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ORIGINAL ARTICLES

Histopathological Pattern of Bronchial Carcinoma in Smokers in Bangladesh

A.K.M. Mustafa Hussain[1], Mirza Mohammad Hiron[5], Md. Abdur Rouf[3], Md. Abdul Quayyum[4], Md. Mostafizur Rahman[5], Md. Delwar Hossain[6]

Abstract

This analytical, prospective & cross-sectional study was conducted at the National Institute of Diseases of Chest & Hospital, Dhaka, with a view to finding out the relation of major histological types of lung cancer with smoking habit. A total 110 histologically proven primary lung cancer cases were included in the study. Nearly 87% of the cases were male and 13% of the cases were female. Most of the patients belong to the age range of 55-74 years.

In this study, all cases were randomly selected among the patients having diagnosed a s lung cancer. A standardized proforma with questionnaires was designed & clinical examinations were carried out followed by necessary investigations for histological confirmation of the diagnosis. The questionnaire included a detailed smoking history ir.cluding patterns of smoking, number of cigarettes smoked per day, dose and duration of smoking habits and also number of years since quitting. The results were recorded in the proforma & then statistical analysis was done & results were recorded. Tobacco smoking is common in developing countries including Bangladesh with bidi and cigarette smoking being main types. It was observed that nearly 53% of the patients were current smokers and 31 of patients were ex-smokers. Among females about 65% were non-smoker and 3% were smoker. Among male 9, 7% were smokers and 35% were non-smoker. Bidi smoking is overall the common type of smoking in our community. The rich people prefer mainly cigarettes and the poor prefer bidi in this country.

Squamous cell carcinoma was more frequent among the smokers (44.0%) followed by Small cell carcinoma (30.0%, Adenocarcinoma (17.0%) and large cell carcinoma (6.0%). Among non-smokers, highest percentage was Adenocarcinoma (70.0%, followed by Squamous cell carcinoma (20%) and Small cell carcinoma (10%). Among the smokers mean dose of smoking was around 40 pack-years. The mean dose of smoking was higher among the squamous cell carcinoma, nearly 41 pack-years.

[Chest & Heart Journal 2005; 29(1) : 1-14]

Introduction

Among all human cancers, carcinoma of the lung has the highest mortality rate and is the leading cause of all cancer death[1]. Lung cancer is the most common malignant disease in developed countries, causing more deaths than breast, colorectal, prostate and pancreatic cancer combined[2]. It is one of the health problems in Bangladesh of which smoking plays the most vital role. It falls into four major histological types: viz. Squamous cell (epidermal) carcinoma, small cell carcinoma, large-cell carcinoma and

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adenocarcinoma. These four types account for about 95% of all cases of primary lung cancer[3]. Kteyberg L[4] divided cases of lung cancer into two broad categories; the first one included squamous-cell and small-cell carcinomas, while the second group included adenocarcinomas, carcinoids and bronchial gland tumours.

Histopathological gradation of bronchial carcinoma in order of frequencies was squamous cell arcinoma 54.7%, small cell carcinoma 24.1%, adenocarcinoma 16.9% and large cell arcinoma 4.3%[3] In another study, squamous cell carcinoma was found 18%, adenocarcinoma 34%, small cell carcinoma 24% and large cell carcinoma 9%, adenosquamous 9% and bronchioalveolar carcinoma 6%[5] Although squamous cell carcinoma has for many years been the most common histological type, adenocarcinoma has been increasing in incidence over last 20 years[6,7,8].

There are also reports that adenocarcinoma has become today the most frequent histological type of lung cancer and is responsible for 50% of all lung cancer. 6,7,8 a Squamous cell carcinoma represents only 30% of all lung cancers and small cell carcinoma represents 15%.[9] An opposite picture however, is given in Jockel et al.[10] where only 14% adenocarcinomas were found in a series of male cases. An increasing incidence of adenocarcinoma may be due to changes in the criteria of the histopathological diagnosis of lung carcinoma or may result from new environmental and occupathional hazards. However, it is also possible that the increase in lung adenocarcinoma cases, in fact, may be caused also by increasing smoking prevalence. A direct association between smoking and various histologic types of lung cancer has been observed for measures of intensity, duration and dose.[11]

The relationship between tobacco smoke & lung cancer was suspected for many years. The cause and effect was obtained b y many retrospective and prospective studies during the middle third of the twentieth century. Cigarette smoking is causally related to lung cancer in men, the magnitude of the effect of cigarette smoking far outweighs all other factors. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day and is diminished by discontinuing smoking. In comparison with non-smokers average men smokers of cigarette have approximately a 9-10 fold risk of developing lung cancers and heavy smokers at least a 20-fold risk. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers and a pipe and cigar smokers is greater than non-smokers but much less than for cigarette smokers. This is probably due to the difference in the amount of tobacco smoked, the chemicals in the smoke and the fact that most pipe and cigar smokers inhale less of the smoke. Moreover, cigarette smoking is much more important that occupational exposure in the causation of lung cancer in the general population. It is now generally agreed that the risk of lung cancer is proportional to the number of cigarette smoked each day, the number of years of smoking, the age at which smoking begins, the depth of inhalation of the smoker and amount of tar in the cigarette.[12]

On the contrary, quitting the use of the tobacco has been shown to reduce the risk of getting lung cancer regardless of how long the smoker has been smoking or the quantity smokes per day. The risk decreases slowly for 10-20 years after which it becomes almost the same as the risk for person who has never smoked.

There are several studies in Western Europe, America and China showing that lung cancer histology varied with smoking status. Differences in histological type also exist between smokers and nonsmokers and between males and females. Accurate cancer cell typing is essential for selecting appropriate therapies, such as surgical procedures or anticancer chemotherapeutic regimens, as well as for making prognosis of the disease. The

establishment of relation between smoking and bronchogenic carcinoma in Bangladeshi population is necessary.

Materials and Methods

This analytical prospective and cross-sectional study was conducted during the period from January 2003 to December 2004. It was carried out in the department of Respiratory Medicine in collaboration with the department of Pathology & Microbiology, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka. A total number of 120 patients admitted in NIDCH were studied. Among them 100 patients were selected on the basis of smoking habit and 20 patients were selected as non-smokers having diagnosed as bronchogenic carcinoma.

Aims & Objectives of the Study

- To find out the specific histological type of lung cancers in smoker patients of Bangladesh people;
- To assess the differential lung cancer risk pattern due to smoking habits in various histological types of lung cancer;
- The study also reflects the evaluation of the risk of various histological types of cancer attributable to smoking while controlling for the confounding effect of age and occupational status;
- It also provides the facility to investigate occupational risks contributing to lung cancers.

Criteria for Selection of Patients

a) Clinical features suggestive of carcinoma of lung: cough, haemoptysis, dyspnoea, chest pain, weight loss, anorexia, fever, Hoarseness of voice, Clubbing of fingers, Palpable lymph nodes.

b) Chest radiography suggestive of bronchogenic carcinoma, such as prominence of hilar shadows; complete or partial collapse of lung; consolidation of lung, central or peripheral, cavitation, segmental emphysema.

Criteria Exclusion

a) When detailed history, clinical examination and roentgenographic findings raised the possibility that the lung cancer is a secondary one as opposed to primary tumour.

b) Patients having poor level of cooperation.

c) Very old patients with bad physical condition.

d) Patients having major concomitant diseases, i.e. recent MI, CVD, serious cardiac dysrythmia, unstable angina.

e) Patients having bleeding diathesis.

f) Poorly controlled bronchial asthma

g) Sputum positive for acid-fast bacilli (AFB)

h) Patient was on anti-TB drugs and the lesion was improving

i) Patients who did not sign the contract from.

A standard proforma with questionnaire was designed and filled to select patients with suspected primary lung cancer. The patients were identified according to the predetermined criteria as well as inclusion and exclusion criteria. A detailed history and thorough physical examination followed by investigations were performed for inclusion criteria and to rule out exclusion criteria. Blood for total count of WBC, differential count of WBC, ESR, haemoglobin c concentration, bleeding time and clotting time, platelet count, prothrombin time, blood sugar, blood urea, serum creatinine, x-ray chest PA view and lateral view, sputum for AFB and malignant cells, MT, ECG, Spiromentry and ABG. Bronchoscopy with brushing, washing and biopsy in relevant cases and FNAC of lung lesions was done to establish the ti tissue diagnosis.

After collection. of all the datas, statistical analysis was done

Observations and Results

It was an analytical, prospective and cross-sectional study conducted at the NIDCH, Dhaka. A total of 120 cases of diagnosed bronchial carcinoma were studied with a view to assess the pattern of histological diagnosis of lung cancer in relation to tobacco smoking. The results are as flows:-

Table-I

Age and sex distribution of the study subjects

Age (Year)	Male No	Male %	Mean+ SD	Female No	Female %	Mean+ SD	Total No	Total %	P Value
<45	8	7.7	57.7+11.2	1	6.3	56.2+ 11.5	9	7.5	0.522NS
45-54	20	19.2		2	12.5		22	18.3	
55-64	42	40.4		8	50.0	50	41.7		
65-74	30	28.8		4	25.0	34	28.3		
> 75	4	3.8		1	6.3	5	4.2		
Total	104	86.7		16	13.3	120	100.0		

N.B. Figure in parenthesis indicate percentage

Mean±SD =57.5+11.3 years (Range 25-82 years)

Mean +SD(Male)=57.7+11.2 years (Range 25-82 years)

Mean+SD (Female)=56.2+11.5 years (Range 28-80 years)

Male :Female=6.5:1

p value reached from chi square analysis NS= Not significant (p >0.05)

The mean age of the patients was 57.5+11.3 years. it was 57.7+[1]12 for male and 56.2+11.2 years for female It was observed that among male patients highest percentage of patients were in the age range of 55-64 years 42(40.0%) followed by 65-74years 3(128.8%),20(f9.2%) in age range 45-54 years whereas among female patients highest percentage in the age range of 55-64 years 8(50.0%) followed by 4(25.0%) in 65-74 years , 2(12.5%) In 45054 years and 1(63.3) 111

<45 years It was evident that no statistically significant age difference was found between male and female patients (p>0.05)

Table-II

Distribution of study subjects by age and smoking status

Age in years	Smoking status			Total	P value	
	Smokers Current	Ex.	Sub- total	Non - smokers		
< 45	10(12.5)	1(5.0)	11(11.0)	8(40.0)	19(50.8)	0.001'
45-54	20(25.0)	4(20.0)	24(24.0)	5(25.0)	29(242)	
55-64	28(35.0)	8(40.0)	36(36.0)	4(20.0)	40(333)	
65-74	20(25.0)	5(25.0)	25(25.0)	2(10.0)	27(22-5)	
> 75	2(2.5)	2(10.0)	4(4.0)	5(5.0)	5(4.2)	
Total	80(66.7)	20(16.7)	100(83.3)	20(16.7)	120(100.0)	

Mean +SD (Current Smoker) = 56.8+9.8 years

Mean +SD (ex smoker) = 61.5+11.3 years

Mean +SD (Smoker) = 57.5 + 11.3 years

Mean ±SD (Non-smoker) = 47.0 + 13.9 years

The table Shows the percentage distribution of smoking status and age c f the patients. The mean age of the current smoker was 56.9 + 9.8 years and that on ex-smoker was 61.5+ 10.5 years. So, the overall mean age of the smokers was 57.5 ± f1.3 years. It was also observed that the mean age of the non-smokers was 47.0 + 13.9 years. A statistically mean age difference was found between smokers and non-smokers ($p<0.05$).

The table shows the percentage distribution of smoking status by sex of the patients. It was found that among the smokers 97(97.0%) were male and remaining 3 3.0%) o) were female, whereas among the non smokers 7(35.0%) were male and 13(65.0%) were female $p<0.01$ in Z-test and the difference was statistically significant.

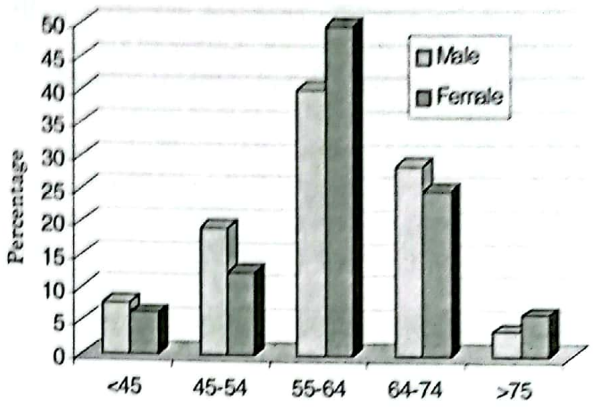

Fig.-1 : *Age & Sex distribution of the study subjects.*

Table-III

Distribution of study subjects by sex and smoking status

Sex	Smoking Status										P Value
	Smokers						Non- Smokers		Total		
	Current		Ex.		Sub total						0.001[S]
	No.	%	No.	%	No.	%	No.	%	No.	%	
Male	62	98.4	35	94.6	97	97.0	7	35.0	104	86.7	
Female	1	1.6	2	5.4	3	3.0	13	65.0	16	13.3	
Total	63	52.5	37	30.8	100	83.3	20	16.7	120	100.0	

Table-IV

Distribution of study subjects by occupation and smoking status

Occupation	Smoking status				Total	P value
	Smokers			Non -		
	Current	Ex.	Sub- total	smokers		
Farmer	25(39.7)	14(37.8)	39(39.0)	2(10.0)	41(34.2)	0.001·
Service	5(7.9)	6(16.2)	11(11.0)	1(10.0)	12(10.0)	
Housewife	1(1.6)	2(5.4)	3(3.0)	13(65.0)	16(13.3)	
Business	7(11.1)	8(21.6)	15(15.0)	1(5.0)	16(13.3)	
Labourer	18(286)	5(35.5)	23(23.0)	2(10.0)	25(25.8)	
Others	7(11.1)	2(5.4)	9(9.0)	1(5.0)	10(83)	
Total	63(52.6)	37(30.9)	100(83.3)	20(16.7)	120(1 00.0)	

The table shows the percentage distribution of smoking status by occupation of the patients. It shows that among the smokers highest percentage were farmer 39(39.0%) followed by labourer 23(23.0.%), businessmen 15(15.0%), service holder 11(11.0%). etc whereas among non smokers, highest percentage were housewife f3(65.0%) followed by farmer 2(10_0), businessmen etc. and the difference was statistically significant ($p<0.05$).

