <30, normal spirometry study, persons with no past history of chronic cough or asthma and the duration of smoking >2 years.

Exclusion criteria

COPD patients, people working in the gas station, anemia or thyroid dysfunction.

Exclusion on Echo Doppler study

The study was left atrial enlargement, mitral valve regurgitation, Hypertrophic obstructive cardiomyopathy, significant tricuspid valve regurgitation.

Early clinical evaluation

All subjects were examined clinically to exclude chronic obstructive lung disease by absence of dyspnoea, tachypnea or cyanosis. Examination was done for detection of leg edema, basal crackles and expiratory wheeze. Precordial examination was also done to evaluate any left parasternal heave or abnormal precordial auscultation such as loud pulmonary second heart sound and evidence of tricuspid regurgitation or mitral regurgitation. All subjects had their height and weight to estimate the BMI (those with BMI >30 where excluded). ECG was done for detection of any abnormal features like R wave in VI, increase P wave amplitude in lead 2, incomplete right bundle branch block or right axis deviation.

Spirometry examination

This test was done to all subjects in the study and any abnormal results exclude the person to complete the study.

Echocardiography and Doppler study

Every subject was examined by Echocardiography and Doppler study using the (Vivid S5 N GE Healthcare 2D Transthoracic Echocardiography). Every subject was asked to rest and to be on left lateral position with normal breathing and to be relaxed. Pulse wave Doppler was done using the left parasternal, short axis and apical four chamber views [8,9]. Measurements were done to estimate the right ventricular wall thickness so to evaluate the right ventricular hypertrophy by using subxiphoid area and in M mode Echocardiography the transducer beam was used to approve the best left ventricular dimension and in case the right ventricular wall was not clearly visualized we directed the transducer gradually toward the apex and measurement was done at the end right ventricular diastole that is at R wave in the ECG record and when there is distinct epicardium and endocardium measurement of right ventricular posterior wall was done through perpendicular line from the epicardium to endocardium of right ventricular posterior wall [10]. Right ventricular hypertrophy is considered when the right ventricular wall thickness (RVWT) >5 mm. Assessments of any abnormality in the tricuspid valve or the pulmonary valve were done. The Continuous pulse wave Doppler line align parallel to the direction of tricuspid flow was done to evaluate the peak flow systolic wave and the tricuspid maximum velocity (TG max). Three reading were done for every subject in the study and the mean of the three readings was taken in

consideration. Pulmonary arterial pressure was estimated by using the modified Bernoulli equation where:

$$PAP=4X TG_{max}^2$$

PAP Pulmonary Arterial pressure,

TG_{max} Tricuspid Maximum Velocity,

Smoking amount (Smoking Index) was calculated for every subject.

Statistical method

This is retrospective cohort study and p value less than 0.05 considered significant. Data of the participants were transformed into computerized data form and analyzed using the statistical package for social sciences SPSS version 22, IBM, Chicago, US, 2013. Descriptive statistics were expressed as mean, standard deviation, frequency (No.) and proportions %. Students to test independent was used to compare two variables such as age, BMI, Max tricuspid valve velocity, Mean pressure gradient and pulmonary artery pressure between the smoker and non-smoker groups. Chi square test was used to compare BMI categories between the studied groups. Pearsons correlation and regression curve estimation curve estimation tests was used to assess the correlation between the pulmonary artery pressure and other variables, amount and duration of smoking among smokers. Correlation Coefficient r was calculated which statistical ranged between 0 indicates no correlation and 1 means perfect correlation, value less 0.4 indicate weak correlation while 0.7 and above indicate strong correlation and that 0.4-0.7 moderate relation.

Results

There were 186 participants enrolled in this retrospective cohort study, 93 participants were smokers (study group) and 93 participants were non-smokers (control group). The mean age of smokers was 25.2 ± 4.1 (range: 18-35) years and for non-smokers. The mean age was 24.9 ± 3.1 (range: 19-32) years. The mean body mass index (BMI) in smokers group was 23.7 ± 1.8 (range: 20.1-29.2) kg/m² and it was 23.6 ± 1.2 (range 20.9-26.3) kg/m² in non-smokers. Furthermore most of participants in both group had normal range of BMI and only 20.4% and 15.1% were overweight in smokers and non-smoker group respectively. No statistically significant difference between both group had been found either in age (P=0.60) or in BMI (p=0.51) as shown in (Table 1).