Aneamia, but the difference was not statistically significant (p>0.05). It was observed that among the smokers, 35(35.0%) had clubbing and among non-smokers 6(30.0) had clubbing, but the difference was not statistically significant (p>0.05). Similarly, no statistically significant difference was found between smokers and non smokers in terms of neck vein, lymph node and bony tenderness (p>0.05).

The above table shows the pattern of chest skiogram between smokers and non-smokers. Among the smokers, highest percentage had 38(38.0%) pulmonary mass foll°wed by perihilar opacity 23(23.0), hilar enlargement 11(11.0%), consolidation 9(9.0), pleural :fusion 7(7.0%), Among non-smokers, highest percentage has peripheral pulmonary mass 10(50.0%) followed by 9(30.0%) perihilar opacity, pulmonary nodule 6(30.0%), hilar enlargement 1(5.0%) etc.

Table-V

Distribution of study subjects by X-ray findings and smoking status

X-ray Findings	Smoking status				Total
	Smokers			Non -	
	Current	Ex.	Sub total	smokers	
Hilarenlargement	6(9.5)	5(13.5)	11(11.0)	1(5.0)	12(9.8)
Pulmonary. nodule	0.(0.0)	1(2.7)	1(1.0)	0(0.0)	2(1.6)
Perihilar opacity	16(258.4)	7(18.9)	23(23.0)	6(:0.0)	28(23.0)
Pulmonary mass	25(39.7)	13(35.1)	38(38.0)	1050.0)	47(38.5)
Collapse	3(4.8)	2(5.4)	5(5.0)	0(0.0)	5(4.0)
Broadening mediastinum	1(1.6)	0(0.0)	I(1.0)	1(5.0)	2(1.6)
Pleural effusion	4(6.3)	3(8.1)	7(7.0)	1(5_0)	10(8.2)
Consolidation	5(7.9)	4(10.8)	9(9.0)	(5-0)	11(9.0)
Cavitary lesion	3(4.8)	2(5.4)	5(5.0)	0(0_0)	5(4.1)

Table-VI

Distribution of study subjects by diagnostic procedure and smoking status

Diagnostic Procedure	Smoking status				Total
	Smokers			Non -	
	Current	Ex.	Sub total	smokers	
Sputum cytology	2(3.2)	1(2.7)	3(3.0)	1(5.0)	4(3.3)
Bronchial biopsy	19(30.2)	7(18.9)	26(26.0)	4(20.0)	30(25.0)
Bronchial brushing	2(3.2)	1(2.7)	3(3.0)	1(5.0)	4(3.3)
Bronchial washing	1(1.6)	1(2.7)	2(2.0)	0(0.0)	2(1.7)
FNAC Lung	30(47.6)	21(56.8)	51(51.0)	13(65.0)	64(53.3)
FNAC Lymph node	7(11.1)	5(13.5)	12(12.0)	0(0.0)	12(10.0)
Pleural tissue biopsy	1(1.6)	1(2.7)	2(2.0)	1(5.0)	3(2.5)
Pleural fluid cytology	1(1.6)	0(0.0)	1(1.0)	0(0.0)	1(0.8)

The table shows the pattern of diagnostic procedure applied among the smokers and non-smokers. It was observed that among smokers highest percentage of patients were diagnosed by fine Needle Aspiration Cytology (FNAC) of lung tissue 51(51.0%) followed by Fibreoptic bronchoscopy 26(26.0%), Fine Needle Aspiration Cytology of Lymph rode 12(12.0%), Whereas among non smokers, highest percentage of patients were diagnosed by FNAC of lung 13(65.0%) followed by fibreoptic bronchoscopy 4(20.0%).

The table shows the pattern of bronchial carcinoma among the studies subjects, It was found highest percentage had squmous cell carcinoma 48(40.0%) follow°d by small cell carcinoma 32(26.7%), adenocarcinoma 31(25.8%), large cell carcinoma 6(5.°/a), alveaolar cell carcinoma 1(0.8%), adenosqamous carcinoma 1(0.8%) and fibrocytoma I 1(0.8%) It was observed that among the smokers highest percentage of bronchial carcinoma was sq umous cell carcinoma 44(44.0%) followed by small cell carcinoma 30(30.0%), adenocarcinoma 17(17.0%), whereas among non smokers, highest percentage were adenocarcinoma 14(70.0%) %) followed by squamous cell carcinoma 4(20.0%) etc and the difference was statistically· sigriifcant ($p<0.05$) indicating adenocarcinoma was high among non smokers whereas among smokers highest percentage of bronchial carcinoma was squmous cell carcinoma.

Table-VII

Distribution of study subjects by histologic pattern and smoking status

Histologic Pattern	Smoking Status										P Value
	Smokers						Non-Smokers		Total		
	Current		Ex.		Sub total						0.001[5]
	No	%	No	%	No	%	No	%	No	%	
Squamous cell carinoma	30	47.6	14	37.8	44	44.0	4	20.0	48	40.0	
Small cell carcinoma	22	34.9	8	21.6	30	30.0	2	10.0	32	26.7	
Adenocarcinoma	6	9.5	11	29.7	17	17.0	14	70.0	31	25.8	
Large cell carcinoma	3	4.8	3	8.1	6	6.0	0	0.0	6	5.0	
Adenosquamous Carcinoma	0	0.0	1	2.7	1	1.0	0	0.0	1	0.8	
Alveolar cell Carinoma	1	1.6	0	0.0	1	1.0	0	0.0	1	0.8	
Fibrocytoma	1	1.6	0	0.0	1	1.0	0	0.0	1	0.8	

Table-VIII

Distribution of study subjects by histologic pattern and pattern of tobacco used

Tobacco used	Pattern of Carcinoma				Total	p Value
	SQCC	SCC	AC	LCC & others		
Cigarette only	9(23.1)	6(21.4)	12(44.4)	1(16.7)	28(28.0)	0.13[NS]
Bidi only	10(25.6)	12(42.9)	2(7.4)	2(33. 3)	26(26.0)	
Both	20(51.3)	10(35.7)	13(48.1)	3(50.0)	46(46.0)	
Total	39(39.0)	28(28.0)	27(27.0)	6(6.0)	100(100.0)	

N.B
SQCC= Squamous Cell Carcinoma
SCC= Small Cell Carcinoma
AC= Adenocarcinoma
LCC & others = Large Cell Carcinoma and others

The table shows the percentage distribution of study subjects by pattern of pattern of bronchial carcinoma and pattern of tobacco smoked. . It was found that highest percentage of patients smoked both cigarette and bidi 46(46.0%) followed by cigarette 28(2b.0) and bidi 26(26.0%). It was observed that no statistically significant difference was found in terms of different histologic pattern of bronchial carcinoma and pattern of tobacco smoked (p>0.05)

The table shows the distribution of study subjects by histologic patt-r,, of bronchial carcinoma and smoking status. It was found that mean number of stick/day smoked was 21.1+ 0.6/ day. The mean number of stick/dav was 20.1+ 2.2/day for large cell carcinoma. 26.8± 0.8/day for squamous cell carcinoma, 20.9± 1.0/day for small cell carcinoma and 20.8± 1.4 stick/day for adenocarcinoma and the mean difference was not statistically significant (p>0.05).

Table-IX

Distribution of study subjects by histologic pattern and smoking status (No. of stick / day)

Smoking Status	Pattern of Carcinoma				Total	p Value
	SQCC	SCC	AC	LCC & others		
No. Of stick/day						
Non-smokers	4(8.3)	2(6.3)	14(45.2)	0(0.0)	120(16.7)	0.235^{NS}
<15	6(12.5)	8(25.0)	2(6.5)	3(33.3)	19(15.8)	
15-24	13(27.1)	7(21.9)	1(3.2)	2(22.2)	23(19.2)	
>25	25(52.1)	15(46.9)	14(45.2)	4(44.4)	158(48.3)	
Total	48(40.0)	32(2,6.7)	31(25.8)	9(7.5)	i 120(100.0)	
Mean +SE	20.8±0.8	20.9±1.0	20.1±1.4	20.2±2.2	21.2±0.6	
(Range)	(6-45)	(6-42)	(6-40)	(6-60)	(6-60)	

N.B
SQCC= Squamous Cell Carcinoma
SCC= Small Cell Carcinoma
AC= Adenocarcinoma
LCC & Others= Large Cell Carcinoma and others

Table-X

Distribution of study subjects by histologic pattern and smoking status (duration of smoking)

Smoking Status	Pattern of Carcinoma				Total	p Value
	SQCC	SCC	AC	LCC & others		
Duration of smokings(Years)						
Non smokers	4(8.3)	2(6.3)	1445.2)	0(0.0)	20(16.7)	0.001[2]
<25	8(16.7)	4(12.5)	2(6.5)	2(22.2)	16(13.3)	
25-34	7(14.6)	4(12.5)	3(9.7)	1(11.1)	15(12.5)	
35-44	11(22.9)	8(25.0)	7(22.6)	2(22.2)	28(23.3)	
≥	18(37.5)	14(43.8)	5(16.1)	4(44.4)	41(34.2)	
Total	48(40.0)	32(26.7)	31(25.8)	9(7.5)	120(100.0)	
Mean + SE	38.0±0.9	42.0+ 1.0	39.9+ 1.5	35.9+2.5	38.9±0.6	0.215^{NS}
(Range)	(17-61)	(18-54)	(11-61)	(15-52)	(11-61)	

N.B
SQCC= Squamous Cell Carcinoma
SCC= Small Cell Carcinoma
AC= Adenocarcinoma
LCC & others = Large Cell Carcinoma and others

The table shows the distribution of study subjects by histologic patterns and smoking status. It was found that among the non-smokers adenocarcinoma was s cantly higher whereas squamous cell carcinoma and small cell carcinoma was higher among smokers (p<0.05). Regarding mean duration of smoking, Among the smokers, no statisti^{c}ally significant mean duration was found among the different categories of bronchial carci^{n}oma (p>0.02) although mean duration of smoking was higher among the small cell carcinoma.

The table shows the patient of bronchial carcinoma among the study subjects in relation with dose of smoking. Among the smokers, the mean dose of smokmg was 39.7 + 1.2 pack year. Although the mean dose of smoking was higher among the squmotrs cell carcinoma (40.8 ± 1.8 pack year) compared to other variety of carcinoma, but the mean difference was not statistically significant (p%0.05).

Table-XI

Distribution of study subjects by histologic pattern and smoking status (dose of smoking)

Smoking	Pattern of Carcinoma				Total	p Value
	SQCC	SCC	AC	LCC & I others		
Dose of smoking						
Non -smokers	4(8,3)	2(6.3)	14(45.2)	0(0.0)	20(16.7)	0.001s
<20	3(6.3)	2(6.3)	1(3.2)	0(0.0)	6 (5.0)	
20-29	6(12.5)	7(21.9)	2(6.5)	3(33.3)	18(15.0)	
30-39	5(10.4)	2(6.3)	2(6.5)	1(11.1)	10(8.3)	
40-49	20(41.7)	15(46.9)	11(35.5)	4(44.4)	50(41.7)	
> 50	10(20.8)	4(12.6)	1(3.2)	1(11.1)	10(13.3)	
Total	48(40.0)	32(26.7)	31(25.8)	9(7.5)	120(100.0)	
Mean + SE	40.8+1.8	37.9+2,3	39.3 + 3.2	38.6+4.1	39.7 +1.2	0.067^{NS}
(Range)	(9.0-94.5)	(9.0-96.6)	(4.4-150)	(6.0-84.0)	I (4,4-150) I	

N.B : SQCC= Squamous Cell Carcinoma , SCC= Small Cell Carcinoma , AC= Adenocarcinoma, LCC & Others= Large Cell Carcinoma and others

Table-XII

Distribution of study subjects by histologic pattern and smoking status (age of starting of smoking).

Smoking	Pattern of Carcinoma				Total	p Value
Status	SQCC	SCC	AC	LCC & others		
Age of starting smokings						
Non -smokers	4(8.3)	2(6.3)	14(45.2)	0(0.0)	20(16.7)	0-001^{s}
<15	5(10.4)	4(12.5)	4(12.9)	1(11.1)	14(11.7)	
15-19	19(39.6)	16(50.0)	6(19.4)	5(55.6)	46(38.3)	
>20	20(41.7)	10(31.3)	7(22.6)	3(33.3)	40(33-3)	
Total	48(40.0)	32(26.7)	31(25.)	9(7.5)	120(100.0)	
Mean+SE	18.6+0.2	17.9+0.4	17.6+0.6	18.4+0.8	18.4+0.2	
(Range)	(12-26)	(12-25)	(12-26)	(12-28)	(12.28)	

N. B : SQCC= Sduamous Cell Carcinoma , SCC= Small Cell Carcinoma, AC= Adenocarcinoma
LCC & Others= Large Cell Carcinoma and others

The table shows the distribution of study subjects by histologic pattern and age at starting smoking. It was observed that mean age of starting of smoking was earlier among the patients of adenocarcinoma (17.6 + 0.6 years) compared to large cell carcinoma and others (18.4 ± 0.8 years) and the mean difference was statistically significant (p<0.05).

Table-XIII

Distribution of study subjects by histologic pattern and smoking status (year since quitting)

Smoking Status	Pattern of Carcinoma				Total	p Value
	SQCC	SCC	AC	LCC & others		
Years since quitting						
Non -smokers	4(8.3)	2(6.3)	14(45.2)	0(0.0)	20(16.7)	0.001*
<5	4(8.3)	2(6.3)	1(3.2)	2(22.2)	9(7.5)	
5-9	1(2.1)	0(0.0)	1(3.2)	1(11.1)	3(2.5)	
10-14	1(2.1)	1(3.1)	2(6.5)	0(0.0)	4(3.3)	
≥15	9(18.8)	5(15.6)	8(25.8)	2(22.2)	24(20.0)	
Current smokers	29(60.4)	22(87.4)	5(16.1)	4(44.4)	60(50.0)	
Total	48(40.0)	32(26.7)	31(25.8)	9(7.5)	120(100.0)	

N. B
SQCC= Sduamous Cell Carcinoma
SCC= Small Cell Carcinoma
AC= Adenocarcinoma
LCC & Others= Large Cell Carcinoma and others

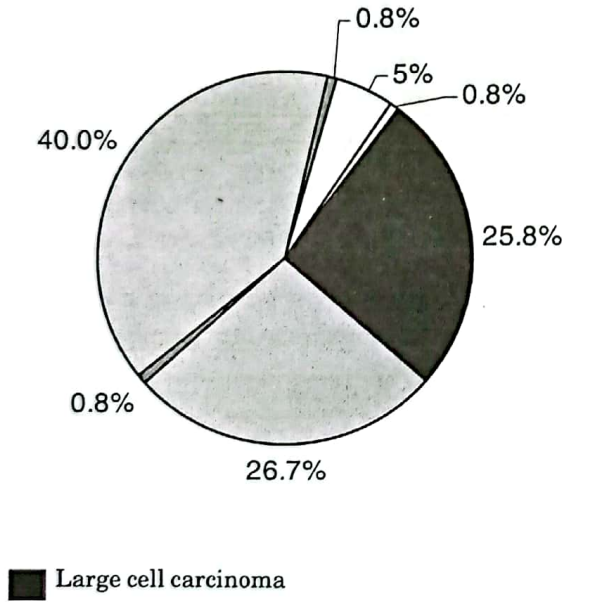

Fig.-1 : *Distribution of study subjects by histologic patterns of carcinoma.*

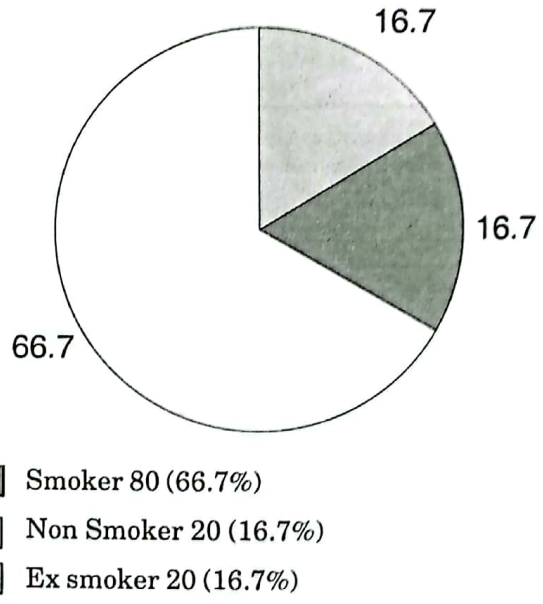

Fig.-2 : *Percentage distribution of the study subjects by smoking status.*

Discussion

It has been observed by different studies that in both developed and developing countries, tobacco smoking is widely prevalent. It is found in all classes of people from very high to low class, which is one of the important preventable causes of premature death. In developing countries, it has

been estimated that nearly 50% of men are dependent on some form of tobacco use where as less than 50% of women are smokers.[14] The main objective of the present study was to assess the different histological types of lung cancer in relation to smoking status. The study also has reflected whether age of starting, dose and duration of smoking habit differ among smokers of different categories. This was an analytical, prospective and cross-sectional study conducted in the NIDCH, Dhaka during the period of 2002-2004. A total of 120 histologically proven primary lung cancer patients were included in the study. Out of 120 patients, 104 (86.7%) were male and 16 (13.3%) were female with Male: Female ratio 6.5:1. The number of female patients are small in this study which can be explained by the fact that in our country females are dependent mostly on husband and or guardian, religious and social grounds; over and above bronchogenic carcinoma is uncommon in females of our country. The finding was consistent with Quayyum.[15] But Crofton and Douglas[16] have shown that the male-female ratio was approximately 5:1 in the USA & in the UK in 1970, but fell to around 2.5:1 in 1982. This finding is not consistent with the present study. This might be due to fact that tobacco smoking in women of those countries became increasingly popular day by day.

Regarding the age of the study group, it was found that most of the patients belonged to the age range of 55-64 in both current & ex-smokers; among current smokers 28 (35%) and among ex-smokers (8 (40%) belonged to the age range of 55-64 years, which is similar to Qayyum's study[15] (2002). This finding is also consistent with the finding of Mahmud et al.[16] Baum[17] showed that out of 473 patients, 51% were above 50 years of age which is consistent with this study.

Among non-smokers most of the patients belong to less than 45 years of age 8 (40%) which is similar to Limsila et al .16 where they showed most of the non-smokers were in the below 45 years are group.

Among 120 patients, 100 (83.3%) were smokers and 20 (16.7%) were non-smokers. Qayyum1[6] and Huhti et aI.[18] found similar results. M ale and female ratio among smokers was 32:1 and among non-smokers was 1:1.9. Limsila et al.[19] found a male and female ratio 13:1 among smokers and 0.4:1 among non-smokers. Huhti et al.[18] found 37.1 male and female ratio among smokers and 0.16:1 among non-smokers.

As to occupation, highest number of patients were farmers in the present study. It was found that among smokers higher percentage was farmers 39 (39%), this is because more than 70% of the population of our country belong to cultivation. Among the non-smokers highest percentage were housewives 13 (65.0%) considering overwhelming proportion of non-smokers among females and an expected observation considering that smoking is a socially unacceptable behavior among female community in our socio-cultural milieu. This is consistent with AIam.[20]

Analysis of smoking habit by the educational status showed that highest frequency of smokers existed among the illiterate groups, whereas non-smoker were greater among the patients having education secondary and above. This might be due to the development of awareness among the educated groups regarding bad effects of smoking.

Considering the smoking status and place of works, it was evident that non-smokers were found to be engaged in indoor works whereas smokers were more in outdoor works. This might be due to fact that in this study most of the patients working in indoors were housewives, whereas outdoor workers were mainly farmers, labourers etc.

Comparing the socio-economic status and pattern of tobacco used, it was found that most of the smokers habituated to either cigarette and bidi and almost equal percentage of patients were habituated to either cigarette or bidi. A statistically significant difference was found between socio-economic status and pattern of tobacco used ($p<0.05$) indicating poor peoples were habituated to bidi whereas the average socio-economic groups were habituated to both bidi and cigarette. T his is consistent with AIam20[4]

X-ray was done in all patients; among the smokers highest percentage of patients had pulmonary mass lesion 38.0% followed by peri hilar opacity 23%. Among non-smoker highest percentage of patients has mass lesion 50% followed by perihilar opacity 30%. Regarding procedure of final diagnosis, it was observed that among smokers highest percentage of patients were diagnosed by Fine Needle

Aspiration Cytology of the lung (51.0%), followed by Fibreoptic Bronchoscopy (31.0%), FNAC of lymph node (12.0%) and others. On the other hand, highest percentage of non-smoking patients were diagnosed by FNAC of lung (65.0%) followed by Fibreoptic Bronchosocpy (20%). The two main diagnostic procedures cover more than (78.3%) of tissue diagnosis in lung cancer.

It was observed that out of 120 cases, highest percentage had squamous cell carcinoma (40%) followed by small cell carcinoma (26.7%), adenocarcinoma (25.8%), large cell carcinoma (5.0%) and others such as adenosqumas carcinoma, alveolar cell carcinoma, fibrocytoma etc. (2.4%). Crofton et al.[20] found SQCC (40-60%), SCC (7.25%), ACC (10-25%) and LCC (5-15%). The findings of NIDCH are similar to the findings of Crofton. Strauss[21] observed S QCC (30-40%), Large cell (10%), Small cell (25%). Barbone et al[22] showed SQCC (35%), SCC (29%), AC (21 %) a nd L CC (12%) a nd o ther h istologic t ypes (3%). These findings are almost similar with the present findings. The SQCC in few study has lesser amount, may be due to the changing smoking habit in the western world.

Limsila et al.[18] in a series of 1600 histologically diagnosed lung cancer cases showed SQCC (29%), AC (29%), LCC (24%) and SCC (13%). The findings are not similar with the present study. Gil et al [2]s observed SQCC (51.7%), SCC (21.2%), ACC and others (16.9%), these findings are consistent with the present study group. Jedrychowski et al.[24] described SQCC (54.7%), SCC (24.1%), AC (16.9%), LCC and others (4.3%, these findings are closely consistent with the present study. Above findings strongly suggests that smoking is related to all major histological types of lung cancer.

It is observed from the present study that highest percentage of bronchogenic carcinoma is SQCC (44%) among the smokers (ex & current) followed b y SCC (30%), A C (17%) a nd lastly large cell carcinoma (6%). Among non smokers, highest percentage is Adenocarcinoma (70%), followed by SQCC (20%) and SCC (10%), the difference is statistically significant ($p<0.05$) indicating AC is higher among non-smokers. On the country as mentioned earlier among smokers highest percentage of bronchial carcinoma is SQCC.

Regarding the intensity of smoking in terms of number of sticks of cigarettes used by the smokers, it was observed that mean number of stick used by smokers was 21.2/day. The mean number of stick/day was 20.2/day for LCC, 20.8/day for SQCC, 20.9/day for SCC and 20.1/day for AC; the mean difference was not statistically significant. It is evident that heavy (intense) exposure is almost equally important for the major histologic types of lung cancer. Highest number of patients in all histologic categories smoked more than>25 stick per day. It was almost similar to the observation of Barbone et al.[22] where they observed that 30.3% of the squamous cell carcinoma group, 31.19% of small cell, 26.6% large cell and 27.2% adenocarcinoma group smoked between 20-29 stick/day and similar. Jedrychowski et al .2a found a higher percentage of patients with SQCC (45.1%), SCC (46.62%), and found a higher percentage of patients with SQCC (45.1 %), SCC (46.62%) & AC (52.52%) used 20-29 cigarettes/day in their study.

In case of adenocarcinoma, majority of the patients (45.2%) used more than 25 stick/day, but Barbone et al.[24] found most of the pateints of Adenocarcinoma (27.2%) had used 20-29 stick/day. Jedrychowski et al.[24] found 49.0 of adenocarcinoma smoked 20-29 stick/day. In large cell carcinoma, also higher proportion of patients (44.4%) smoked more than 25 stick/day. Barbone et al.[22] found (26.7%) in their study.

Differences in duration of smoking habit have been observed among the different histologic pattern of lung cancer. In the present study majority of patients of SQCC, SCC and LCCC had a duration of smoking more than 45 years and similar was found by Jedrychowski et al .[24] where majority of the patients smoked between 30-50 years. Barbone et al.[22] also observed majority of the patients having major histologic types of lung cancer continued their smoking habit for more than 50 years.

Dose (i.e., life cigarette consumption) was calculated multiplying intensity (packs of 20 cigarettes per day) by total duration (years). It was calculated also easily by the following formula; Dose number of stick used per day x duration of habit in years 20. Pack-year is an unit equivalent to 7300 cigarettes. In this study duration of smoking habit was measured by subtracting the

age of starting smoking from the current age (in years) in case of current smoker, where as in case of ex-smoker, by adding the quitting year/years with the age of starting smoking then subtracting the two from the current age.