The mean posterior right ventricular wall thickness was 3.2 mm for the smokers group and 2.8 mm for the non-smokers group. As it shown in Table 2, it had been found that all clinical parameters including maximum tricuspid valve velocity, mean pressure gradient, JVP and pulmonary artery pressure were higher in smoker group than non-smoker group and in all comparison P value was highly significant (<0.001). Pulmonary hypertension was not reported among the participants where none of the participants had the value of pulmonary artery pressure corresponding to pulmonary hypertension with an incidence of (0%).

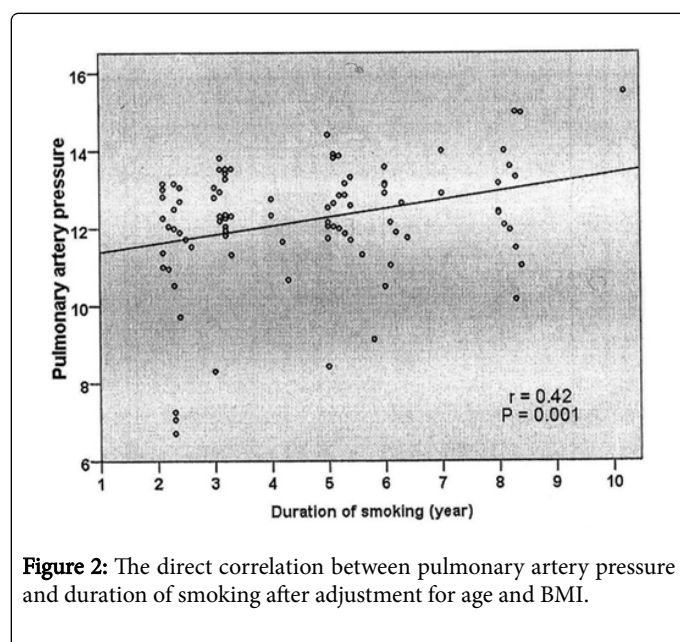
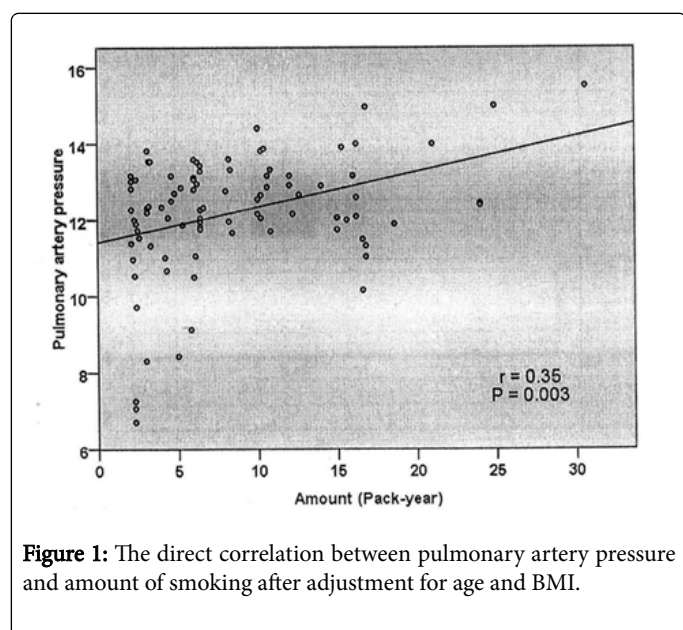
Figure 1 demonstrates the relationship between the pulmonary artery pressure with the duration and amount of smoking as it shown in this table a direct correlation of the pulmonary artery pressure had been found with amount of smoking (r=0.27, while the p=0.002) when the amount measured in cigarettes/day and (r=0.35 while the p=0.003) when measured in pack-year.