Among smokers mean dose of smoking was 39.7 pack-year. It was slightly higher for SQCC, 41 pack-years, which was not statistically significant. From the present observation it evident that all major histological types of lung cancer require almost equal amount of exposure to smoking. Barbone et al.[22] found more than 40% of the patient of all histological categories smoked 45-89 pack-year. Jeddrychowsky also found in a similar observation that more than 60% of their patients smoked 30-49 years.

Number of the patients in the present in the study is small, it is evident that intensity of smoking in terms of pack-year is strong among SQCC, SCC, and adenocarcinoma as well as large cell carcinoma. It is also evident that SQCC is more frequent among smokers and incidence of adenocarcinoma is higher among non-smokers and females. Similar observation was made in a study of Chinese patients of Cantonese decent in Hong Kong were high prevalence of adenocarcinoma was detected among female non-smoker; it is possible that a factors other than smoking are operating among female patients or small sample size inference cannot be drawn, warranting further investigation.

Total sample size was small and among them the proportion of non-smokers were also minimum, s o c omparison a mong t he g roups w as n of j ustified s tatistically in all situations. The histological diagnosis of the patients was not uniform and all diagnosis was not reviewed by second opinion. Majority cases came from lower socioeconomic condition and were illiterate, so they could not give the smoking details clearly.

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Assessment of Effect of Inhaled Furosemide Compared to Salbutamol in Asthmatic Patients

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Abstract

This prospective, randomized, controlled, clinical trial was conducted in the Asthma center, NIDCH, Mohakhali, Dhaka during the period of January 2003 to December 2004 with a view to assess the bronchodilator effect of inhaled furosemide in comparison with inhaled salbutamol in asthmatic patients.

A total number of 120 patients were taken initially for the study by random lottery method. Out of them, 10 patients could not complete the procedure and 3 patients were excluded due to syncopal attack. Finally at the end of follow up total 107 patients were included in the study. Among the 107 patients who completed the study, 85 patients achieved the discharged thresold after the end of protocol and 22 patients got admitted in the hospital and were treated accordingly.

After the baseline measurement of FEV 1, PEFR, pulse rate, respiratory rate, blood pressure 50 patients were given inhaled salbutamol and 57 patients inhaled furosemide. All the parameters were measured at 15 minutes and at 30 minutes after inhalation. After 15 minutes of inhalation PEFR L/min and percentage predicted of PEFR were higher in both groups and it was 143.66 L/min vs. 140.35 L/min and 42.5% vs. 40.15% respectively which was statistically not significant ($p>0.05$).

Similarly FEV 1 L and percentage predicted of FEV 1 was higher in both gtoups after inhalation which were 1.47 L vs 1.45 L and 67.3% vs 66.8% respectively, but statistically not significant ($p>0.05$). Pulse rate 3.85% increased in salbutamol group and 3.07% decreased in furosemide group which is stastically significant ($p<0.05$).Systolic blood pressure increased 3.85% in salbutamol group and decreased 3.07% in furosemide group which is stastically significant ($p<.001$). Diastolic blood pressure increased 2.06% in salbutamol group and decreased 2.47% in furosemide group, which is stastically significant ($p<.001$).

This prospective case control study concluded that inhaled furosemide has bronchodilator effect. The bronchodilator effect of inhaled furosemide is same as that of inhaled salbutamol. Inhaled furosemide also reduces respiratory rate, pulse rate and systolic and diastolic blood pressure.

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Introduction

Asthma is an important disorder of the airways with significant morbidity and mortality. Asthma is a chronic inflammatory disorder causing hyper-responsiveness of airways to certain stimuli resulting in recurrent variable airflow limitation, at least partly reversible, presenting as wheezing, breathlessness, chest tightness and coughing[1].

It is a major public health problem. Globally it affects about 100 million people. In our country, about 7 million people (_5.2% of population) suffer from asthma, defined as at least three episodes of asthma attack in last 12 months more than half of these patients are children, that is 7.4% of total pediatric population (1-15 years of age). Proper scientific management practiced uniformly is imperative for amelioration of the sufferings of our fellow countrymen.[2]

Currently, the corner stone of therapy for acute asthma is the rapid reversal of the patient's airway obstruction. The main stay of therapy for acute severe asthma is beta 2-agonist therapy repeatedly every 20 minutes for one hour (serial three nebulization) as initial therapy.[1]

In recent years, it has been demonstrated that furosemide aerosol administered to asthmatic patients prevents bronchoconstriction induced by different bronchial challenge tests such as hyperventilation, adenosines monophosphate, lysine-aspirin, chloride sodium, and prostaglandin .

The mechanism of the protective effect of furosemide in asthma is poorly understood and may be multifactorial. According to studies of the kidney, it appears that furosemide exerts its main effect on the inhibition of electrical neutral transport of sodium, chloride and potassium ions across the cell membrane.[4]

Many reports suggest that there is a strong case favouring the effect of inhaled furosemide on modificatin of ionic transport through the airway epithelium[5]. The idea has also been expressed that action of inhaled furosemide is related to the metabolism of prostanoid and vasodilator effect on the pulmonary vacularbed[6]. It has been proved that action of this drug is dose dependent. Almirall et al[7] have reported on the bronchodilation of a high dose of inhaled furosemide in rates probably caused through inhibition of protein kinase-

Asthma is the most common respiratory crisis encountered in clinical practice .It is estimated that in the USA 1.8 million patient each year seek care or acute episode in emergency department with cost in excess of $430 million. Y et, despite this clinical and financial burden general agreement has yet to be reached about the best way to treat the acutely presenting patient and fundamental issues such as the choice of drugs and duration of treatment have of been resolved. Severe acute asthma with improper treatments is one of the major cause of death in respiratory medicine. Though majority recover with conventional therapy a small percentage requires artificial ventilatory support to get rid of the suffering , which is only available in few center of our country.

Though the inhaled beta-2 agonist is the main stay of treatment of bronchial asthma it has many side effects like tremor, arrhythmia, hypokalaemia, restlessness etc. which are trouble some to the patient.

There are a lot of study showing- bronchodilating effect of inhaled furosemide without the above mentioned adverse effects and its use and efficacy is under trial.

So the goal of the present study was to determine the degree of bronchodilation of inhaled furosemide compared with inhaled beta-2 agonist.

Inhaled furosemide may be a new option in the treatment of bronchial asthma. As furosemide decreases body weight, reduceses pulse rate and blood pressure it would be more effective in patients with cardiovascular diseases where beta-2 agonists use may be dangerous.

Patients and Methods

A prospective, randomized, controlled, clinical trial was carried out in Asthma Center, National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period of January 2003 to December 2004.

Inclusion criteria was

- Patients previously diagnosed and registered as suffering from bronchial asthma, in Asthma Center, NIDCH, Dhaka and who came with sign symptoms of bronchial asthma.
- Age 15 years to 60 years.
- FEV_1 below 65% of predicted value. o Non-smoker

Exclusion criteria was

- o Chronic obstructive pulmonary disease with bronchial asthma.
- o Any concomitant medical problem.
- o Pregnancy.
- o Nebulized beta-2 agonist's solution in previous 6 hours. o Age below 15 years and above 60 years.

In each case, procedure was performed after obtaining informed consent of the patient on a prescribed informed consent form.

A total numbers of 107 patients, who were previously diagnosed and registered as suffering from bronchial asthma in the Asthma Centre, NIDCH, Dhaka and who came with the signs symptoms of acute asthma, meet the selection criteria and gave written consent were taken for the study. Of 107 patients 50 patients were given nebulized salbutamol and 57 patients were given nebulised furosemide by random lottery method. The mean age of the studied patients were 28.28±9.84 years ranging from 15-49 years. Among them 47 (43.9%) were male and the rest 60 (56.1%) were female.

A standard proforma and questionnaire was designed and filled to identify patient with acute asthma. The patients were identified as acute asthma patients according to predominant criteria following history, clinical examination and objective measurement of the airway obstruction. Base line spirometry was done in both groups and repeat spirometry done after 15 and 30 minutes after nebulization in both groups. Injection furosemide was given by nebulizer in similar manner to salbutamol nebulization according to methods-Brain J. et al., (1991). Results was compared with each other.

As the patient presented to the emergency department of Asthma center with acute respiratory distress, they were clinically assessed with brief history of attack, duration, medication used etc., with a view to establish the diagnosis of asthma as well as severity assessment with the help of severity assessment chart.

Physical examination of the patients were done with regards to the vital signs of acute attack as well as the chest findings.

The exclusion criteria were ruled out.

Questionnaire (Appendix) was filled by face to face interview of patients or patients close attendant

Objective measurement of airway obstruction was recorded with portable spirometer. Salbutamol group of patients received 0.5 ml salbutamol (2.5mg) diluted in 3 ml normal saline via wet nebulizer and furosemide group patients, received 40 mg of furosemide in 4 ml of solution (injection) according to methods-Brain et al., (1991). Spirometry was performed at 15 min and 30 min interval (after completion of inhalation) in both groups.

Statistical analysis was done by using the statistical package for the social science (SPSS) program in computer.

Unpaired t-test was applied to determine any statistical significance in sex distribution and age. Chi square test was applied to determine any statistical significant difference in medication use among the two groups.

The mean distribution of respiration, heart rate, systolic and diastolic blood pressure, FEV 1 in L/ min, FEVI in percent predicted, PEFR, accessory muscles use, presence of wheezing dyspnoea before and after treatment at 15 and 30 min were measured and paired t-test was applied to find out any statistical significance of their difference.

To eliminate the bias of gender, age and weight the values of observed PEFR were expressed as percentage of normal PEFR value.

A 'P' value less than 0.05 was considered as significant.

Results and Observations

A total of 107 patients were evaluated. The mean age of the patients was 28.28±9.89 years ranging from 15-49 years. Among the studied patients, 47 (43..9%) were male and the rest were female 60 (56.1%). The mean age of the male patients was 30.02±9.78 years and the female patients was 26.91±9.75 years. Highest percentage of studied patients 41(38.3%) were in the age group below-25 years and followed by 33 (30.8%) in the age group of 25-34 and 22 (20.6%) in the age group of 35-44 years. Only 11 (10.3%) were in the age group of > 45 years. Analysis revealed that no statistically significant mean age difference was found between male and female patients (p=>0.05), although the mean age was higher among male patients compared to female patients (Table-I) .

Table-I

Age and sex distribution of the study subjects

Age in years	Male		Female		P value
	No	%	No	%	
<25	16	15	25	23. 3	
25-34	12	11.2	21	19.6	0.083
35-44	15	14	7	6.6	(NS)
>45	4	3.7	7	6.6	
Total	47	43.9	60	56.1	
Mean±SD	30.02±9.78		26.91±9.75		
Range	15-49		15-47		

P value reached from unpaired student's t test (p>0.05)

It was observed that cent percent of the attended patients had presented with chest tightness, breathlessness, wheeze and straining in accessory muscle followed by cough and sweating. But no patients presented with cyanosis. No statistically significant difference was found between two groups of patients (p>0.05) regarding clinical presentation.

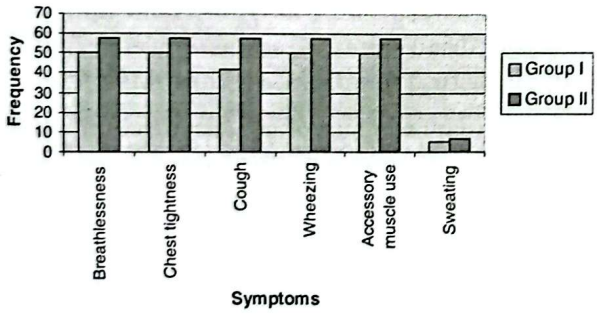

Fig.-1 : *Clinical presentation of the study subjects*

In the present study, the pulmonary function was evaluated by measuring the forced expiratory volume in first second in percentage, forced expiratory volume in first second in L/second, percent predicted PEFR, PEFR in L/min.

The initial PEFR L/min was 125.58±48.34 L/mm in salbutamol group of patients and 125.21±45.48 L/min in furosemide group of patients. After administration of medicine it increased to 143.66±50.77 L/mm in salbutamol group of patients and 140.35±45.58 L/min in furosemide group of patients. Analysis also revealed that the mean percent improvement was not statistically significantly between the two groups. It was also noted that within the group, PEFR was significantly increased from baseline (p—0.001) (Table-II).

Table-II:

PEFR L/min before and after treatment between groups

	PEFR L/min	Salbutamol (N=50)	Furosemide (N=57)	P value
Before	Mean±SD	125.58± 48.34	125.21± 45.86	0.052 (NS)
After 1 5 minutes	Mean_±SD	143. 43.66 ±50.77	140.3-5± 45.58	0.207(NS)
After 30 minutes	Mean±SD	143.50±40.45	140.56±45.60	0.209
% Change after 15 minutes	Mean±SD	15.01 ± 19.10	12.80± 9.06	0.408(NS)
% Change alter 30 minutes	Mean±SD	15.00±19.11	12.81±9.04	0.412 (NS)

P value reached from unpaired student's t test.

Table-III

PEFR, L/min and PEFR, % predicted before and after treatment

	PEFR L/min		% predected	
	Salbutamol Group (N=50) Mean±SD	Furosemide Group (N=57) Mean±SD	Salbutamol Group (N=50) Mean±SD	Furosemide Group (N=57) Mean±SD
Before	125.58± 48.34(NS)	125.21± 45.86	32.7±4.3NS	32.8±4.5
After 15 - minutes	143.66 ± 50.77 (NS)	140.35±45.58	42.5±4.3 NS	40.1±3.2
After 30 minutes	143.50±40.45 (NS)	142.26±45.60	42.7±4.5NS	40.5±3.4
Change after 15 minutes	15.01 ± 19.10 (NS)	12.80± 9.06	30.2±5.3NS	24.1±7.6
Change after 30 minutes	15.00±19.1 1 (NS)	12.81±9.04	30.4±5.1 NS	24.3±7.5

P value reached from unpaired student's t test

Analysis revealed that the PEFR, percentage predicted increased significantly from baseline after administering the drugs in two groups of patients. The percent of improvement was statistically significantly within groups ($p< 0.05$) but not significant between groups ($p>0.05$)

Table-III shows the comparative assessment of two treatment modalities. Analysis revealed that in both the groups the significant changes of PEFR and percent predicted PEFR was found, but the percentage of improvement was not statistically significant between groups, but significant within groups of patients ($p<0.05$).

It was evident that the FEV_1 L was increased from baseline 1.19±.25 L in-salbutamol group and 1.28±.26 L in furosemide group to 1.47±.40 L in salbutamol group and 1.45±.37 in furosemide group of patients respectively and the difference was not statistically significant ($p>0.05$). Analysis revealed that the mean percent of improvement was not significantly high among the salbutamol group of patients (18.31±13.16) compared to furosemide group of patients (14.41±15.71) ($p>0.05$).

No statistically significant mean difference was found between two groups of patients in terms of percentage predicted forced expiratory volume ($p>0.05$), Although it was a bit higher in furosemide group of patients (57.08±9.89) than salbutamol group of patients (54.24±6.64). After administration of drugs, it was increased significantly in both the groups of patients ($p<:0.001$) and the mean difference was statistically- significant within two groups of patients. Analysis also found that mean percent of improvement was not significantly high among the salbutamol group of patients (24.87±17.84) compared to furosemide group of patients (19.59±18.85) ($P>0.05$).

Table-IV

FEV1, L and FEV1, % predicted before and after treatment

	Salbutamol Group Mean±SD	Furosemide Group Mean±SD	Salbutamol Group Mean±SD	Furosemide Group Mean±SD
Basal	1.19-±. 3(NS)	1.28±. 26	54.24±6.64(NS)	57.08±9.89
After 15 minutes	1.47±. 4(NS)	1.45±. 37	67.3±6.79(NS)	66.80±7.16
After 30 minutes	1.48± 4(NS)	1.46±. 37	67.48±7.03(NS)	-66.87±7.11
%Change after 15 minutes	18.31±13.16(NS)	14.41±15.71	24.87±17.84(NS)	19.59±18.85
%Change after 30 minutes	18.32±13.15(NS)	14.43±15.69-	24.98±17.89(NS)	19.61±18.85

P value reached from unpaired student's t test

Table-IV shows the comparative assessment of improvement in two treatment modalities in terms of FEV_1 L and FEV_1 % predicted. Analysis revealed that in both the groups the significant changes of FEV_1 L and FEV_1 % predicted was found. And the percentage of improvement was not statistically significant between groups but significant within the group of patients ($p<0.001$).

The initial pulse rate was 87.28±5.15 per minute in salbutamol group of patients and 87.36±5.34 per minute in furosemide group of patients and no statistically significant mean difference was found between two groups of patients (p:>0.05). After administration of drugs the pulse rate increased in-group 1(89.20±5.52) and decreased in group 11(85.5±5.54) of patients which is statistically significant ($p<0.05$).

No statistically significant mean difference of respiratory rate was observed between two groups of patients ($p>0.05$) and the respiratory rate was remained static after treatment. The initial systolic blood pressure was 127.2±9.04 mmHg in salbutamol group of patients and 126.31±8.99 mmHg in furosemide group of patients and the mean difference was not statistically significant ($p>0.05$). After administration of drugs, the systolic blood pressure was slightly increased in-salbutamol group (03.85±2.55%) of patients and decreased (3.07±3.73%) in furosemide-group of patients. And the mean change of systolic blood pressure was statistically significant ($p<0.05$) .

Table V

Pulse rate before and after treatment

	Pulse rate	Salbutamol Group	Furosemide Group	P value
Basal	Mean±SD	87.28±5.15	87.36±5.24	0.877(NS)
After 15 minutes	Mean±SD	89.20±5.52	85.56±5.54	<0.001
After 30 minutes	Mean±SD	89.20±5.52	85.07±5.68	<0.001
% Change after 15 minutes	Mean±SD	3.85±2.55	-3.07±3.73	<0.001
% Change after 30 minutes	Mean±SD	3.85±5.5	-2 -2.92±3.92	<0.001

P value reached from unpaired student's t test ($p<0.001$)

Table-VI

Systolic blood pressure before and after treatment

	Systolic BP mmHg	Salbutamol Group	Furosemide Group	P value
Basal	Mean ± SD	127.2+9.04	126.31±8.99	.614(NS)
After 15 Minutes	Mean±SD	132+8.51	122.28±7.9	<.001
After 30 minutes	Mean±SD	132.30+8.64	122.45±8.13	<.001
% Change after 15 minutes	Mean±SD	3.85±2.55	-3.07±3.73	<.001
% Change after 30 minutes	Mean±SD	3.87+2.56	-3.11±3.74	<.001

P value reached from unpaired student's t test ($p>0.001$)

Similar to systolic blood pressure, statistically significant mean difference of diastolic blood pressure was found between two groups of patients before and after treatment with drugs (P<0.001).

Table-VII

Diastolic blood pressure before and after treatment

		Salbutamol Group	Furosemide Group	P value
Basal	Mean+SD	81.40±5.15	80.61±4.73	.434(NS)
After 15 minutes	Mean±SD	83±4.73	78.94±4.69	<.001
After 30 minutes	Mean±SD	83±4.74	77.71±4.91	<.001
% Change after 15 minutes	Mean±SD	2.06+3.5	-1.97±3.49	<.001
% Change after 30 minutes	Mean±SD	2.06±3.5	-2.47±3.22	<.001

P value reached from unpaired student's t test (p<0.001)

Table VIII

Percentage of change of selected parameters after two treatment modalities

Parameters (After 15 minutes)	Salbutamol Group (N=50)	Furosemide Group (N=57)	P value
PEFR, L/min	5.01±19.10	12.80±9.06	0.408(NS)
PEFR, % predicted	42.5±4.3	40.1±3.02	0.076(NS)
FEV_1, L	18.31±13.16	14.41±15.71	0.171(NS)
FEV_1, % predicted	24.87±17.84	19.59±18.85	0.141(NS)
Pulse /min	3.85±2.55	-3.07±3.73	<0.001
Respiration	13.58±10.33	12.38±12.35	0.595(NS)
Systolic blood pressure (mmHg)	3.85±2.55	3.07±3.73	<0.001
Diastolic blood pressure (mmHg)	2.06±3.5	-1.97±3.49	<0.001

P Value reached from unpaired student's t test

Parameter (After 30 minutes)	Salbutamol group	Furosemide group	P value
PEFR, L/min	15.±19.11	12.81±9.04	0.412 (NS)
PEFR, % predicted	30.4±5.1	24.3±7.5	0.068(NS)
FEV_1, L	18.32±13.15	14.43±15.69	0.171(NS)
FEV1, % predicted	24.98±17.89	19.61±18.85	0.135 (NS)
Pulse /min	3.85±5.52	-2.92±3.92	<0.001 Respiration
13.56±10.31	12.23±12.14	0.608(NS)	
Systolic blood pressure (mmHg)	3.87±2.56	3.11±3.74	< 0.001
Diastolic blood pressure (mmHg)	2.06±3.5	-2.47±3.22	<0.001

Analysis of the above table revealed that the after treatment with inhaled salbutamol and inhaled furosemide the percentage of improvement was found in terms of PEFR L/min, PEFR predicted, FEV1% and FEVI L which are same in both groups and not significant between the groups (p>0.05). But statistically significant changes were observed in pulse rate, systolic and diastolic blood pressure (p<0.05) . It was observed that after treatment at 15 minutes and 30 minutes all the values remained same.

Discussion

This prospective study was done to evaluate therapeutic response of inhaled fuosemide and to compare the bronchodilator effect of furosemide with that of salbutamol in asthmatic patients. A number of case reports indicate inhaled furosemide is beneficial for treating asthma. Our data suggests that 40mg of inhaled furosemide is same effective as inhaled salbutamol in asthmatic patients. The variables that were mainly studied were respiratory rate, heart rate, blood pressure, FEV 1 in liter per minute and percent predicted, PEFR in liter per minute and percent predicted, accessory muscle use and presence of wheezing.

A total number of 120 patients were taken initially for the study. Out of them 10 patients could not complete the procedure and 3 patients were excluded due to syncopal attack. This prospective study was conducted in National Institute of Chest Disease and Hospital, Dhaka, for a period of two year, starting from January 2003 to December 2004.

The studied patients were divided into two groups. Fifty patients were treated with inhaled salbutamol and fifty-seven patients with inhaled furosemide. Among the studied patients, 47 (43.9%) were male and the rest were female 60 (56.1 %). The mean age of salbutamol group of patients was 28.26±10.01 years ranging from 15 to 49 years and the mean age of the furosemide group of patients was 28.28±9.78 years ranging from 5-47 years. Analysis revealed that no statistically significant mean age difference was found between two groups of patients (p>0.05). It indicates that younger age group is suffering from severe acute asthma more than other age groups. The probable causes might be they are more exposed to pollen, dust and other environmental cause.

It was observed that cent percent of the attended patients had presented with breathlessness, wheeze, chest tightness and straining of accessory muscles followed by coughing and sweating. But no patients presented with cyanosis. No statically significant difference was found between two groups of patients (p>0.05) regarding clinical presentations.

It was evident that although the cent percent of the patients were conscious, but 23(21.5%) were unable to talk and 84 (78.5%) were able to talk in words.

In the present study, the pulmonary functions were evaluated by measuring the PEFR L/min, PEFR % predicted, FEV 1 L and FEV1 % predicted. Analysis revealed that the predicted PEFR increased significantly from baseline after administering the drugs in two groups of patients (p<0.05). The percentage of improvement was significantly higher in both groups of patients after 15 minutes and 30 minutes of inhalation.

The initial PEFR L/min was 125.58±48.34 L/min in salbutamol group of patients and 125.21±45.86 L/min in furosemide group of patients. After administration of medicine it increased to 143.66±50.77 L/min in salbutamol group of patients and 40.35±45.58. L/min in furosemide group of patients after 15 minutes. Analysis also revealed that mean percent improvement was significantly high in both groups after 15 minutes and 30 minutes.

It was evident that the FEV 1 L was increased from baseline 1.19±0.25 L in salbutamol group and 1.28±0.26 L in furosemide group to 1.47±o.4 L in salbutamol group and 1.45±.37 L in furosemide group of patients and the difference was statistically significant (p<0.001). Analysis revealed that the mean percent of improvement was significantly high in both groups after 15 minutes and 30 minutes.

It was evident that no statistically significant mean difference was found between two groups of patients in terms of percentage predicted forced expiratory volume (p>0.05), although it was a bit higher in furosemide group of patients (57.08±9.89) than salbutamol group of patients (54.24±6.64). After administration of drugs, it was increased significantly in both the groups of patients

(p<0.001) and the mean difference was statistically not significant between two groups of patients. Analysis also found that mean percentage of improvement was significantly high in both groups.

In the original article eighty patients were studied, forty of whom were administered salbutamol (mean age 34.5), and the remaining forty of whom received furosemide (mean age 34.7) there was a predominance of women, accounting for 28 cases (70%) in the salbutamol group and 31 cases (77%) in the furosemide group.

Salbutamol induced an improvement in FEV1 1 of 7.9% at 10 min and 30 min post administration, and furosemide induced an improvement of 6.9%. Statistical analysis of both groups did not show a statistically significant difference (P>0.05).

In the Salbutamol group, the blood pressure trend was increased (diastolic and systolic) from 116 (systolic) to 118 mmHg, and 117 mmHg at 10 min and 30 min, respectively. Diastolic readings also changed from 80 to 82 mmHg at 10 min and 30 min. In the furosemide group, the trend was toward a drop from 114 (systolic) to 109 mmHg and 108 mmHg at 10 min and 30 min, respectively. Similar findings occurred in diastolic blood pressure, which oscillated from 73.2 to 75.5 mmHg at 30 min. Statistical analysis of blood pressure modification (systolic and diastolic) in both groups showed a statistically significant difference (P<0.05). Analysis of pulse showed an increase in the salbutamol group from 73.7 to 74.6 beats per min at 10 min and 75.2 at 30 min. Furosemide showed the opposite decreasing from 73.7 (basal) to 71.9 beats per min at 10 min and 71.8 at 30 min. Statistical analysis of this variable between the two groups yielded a statistically significant difference (P<0.05)[9].

In my study change of parameters like FEV1, PEFR, Systolic and Diastolic blood pressure, Pulse rate and Respiration rate are consistent with the original article. No stastically significant difference of FEV 1 and PEFR between the two group. But there is statistically significant change of pulse rate, respiratory rate, systolic and diastolic blood pressure between salbutamol group and furosemide group.