Variable		Groups		Statistical test df	p
		Smoker (n=93)	Non-smoker (n=93)		
Age (Year)	Mean ± SD*	25.2 ± 4.1	24.9 ± 3.1	t test=0.53 df=184	1.60
	Range	18-35	19-32		
BMI Kg/cm ²	Normal n (%)	74 (79.6)	79 (84.9)	Chi square=0.92 df=1	0.44
	Over weigh n (%)	719 (20.4)	14 (15.1)		
	Mean ± SD	23.7 ± 1.8	23.6 ± 1.2	t test=0.67 df=184	0.51
	Range	20.1-29.2	20.9-26.3		

Table1: Age and BMI distribution of the studied groups.

		Groups		t test df=184	p
		Smoker (n=93)	Smoker (n=93)		
Maximum tricuspid Velocity	Mean ± SD	0.9 ± 0.1	0.60 ± 0.20	15.1	<0.001
	Range	0.6-1.5	0.3-1.0		
Mean pressure gradient	Mean ± SD	3.4 ± 1.0	1.5 ± 0.8	14.84	<0.001
	Range	1.7-8.0	0.4-3.6		
JVP	Mean ± SD	8.8 ± 1.3	5.5 ± 1.0	19.9	<0.001
	Range	5.0-10.0	5.0-8.0		
Pulmonary artery pressure	Mean ± SD	12.2 ± 1.6	7.0 ± 1.2	25.11	<0.001
	Range	6.7-15.5	5.5-10.4		

Table 2: Comparison of Echocardiographic Doppler findings of Smokers group and the non - Smokers group participants.



A direct correlation was also found with the duration of smoker (r=0.42 while the p=0.001) as shown in Figure 2. It is worth

mentioning that these significant correlations were obtained after adjustment for age and BMI to exclude any confounding effect of these two variables on the results.

Discussion

This current study demonstrated that there is an increase in the arterial pulmonary pressure in the young age smokers population even before the development of the clinical COPD or the abnormal Pulmonary Function Test. Wright J L and Churg in 1991 described an increase in the pulmonary vascular structure mainly an increase in the masculinization of the arterioles in the guinea pig exposed to the smoke after one month and when there was no histological evidences of emphysema [11]. Animal model of smoke induced emphysema and pulmonary hypertension suggested that Pulmonary hypertension associated COPD is due in some part to hyperinflation and gas trapping that compress the pulmonary vessels [12], however Pulmonary hypertension has not shown to improve after lung volume reduction surgery (LVRS) which was attributed to the reduction in the pulmonary capillary bed [13]. This showed that pulmonary hypertension occurs in the smokers by added mechanisms to that caused by COPD. Jugular venous pressure was looked after in this study as raised jugular venous pressure is usually found in patients with pulmonary hypertension and should be looked early for proper evaluation of the patients [14].

Peaked tricuspid velocity was studied in this current study with the Bernoulli equation to detect and to measure the pulmonary pressure and was found to have significant difference between smokers group and those non-smokers. To make more valuable results, the right ventricular hypertrophy was studied according to the European Guideline Echocardiography detection of pulmonary hypertension 2015 [15] and the mean right ventricular wall thickness in this study was (3.2 mm for the smokers group vs. 2.8 mm for non-smokers group) which excluded the right ventricular hypertrophy. The pulmonary pressure in smoker group and in non-smoker group in the our study was not reaching the elevated level of high pulmonary pressure i.e above 25 mmHg but the difference between the pulmonary pressure level in the smokers group is more and still significant when was compared with the non-smokers group. Reports from Barbara and associates from Spain indicated that vascular remodelling process is also associated with and possibly preceded by an inflammatory process in which the vessels become infiltrated with a population of cells similar to those found around the small airways [16].

The precise meaning of this finding and its role in the pathogenesis of the peripheral lung lesions observed in COPD is under investigation. Normal level of the pulmonary arterial pressure which is detected by Echo Doppler study is estimated to be 8-20 mmHg and pulmonary hypertension is considered when the pulmonary pressure >25 mmHg (American Heart Association 2016) [17]. The mean pulmonary pressure in the smokers group in the current study was (12.2 ± 1.6) and that of non - smokers was (7.0 ± 1.2) and both in the normal range and still we found a significant difference between both groups. The age of the smoker group and that of the non-smoker group was relatively the same (smokers 25.2 ± 4.1) and (non-smoker 24.9 ± 3.1). The age showed no statistical difference. In this study we tried to avoid old population for possible association with emphysematous lung changes [18,19]. Pulmonary hypertension can develop at any age according to underlining cause. It was found that the mean age at diagnosis of pulmonary hypertension is 45 years in USA. It was also found that pulmonary pressure prevalence increase in 6% when the age