Ultimately the study substantiates my hypothesis that inhaled furosemide has same bronchodilator effect as that of inhaled beta-2 agonist. And it may be a new treatment modalities but for which multicentered extensive studies are required.

Similar type of study was carried out by Bianco et al[9]. Prevention of exercise induced bronchoconstriction by inhaled furosemide. To determine whether inhaled frusemide, a diuretic able to interfere with ion and water movement across airway epithelium, can modify exercise-induced bronchoconstriction, a three-part randomise, double-blind, placebo-controlled study was done in asthmatic patients who had a fall in FEV1 of at least 20% after running up and down a corridor. In the first part the effect of approximately 28 mg frusemide given as an aerosol was compared with that of a placebo. In the second part two doses of inhaled frusemide (approximately 14 mg and 28 mg) were examined. In the third part the effect of 20 mg oral frusemide was tested. Inhaled frusemide had a good and dose-related protective effect, whereas oral frusemide was ineffective. The mean (95% C1) maximum percentage falls in the FEV1 were: 11.5 (14.3-8.7) with frusemide and 33.8 (39.1-28.5) with placebo in the first part of the study, 13.6 (21.6-6.0) with 28 mg frusemide, 19.7 (28.2-11.3) with 14 mg frusemide, and 34.6 (39.4-30.0) with placebo in the second part of the study, and 15.2 (19.9-10.5) with inhaled second part of the study, and 15.2 (19-9-10.5) with inhaled frusemide, 38.2 (47.1-29.3) with oral frusemide, and 35.3 (45.9-24.7) with placebo in the last part of the study. The findings lend support to the hyperosmolarity hypothesis of exercise -induced asthma and may have therapeutic implications. Findings support the bronchodilator effect of inhaled furosemide which is also continent with my study.

Rajalulasingam et al[10] carried out a study on -Effect of inhaled furosemide on responses of airways to bradykinin and adenosine 5 monophosphate in asthma. They showed that on the open visit days the provocative concentrations required to reduce forced expiratory valume in one second (FEVi) by 20% from baseline (PC20) for AMP and bradykinin were 16.23 (1.42-67.16) and 2.75 (0.81-6.6) mg/ml. There was a significant correlation between baseline AMP and bradykinin PC_20 values. For AMP the geometric mean PC 20 values following pretreatment with inhaled frusemide and matched

placebo were 80.97 (9.97->400.0) and 14.86 (2.6-104.6) mg/ml respectively (95% Cl 0.49 to 0.98). For bradykinin the geometric mean PC20 values following pretreatment with inhaled frusemide and matched placebo were 13.22 (2.53->16.01) and 2.52 (0.45-5.61) mg/ml respectively (95%Cl 0.43 to 1.01). Frusemide afforded 5.45 and 5.24 fold protection against AMP and bradykinin-induced bronchoconstiction respectively. Furthermore, there was a significant correlation between protection afforded to the airways against AMP and bradykinin.

These date suggest that inhaled frusemide affords protection against bradykinin-induced bronchoconstiction which is comparable to that against AMP, supporting a common machanism of action for frusemide. This study is also continent with my clinical trial in respect to bronchodilator effect of inhaled furosemide.

Rodwell et al[11]. carried out a study on -Different effects of inhaled amiloride and furosemide on airway responsiveness to dry air challenge in asthmatic subject. They described that Amiloride, a Na^+ channel blocker, and frusemide, an inhibitor of the $Na^+/K^+/2C1^-$co- transporter on the basolateral surface of airway epithelial cells, have the potential to affect water transport across the airway epithelium. As isocapnic hyperventilation challenge (ISH) with dry air may provoke airway narrowing in synthetic airway responsiveness by affecting airway hydration.

Fifteen asthmatic subjects (6 females, 6 males), who had a fall in forced expiratory volume in one second (FEV1) of 20% after ISH, inhaled amiloride (11 mg), or its vehicle, from a fisoneb (TM) ultrasonic nebulizer, within 10 min before ISH. On a separate day, eight of these subjects inhaled frusemide (38 mg), from the same Fishoneb(TM), 10 min before ISH. After breathing, 30/at resting ventilation, subjects breathed at 30% of their maximum voluntary ventilation (MVV i.e. predicted FEV I x35), then at 60% MVV, and finally at MVV for 3 or 4 min. FEV_1 was measured 1,3,5,7 and 9 min after each period, or until it was stable. Airway sensitivity was expressed as the ventilation which provoked a 10, 15, 20 or 30% fall in FEV1, (PVE10, PVE15, PVE20 and PVE 30, respectively).

There was no significant difference in the PVE, 10, 15,20,30 between the vehicle and amiloride treatment day; however, in the 8 subjects who inhaled frusemide, frusemmide caused a significant increase in the PVE20 when compared to amiloride. In conclusion, inhaled amiloride failed to protect. against ISH whereas furosemide was effective at reducing airway responsiveness. This study also proved bronchodilator effect of inhaled furosemide.

Hossain et al[12] is carried out a similar work-Role of furosemide in severe acute asthma. Their study included 30 patients suffering from acute asthma. Fifteen patients were given nebulized salbutamol and fifteen were given nebulized furosemide. Respiratory function were conducted at 10 minutes and 30 minutes as well as measurement of pulse and blood pressure. Peak expiratory flow rate (PEFR) showed an improvement of 80ml in salbutamol and 75 ml in furosemide group (p>.05). They concluded that treatment with inhaled furosemide may provide new options for asthmatic patients specialty in case of cardiovascular diseases in which beta -2 agonist is dangerous, which is consistent with my study.

Seidenberg, Dehning Hardt et al[13] showed that inhaled frusemide prevents bronchoconstriction in asthmatic adults induced by various triggers. To determine if frusemide provides similar protection in children, whether this is age dependent and equally effective for central and peripheral airways, they performed a double blind, placebo controlled, randomised, crosssover study on the effect of inhaled frusemide on lung function changes induced by cold air challenge in 21 asthmatic children. In addition, they measure diuresis before and after inhalation. Bronchodilatation after frusemide was not observed. However, deterioration in lung function after frusemide, compared with placebo, was significantly diminished: forced expiratory volume in one second (FEV 1) was -5.7% V- 11.5%, peak expiratory flow (PEF)-7.7% V-23.3%, maximum expiratory flow at 50% or vital capacity (MEF 50VC)-16.0% V-35.2%, and at 60% of total lung capacity (MEF 60TLC) - 32.4% V-61.6% and specific airways conduction-42.0%v-57.7%, respectively. This effect was not age devendent. Diuresis was significantly increased from a mean (SEM) of 198 (34) ml/3 hours before inhaled frusemide to 379 (62) ml/3 hours after nebulisation. They conclude that inhaled frusemide prevents cold air induced bronchoconstiction in

asthmatic children and that increased diuresis can be expected with a dose as low as 28 mg of frusemide given by nebulizer. As their study revealed the bronchodilator effect of inhaled furosemide it can be concluded that present study is constient with their study.

These findings supports the findings of my- study. The data showed no significant difference observed in the out come parameter between salbutamol group and furosemide group. Ultimately the study substantiates my hypothesis that inhaled furosemide has same bronchodilator effect as that of inhaled beta-2 agonist. And it may be a new treatment modalities but for which multicentered extensive studies are required.

Small sample size is one of the limitations of this study.

Measurement of PEFR L/min, PEFR% predicted, FEV 1 L and FEV 1 % predicted could be monitored for longer time.

Use of injection furosemide as nebulized form is also a limitation. Single blind study in stead of double blind study is a limitation.

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Doppler Evaluation of Left to Right Shunt (Qp/Qs) in Patients with Isolated Atrial Septal ASD

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Abstract

Material & Method: A prospective observational study was carried out in the department of cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU) in collaboration with the department of cardiology, Combined Military Hospital (CMH), Dhaka from January 2000 to October 2001. All the patients were clinically evaluated. ECG & Doppler echocardiography were done. All the patients underwent cardiac catheterization. Complex congenital heart disease & cyanotic heart disease patients were excluded from the study. Doppler estimated Qp / Qs was done by conventional (velocity time integral method) method. In cardiac catheterization Op / Qs ratio derived from oximetric data which has become a well established part of clinical practice. Doppler derived QplQs were compared with catheter derived Qp / Qs.

Results: 32 patients with ASD were included. In those patients Doppler derived Qp / Qs ranged from maximum 10.5 to minimum 1.10. Mean (±SD) was 3.18 + 1.68 In patients with ASD mean (±SD) Qp / Qs at catheterization was 3.31 ± 1.93. Qp / Qs ranged from maximum 12.10 to minimum 1. In those patients the correlation coefficient for invasively determined QplQs versus Doppler estimated Qp / Qs was. 95 (standard error of estimate [SEE] = .28) & the line of regression passed close to the origin.

Conclusion: The results of this study demonstrate that the Doppler technique allows the noninvasive evaluation of Qp / Qs with a high degree of accuracy & allows determination of the stage of ASD by the consecutive assessment of shunt magnititude.

Key words: atrial septal defect, Qp / Qs

[Chest & Heart Journal 2005; 29(1) : 26-32]

From a WHO report, the incidence of congenital heart disease (CHD) is 6% among all cardiovascular diseases in Bangladesh (Malik 1984). In Bangladesh, among the hospitalized children with CHD, the largest share (70%) is occupied by left to right shunt anomalies. In terms of rank, ASD comes as second in the picture as left to right shunt anomalies among the children admitted with CHD in hospital. The incidence of ASD among CHD in the live born is 7.4% & the incidence rate is reported to be 12% from Bangladesh (Islam et al, 1984)

The physiologic consequences of an ASD depend upon the magnitude & the duration of the left to right shunt & upon the behaviour of pulmonary vascular bed. The infrequency of pulmonary vascular disease in patients with ASD has been ascribed in part to the deferred development of a significant left to right shunt. (Campbell et al 1961)

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The brunt of left to right shunt is primarily borne by the pulmonary vascular bed. The response to pulmonary vasculature is so variable that an assessment of pulmonary arterial pressure, pulmonary vascular resistance & pulmonary blood flow by haemodynamic study are mandatory before planning the management.

Therefore determination of pulmonary to systemic blood flow ratio (Qp/Qs) is considered to be important for management of patients with left to right shunts. The Qp/Qs provides information on shunt severity & is usually determined by oximetry & Doppler echocardiography (Evangelista et al, 1993)

Hausler et al in Germany studied the accuracy of Doppler estimated Qp/Qs in ASD. Surgery was performed without cardiac catheterization in a number of patients. (Hausler et al 1994).

Satomi et al in Japan estimated Qp/Qs in ASD using multigated Doppler instrument as the number of patients with ASD who undergo surgery without cathetedzation had increased. (Satomi, 1990)

Progressive increase in pulmonary vascular pressure & development of pulmonary vaso occlusive disease (PVOD) leads to potentially correctable lesions to a state of inoperabiiity (Nadas et al 1960). Particular responsibility is placed on the cardiologist not only in the initial diagnosis but also on subsequent periodical assessment of the haemodynamic status & determination of proper timing for corrective surgery.

The anatomical type of shunt & its haemodynamic status can be satisfactorily assessed by combining clinical examination, ECG, CXR, Doppler echocardiography & cardiac catheterization. Though catheterization is the definitive means for assessment of the haemodynamic state but in the context of our country & socio-economic status, the invasive study is not easily approachable. Keeping in mind the above facts, this study was undertaken to observe how closely the non-invasive data correlate with the invasive data in patients with ASD and determination of Qp/Qs by Doppler echocardiography & cardiac catheterization.

Material & Method:

This prospective observational study was carried out in the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka and Combined Military Hospital, Dhaka Cantonment, Dhaka during the period of January 2000 to October 2001. Inclusion criteria: Those patients who were clinically diagnosed as ASD with or without pulmonary hypertension and who were confirmed as ASD by Doppler echocardiography and by cardiac catheterization at Combined Military Hospital, Dhaka were taken as cases Patients age varied from 1 year to 60 years.

Exclusion criteria:

1) Patients with complex congenital heart disease and associations
2) Patient unwilling to undergo cardiac catheterization
3) Patient with cyanotic congenital heart disease

The study population consisted of 32 patients with ASD. All patients underwent cardiac catheterization within 3 months of the Doppler study. The clinical condition of the patients did not change between cardiac catheterization & Doppler examination.

Apparatus:

Hewlett Packard Sonos 2000 Doppler echocardiograph or System Five General Electric Medical Systems Doppler echocardiograph were used for both imaging and determination of flow velocity. Cardiac catheterization was done with Shimadzu biplane multi directional angiocardiograhic system MH 51-A attached to polygraph EP 1102. Oxygen saturations were obtained with a oximeter model PW A-200 (shu technica, Japan)

Methods:

All information regarding clinical history and physical findings, chest X-ray, ECG, Doppler echocardiographic findings, cardiac cathetedzation report including angiocardiographic report were collected in the preformed questionnaire.

Doppler echocardiographic techniques:

All patients underwent a complete two-dimensional Doppler echocardiographic examination with recording of Doppler flow velocity in the main pullmonary artery and ascending aorta. Patients rested in supine position for the subcostal or suprastemal examination, and in the left lateral

decubitus position for the left parasternal views. Sedation using rectal diazepam was used if indicated. Two dimensional echocardiographic images and pulsed Doppler flow velocity curves were obtained with the same transducer (either 3 or 5 MHz).

The Doppler sample volume could be positioned at any depth along any scan line for measurement of Doppler flow velocity. The localization of the site of the pulsed Doppler flow sampling and the angle (0) of Doppler sampling relative to direction of flow could be accurately determined. No angle correction was applied for the angle 0 (angle between Doppler beam and the direction of flow) because 0 was less than 20.

Ultrasound examination: Two dimensional Doppler echocardiographic studies included interrogation of the main pulmonary artery, ascending aorta in patients with ASD.

Main pulmonary artery flow: This was measured by positioning the sample volume within the main pulmonary artery distal to the pulmonary valve in a parasternal short axis plane echocardiographic view.

Pulmonary artery diameter was measured between the inner walls of the vessel of the two-dimensional echocardiographic short-axis view in early to mid-systole, after most of the noticeable expansion of the vessel had occurred. Pulmonary artery diameter was measured at the level of the pulmonary valve.

Ascending aortic flow: Measurements were made from subcostal or apical left ventricular outflow tract views with the sample volume placed just distal to the aortic valve. Aortic root size was measured as an inner diameter just above the level of the valve in early to mid-systole.

In patients with ASD, Qp (pulmonary flow) was measured in the main pulmonary artery & Qs (systemic flow) was quantified in the ascending aorta.

Doppler data analysis: (Haffy, 1993)

For each Doppler measurement, an average of three or five consecutive cardiac cycles was utilized. Pulmonary and aortic systolic velocity time integrals (VTI) were determined by digitizing and integrating the area under the Doppler flow velocity curve by the computer. From these data, calculation of Qp/Qs ratio was obtained by the following conventional Doppler method:

$$\text{Shunt Flow} = \frac{SV_{PV}}{SV_{AV}}$$

Where SV= stroke volume, PV= pulmonary valve, AV= aortic valve

$$\text{Shunt Flow: } = \frac{.785 \times \text{RVOT } d^2 \times \text{RVOT VTI}}{.785 \times \text{LVOT } d^2 \times \text{LVOT VTI}}$$

Where RVOT = right ventricular outflow tract, LVOT = left ventricular outflow tract, d = diameter

VTI: is the distance in centimeters that blood travels with each stroke. It is calculated by the ultrasound machine software during planimetry of the Doppler spectral curve.

The location for determining the SV depend upon the location of the shunt. In patients with ASD Qp site is pulmonary artery & Qs site is mitral valve or aorta. (Reynolds, 1993).

Shunt flow can also be measured by the simplified Doppler method using the following formula: (Cloez et al, 1988).

$$\frac{QP}{QS} = \frac{\text{Pulmonary luminal d } m^2 \times \text{oeak velocity}}{\text{Aortic luminal dm}^2 \times \text{peak velocity}}$$

Ten patients were also calculated for Qp/Qs by the second method.

Cardiac catheterization: (Grossman, 1991)

The level and magnitudes of the shunts of all 36 patients were confirmed at cardiac catheterization and angiography. Shunt magnitude was determined by standard oximetric techniques using the following formula:

$$\frac{Qp}{QS} = \frac{(SAO_2 - MVO_2)}{CVO_2 - PAO_2}$$

Where, SAO_2 = systemic artery oxygen saturation

MVO_2 = mixed venous oxygen saturation

PVO_2 = pulmonary vein oxygen saturation

PAO_2 = pulmonary artery oxygen saturation

Table I

Age distribution in ASD (n=32)

Sex	Number	Mean (year) ± SD
Male	14	27.57 ± 13.77
Female	18	24.80±14.1
Total	32	20.00±1.00

The above table shows mean age in male patients was 27.57 ± 13.77 years and in female patients 24.8 ± 14.1 years. There was no significant age difference in presentation between both sexes.

Table II

Presenting complaints of patients (n=32)

Complications	Frequency	Percentage
Shortness of breath	18	56
Recurrent RTI	2	6.2
Asymptomatic	2	6.2
Chest pain	5	15.6
Palpitation	5	15.6

Table III

ECG pattern in ASD (n=32)

ECG Pattern	Frequency	Percentage
Partial RBBB	13	40.6
RBBB	6	18.8
RVH	10	31.3
Normal	2	6.3
RBBB + RVH	1	3.1

Cardiomegaly

Intracardiac shunt

Normal

Pulmonary plethora

Total

The above table shows CXR pattern in ASD. Features consistent with final cardiac shunt and pulmonary plethora with cardiomegaly accounts for 50% of cases. 21.9% patient had normal chest x-ray. Isolated cardiomegaly was found in 18.8% cases.

Table 5

Echocardiographic pattern in ASD

Echo pattern of ASD	Frequency	Percent
Secundum type	25	78.1
Sinus venosus type	7	21.9
Total	32	100

All patients with ASD had 2D, M mode & colour Doppler echocardiography. 25 patients had secundum type of ASD (78.1%) & 7 had sinus venosus type (21.9%).

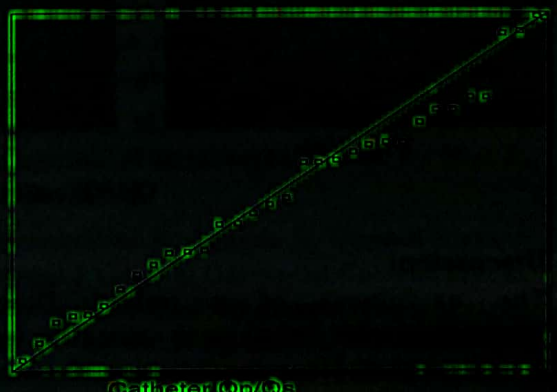

Fig.-1

The above figure shows regression analysis comparing Qp/Qs by Doppler echo & cardiac catheterization in ASD (r = .95, SE = 23).

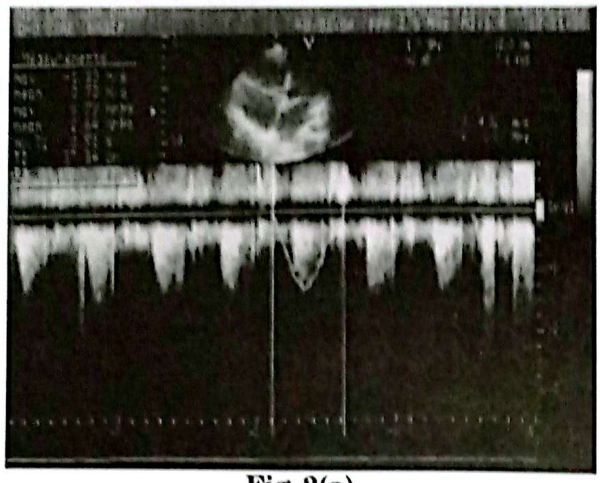

Fig. 2(a)

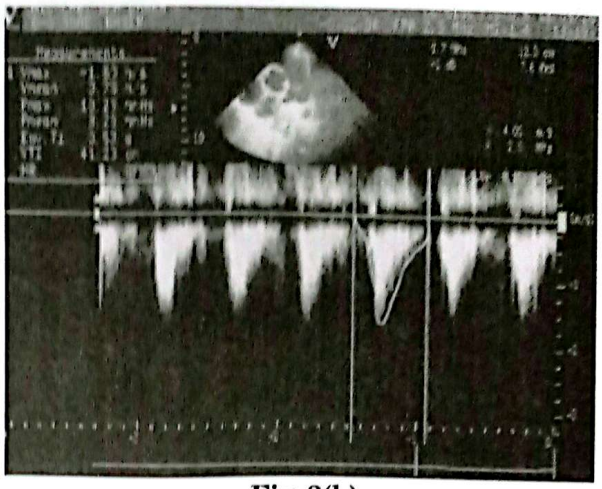

Fig. 2(b)

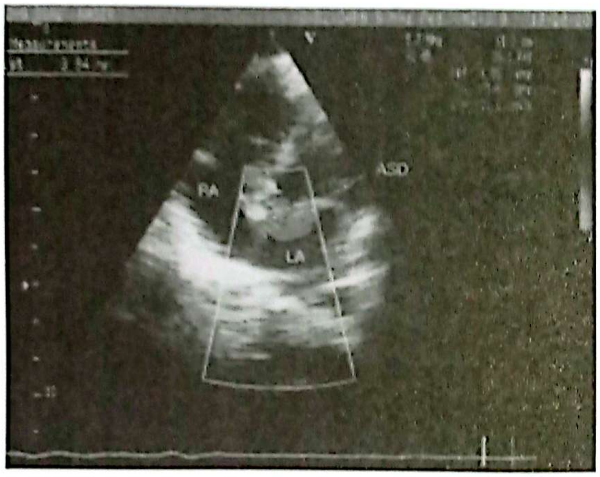

Fig. 2(c)

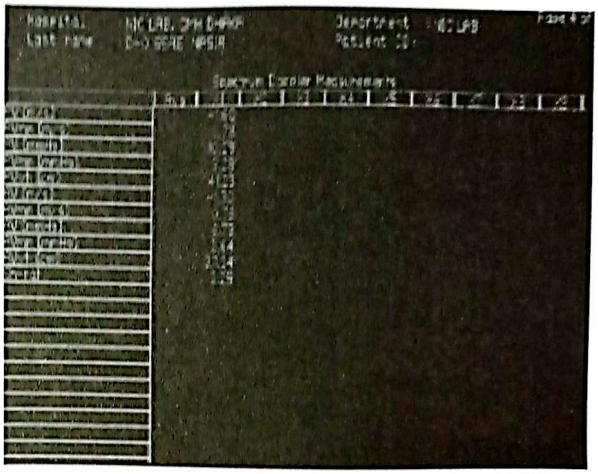

Fig. 2(d)

ASD : Qp / Qs estimation

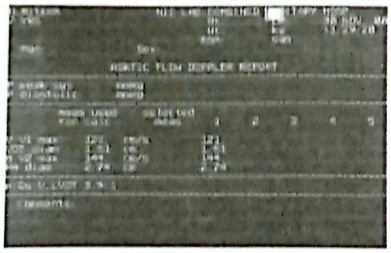

Fig. 3(a)

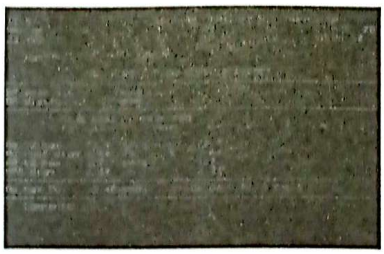

Fig. 3(b)

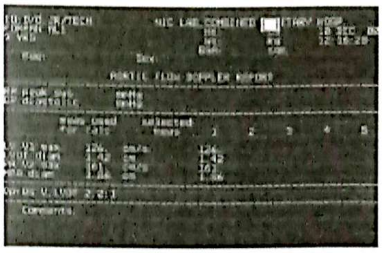

Fig. 3(c)

Qp / Qs estimation : Simplified method

Discussion:

The usefulness of a pulsed Doppler echocardiographic technique in estimating Qp/Qs has been reported in young patients with a variety of congenital intracardiac shunt diseases. Previous work has suggested that the noninvasive Doppler echocardiographic technique can be used to measure blood volume accurately when compared with invasive measures of cardiac output. In these reports, the right & left ventricular output values were obtained from the measurements of pulmonary & aortic flow velocities & diameters respectively. However, patients with ASD frequently have disturbed pulmonary flows due to high flow rates with or without dilated main pulmonary arteries.

All patients with ASD had 2D, M mode & colour Doppler echocardiography. 25 patients had

secundum type of ASD (73.1%) & 7 had sinus venosus (21.9%). Doppler derived pulmonary to systemic shunt ratio (Qp/Qs) ranged from maximum 10.5 to minimum 1.10. Mean (± SD) Qp/Qs was 3.13 ± 1.83.

Doppler estimated Qp/Qs was done by conventional method (VTI method) in all the patients. It showed a significant correlation with catheter derived Qp/Qs.

All patients underwent cardiac catheterization. The development of the Qp/Qs ratio from oximetric data was undertaken because of difficulties in measuring oxygen consumption & oxygen content. This ratio has become a well established part of clinical practice. The presence of a shunt was demonstrated by visualization of contrast passage from left to right on cineangiogram.

In patients with ASD mean (± SD) Qp/Qs at catheterization was 3.31 ± 1.93. Qp/Qs ranged from maximum 12.10 to minimum 1.

Correlation with Doppler flow with catheterization-derived Qp/Qs:

In patients with ASD the correlation coefficient for invasively determined Qp/Qs versus Doppler estimated Qp/Qs was .95 (standard error of estimate .28) & the of regression passed close to the origin.

Cloez et al (1988) described that Doppler derived Qp/Qs correlated well with oximetric Qp/Qs ratios (r= 94). Kitabatake et al (1984) described a similar correlation between these methods (r= .92). Barron et al (1983) described a similar study in which they found a good correlation between Doppler & catheter derived studies (r= 85). This good agreement was found even in patients with pulmonary hypertension.