>40 and 17% when the age above 65 [20]. BMI of the smokers group and in non-smokers in the study was <25 (normal BMI level) and the pulmonary pressure was not showed statistically difference between two groups. Obesity was found in several studies to be associated with hypoventilation and elevation in the pulmonary pressure [21]. It was estimated that BMI above 35 associated with prevalence of 31% in pulmonary hypertension [22]. In our study there was a positive correlation between the amount and the duration of the smoking with an increase in the pulmonary pressure. The least duration of the smoking in this study was 2 years with a mean of (4.3 years) and the mean smoking index was (2.2) which reflects the exposure and the smoking severity.

In experimental model of smoking in animals smoking was induced pulmonary hypertension within four weeks of exposure and vascular remodelling was achieved within 6 months from cessation of the smoking. Barbara et al. had found that many changes that occur in the pulmonary vessels actually occur in the early stages before the airway obstruction. The pathological changes include intimal hyperplasia proliferation that resulted from proliferating mesenchymal cells with elastic and collagen deposition as well as endothelial dysfunction. The endothelial dysfunction associated with the vessel remodelling and an increase in the inflammatory cells that invade the vascular adventitia [23]. Salud Santos et al. found an increase in the expression of vascular endothelial growth factor (VEGF) in smoker population when was compared with non- smoker without the development of COPD with significant increase in both the intimal and the medial vascular layers in the smokers when was compared to people who are not smoke and in the absence of the emphysematous lung changes [24].

Lahm T et al. found that smoking leads to the development of pulmonary hypertension without the emphysematous changes by expression of Nitrous Oxide Synthase (NOS). The Nitrous Oxide helps to modulate vascular tone, insulin secretion, and airway tone is involved in the angiogenesis [25]. Pulmonary function test was done in all cases in the current study to exclude serious pulmonary diseases. Chest CT was not done as the radiation dose of the high resolution CT which is needed for the proper evaluation of parenchymal lung disease expose the person to high radiation dose approaching 100 times and should be reserved for selective and proper diagnosis of cases like interstitial fibrosis or patients with immunodeficiency [26]. In our study we excluded Hypertrophic obstructive cardiomyopathy (HOCM) cases as there is more evidences of associated pulmonary hypertension with HOCM which was found to be associated with increased mortality in HOCM patients [27]. Abnormal thyroid function whether thyroiditis or hyperthyroidism also excluded from the study as there is high association with the pulmonary hypertension which is reversed when the thyroid function returns to the normal [28]. Patients with the anemia were excluded as many chronic anemia and those who had hemoglobinopathy like sickle cell anemia had elevated pulmonary arterial pressure [29].

Our study tested only male gender because young females don't announce they are smokers because society believes smoking for young females is an embarrassing habit. Nearly all form of World Health Organization (WHO) demonstrated a skewed gender ratio with more females affected with pulmonary hypertension than males and the last fact explained by the possible effect of estrogen hormone [30]. Echocardiography and Doppler study has proved to be highly useful in detecting the abnormalities and the function of the heart by using the flow velocities with pulse or continuous wave study. It is less expensive and widely available bed site technique makes the Echocardiography

useful noninvasive method in evaluation of right ventricular chamber and hemodynamic pulmonary disorders in everyday practice. It can be helpful in screening diagnosis and differential diagnosis of pulmonary hypertension, right ventricular hypertrophy evaluation with some clinical difficulties in cases of COPD because of the hyperinflation of the chest that limits the ultrasonic waves transmission [31].

Conclusion and Recommendation

Pulmonary arterial pressure found to be more in the young adults with heavy smoking when was compared to non-smokers young adult and before the clinical or the abnormal lung function. We recommend more care from the health authorities to put a proper program to help young adult for cessation the smoking.

Study Limitations

Only male gender was evaluated in the study.

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