In patients with ASD, right ventricular stroke index increased, but left ventricular stroke index was normal. These findings suggest that the systemic flow is maintained at normal levels in patients with ASD. Although there is still controversy about whether systemic flow is decreased or not in adult ASD patients without heart failure, it seems that the increase in pulmonary flow rather than the decrease in systemic flow accounts for the increase of Qp/Qs in patients with ASD.

Conclusion

The result of this study clearly indicates that the Doppler technique allows the non-invasive evaluation of Qp/Qs with a high degree of accuracy & allows determination of the size of different shunt diseases by the conservative assessment of shunt magnitude.

In isolated congenital heart diseases, surgery without cardiac catheterization had been done in last ten years in different countries including Bangladesh. All the data obtained during cardiac catheterization was not available in Doppler studies previously. Qp/Qs is one such important haemodynamic data. It also indirectly enables to estimate PVR. This study not only enhanced the accomplished in Doppler assessment of haemodynamic measurements but also gives a rough idea of PVR, the single most important determinant of patient undergoing surgery.

The technique appears promising in the evalmation of the surgical closure of different shunt diseases. It is important to consider that high quality Doppler signals are necessary for accurate measurements & reliable results.

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QRS Duration in Patient WITH AMI Predictive of Extensive Myocardial Damage

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Abstract:

This prospective study was carried out in the department of Cardiology in National Institute of Cardiovascular Diseases, Dhaka during the period of January 2005 to June 2005. This study was undertaken to see the relation of QRS duration with indicator of myocardial damage in patients with acute myocardial infarction. A total of 200 patient with acute myocardial infarction admitted in coronary care unit were included in the study by some inclusion and exclusion criteria. These patients were categorized by QRS duration into group I (>O. 10 sec) and group II (<O. 10 sec). Patients were followed up clinically, electrocardiographically and echocardiographically. There were no significant difference found between the two groups in respect to age, sex and risk factors (p>0.05). Indicator of myocardial damage such as CK-MB, anterior myocardial infarction and left ventricular dysfunction determined by LV EF are significantly more in group I than group II. Other evidence of myocardial damage like prolonged hospital stay, recurrent or persistent chest pain, heart failure, death occurred more in group I than group II. So prolong QRS duration in patients with AMI is predictor of more myocardial damage.

[Chest & Heart Journal 2005; 29(1) : 33-37]

Introduction:

Following acute myocardial infarction, prognosis depend on extend of myocardial damage, with a larger infarction leading a worse prognosis[1,2]. The 12 leads electrocardiogram is the most readily available non-invasive test for the detection of myocardial damage. The utility of the ECG has been overshadowed by the ability of the echocardiography and nuclear cardiology to evaluate possible myocardial damage and cardiac dysfunction. However, several studies have shown that a normal 12 leads ECG is a relatively sensitive and specific marker for normal left ventricular function. Resting left ventricular function is one of the most important factors for risk stratification after acute myocardial infarction. The left ventricular function after acute myocardial infarction depends on ischemic area, size of infarction or extends of myocardial damage and functional status of the residual myocardium[2,3]. A number of studies investigate the ability to estimate ischemic area at risk, predict final infarct size or assess prognosis by the admission electrocardiogram. Most of the studies concentrated on either the number of leads with ST elevation (or deviation) or the absolute value of ST elevation (or deviation) and have yielded conflicting results[2,4,5,6]. All these studies were based on the assumption that each lead represents the same amount of myocardium and that a similar size of ischemic area in different segments of the left ventricle will result in similar magnitude of ST deviation in the same number of leads. However, the 12-lead electrocardiogram equally represents not all myocardial regions. Furthermore, involvement of opposite regions may cancel or augment ST deviation. To overcome the unequal representation of the myocardium by the different leads, another

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technique has been suggested[8,9]. In this technique, the maximal points of the Selvester QRS score [10,11] are given for every lead with ST elevation. The sum of these points time three is considered to represent the actual size of the ischemic myocardium at risk as a percentage of the left ventricle. It is time consuming and difficult to practice. Some investigator also concentrated on QRS duration for predicting prognosis after acute myocardial infarction for the developing counties like Bangladesh where medical facilities are very limited and various invasive and non-invasive cardiac investigations are not widely available as well as very costly. Considering these factors a cheaper and easily available 12-leads ECG help to predict the extend of left ventricle damage and prognosis in acute anterior wall myocardial infarction as well as used for planning early management and for long-term therapy.

Materials and methods :

This prospective study was carried out in the department of Cardiology in National Institute of Cardiovascular Diseases, Dhaka during the period of January 2005 to June 2005. This study was undertaken to see the relation of QRS duration with indicator of myocardial damage in patients with acute myocardial infarction. A total of 200 patient with acute myocardial infarction between the age of 29 to 70 years of both sex admitted in coronary care unit were included in the study by some inclusion and exclusion criteria. These patients were categorized by QRS duration into group I (>0.10sec) and group II (<_0.10sec). Patients were followed up clinically, electrocardiographically and echocardiographically. Indicator of myocardial damage such as CK-MB, anterior myocardial infarction, left ventricular dysfunction determined by LV EF, heart failure and death evaluated in both groups.

The LV dysfunction of the study patients was also categorized into following on the basis of ejection fraction

Mild : Mean percent of EF 45-54

Moderate : Mean percent of EF 35-44

Severe : Mean percent of EF <35

Patient with typical left or right bundle branch block, pacemaker rhythm and electrolyte disturbance were excluded from this study.

Results and Observations:

A total of 200 patients were evaluated by electrocardiography. The patients were categorised into Group I, 70(35.0%) having QRS duration >0.10 sec and Group II ,130(65.0%) having QRS duration ≤ 0.10 sec. The mean (±SD) age of the patients was 50.9±8.0 years. No statistically mean age difference was found between Group A and Group B (p>0.05). It was evident that out of 200 patients, 85.0% were male and 15.0% were female. Out of 200 patients, 65.0% were smoker followed by hypertension (32.0%), dyslipidaemia (30.0%), diabetes mellitus (23.0) and family history of ischemic heart disease (15.0%). No statistically significant difference was between two groups. A statistically significant mean difference was found in systolic and diastolic blood pressure between two groups (p<0.05) (Table- 1).

Table 2 shows anterior myocardial infarction more in group I , and statistically significant difference was found between Group I and Group II (p<0.05).

Table I

Clinical Parameter

Clinical parameter	Group I	Group II	Total	p value
	n=70	n=130	N=200	
Systolic BP mmHg	127.0±29.2	167.3±40.7	141.1±38.6	0.001^S
Diastolic BP mmHg	77.5±16.0	99.8±23.0	85.3±21.5	0.001^S

p value reached from unpaired student's t test
NS= Not significant (p>0.05)
S=Significant (<0.05)

Table-II

ECG presentation

ECG presentation n=70	Group I n=130	Group II N=200	Total value	p
Anterior	46(65.7)	64(49.2)	110(55.0)	0.018^{5}
Inferior	24(34.4)	66(50.8)	90(45.0)	

N.B. Figure in parenthesis indicate percentage, p value reached from chi-square analysis S= Significant (p<0.05).

Table 3 shows, a significant difference was found in P-R interval and QRS duration indicating group I had higher P-R interval and QRS duration (p<0.05).

Table 4 shows statistically significant mean difference between two groups both at admission and at 6 hours after admission (p<0.05) indicating serum CK-MB markedly rises among the group I.

Table V shows echocardiographic mean percent of ejection fraction was 38.1±6.4 in group I and 56.4±9.2 in group II. It was found that the mean percent of ejection fraction was significantly lower in group I than group II (p<0.05).

Table-III

Electrocardiographic findings

Findings	Group A n=70	Group B n=130	Total N=200	p value
Rate /min	81.9±18.32	76.3±16.5	85.3±17.5	0.118^{ns}
P-R interval	0.16±0.003	0.14±0.003	0.15±0.003	0.001^{5}
QRS duration in sec	0.12±0.09	0.07±0.02	0.09±0.02	0.001^{5}

N.B. Figure in parenthesis indicate percentage, p value reached from chi-square analysis, NS= Not significant (p>0.05)

Table-IV

Cardiac enzymes

Cardiac enzyme	Group A n=70	Group B n=130	Total N=200	p value
CK-MB at admission mg/dl	49.2±6.2	39.5±6.9	42.9±8.0	0.001^{s}
CK-MB at 6 hours mg/dl	57.3±5.0	47.3±8.5	50.8±8.8	0.001^{s}

p value reached from unpaired student's t test
S= Significant (p<0.05).

Table V

Mean percent of ejection fraction by echocardiography

Ejection fraction	Group I n=70	Group II n=130	Total N=200	p value
<35	24(34.3)	0(0.0)	24(12.0)	0.001^{5}
35-44	28(40.0)	14(10.8)	42(21.0)	
45-54	18(25.7)	30(23.1)	48(24.0)	
>_55	0(0.0)	86(66.2)	86(43.0)	
Mean±SD	38.1±6.4	56.4±9.2	50.0±12.1	$*0.001^{S}$

N.B. Figure in parenthesis indicate percentage, p value reached from chi-square analysis, * p value reached from unpaired student's t test, S= Significant (p<0.05).

Chest pain (persistent/recurrent) developed in 40 patients, 26 in group I and 14 in group II. Killip's class II to IV heart failure developed in 34 patients, 32 in group I and 2 in group II. 6 patients died, all from group I.

Discussion:

The major determinants of the immediate and long-term outcome of acute myocardial infarction are the size of infarct and functional status of the residual myocardium. The value of the electrocardiogram in diagnosis and detection of location of myocardial infarction is well established, however, its use for predicting extent of myocardial damage has not been well defined. Therefore, this study was undertaken to evaluate the relationship between QRS duration and extent of myocardial damage by some indicator like CKMB, location of MI, LVEF. On the basis of QRS duration, the study subjects were categorized into Group I (QRS duration >0.10 sec) and Group II (QRS duration <0.10 sec). It was evident that the cardiac enzymes such as CK-MB was significantly rises among the group I both at the time of admission and after 6 hours of admission ($p<0.05$). The elevation of serum cardiac enzymes are indicative of severity of myocardial damage more in group I. Area of myocardial tissue involvement in anterior surface is larger than others and more in group I. Left ventricular ejection fraction (LVEF %) was determined on every patient by 2D-Echo by modified Simpson method. In patient with QRS duration (>O.10 sec) were with LV systolic dysfunction (EF<55%) that is longer the QRS duration lower the ejection fraction i.e. more LV dysfunction with correlation analysis there was inverse relation between QRS duration and ejection fraction (EF) following AMI. Murkofsy et al. 12 (1998) found that longer the QRS duration on surface ECG predicts the greater is the left ventricular dysfunction. Palmeri et al.[13] (1982) in his study found that more the QRS score lesser is the LVEF but there is no relation with QRS duration in current study. The R-wave score correlate weekly with the value of the LVEF. In hospital complication predominant in group I patients also indicate more myocardial damage.

Conclusion:

Cardiac enzyme CK-MB, less LV EF, more anterior MI in group I indicate more myocardial damage. So, prolonged QRS duration in patients with AMI is the predictor of extensive myocardial involvement, indicative of LV systolic dysfunction. QRS duration also predicted the early hospital out come i.e. longer the QRS duration worse the prognosis. So careful measurement of QRS duration in AMI patient will detect high risk patient and will also help in proper and prompt management of such patients.

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Study of Initial Resolution of Commonly Used Parameters of Acute Phase Response in Patients Receiving Treatment for Pulmonary Tuberculosis

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Abstract:

Monitoring of response to anti-tubercular drugs in PTB patients is an important part in the management of PTB patients. As the different acute phase response parameters resolved at different rates in the course of anti- tuberculosis therapy in PTB patients, the resolution of these parameters may be used as monitoring tool for the initial response to anti-tubercular drugs. In this study the differential rates of resolution - six commonly used simple parameters of acute-phase response - (i) blood C-reactive protein concentration, (ii) blood hemoglobin concentration, (iii) ESR, (iv) body weight and (v) anorexia were evaluated weekly for the first month and lastly at the end of the second month, and (vi) body temperature was recorded daily for the first two months of anti-tubercular drug treatment.

This prospective study was conducted in the National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka for a period of one year starting from January 2004 to December 2004. The main objective of the study was to elucidate the initial resolution of different commonly used acute phase response parameters in PTB patients receiving anti-TB drugs. Total number of enrolled patients was 272. Among them 145 were AFB excretor in their sputum and 127 patients had no AFB in their sputum.

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The mean age of the study subjects was 33.8±12.4 years ranging from 15-54 years with a male: female ratio of 1.6:1. The mean body temperature, blood hemoglobin concentration, ESR, blood C-reactive protein concentration and body weight for the study subjects on admission prior to initiation of specific therapy were 38.37±0.68°C, 9.62±1.03 gm/dl, 80.37±27.06 mm in 1$^{5'}$ hour, 47.58±17.06 mg/Land 41.13±5.55 respectively and 264 (97.1%) had the subjective complaint of anorexia. Blood CRP concentration resolved significantly ($p< 0.05$) at 2 weeks of treatment with mean percent improvement 10.39±8.23%, 43.83± 16.11% and 83.57±7.78% at 2nd week, 1st month and 2$^{"d}$ month respectively. The mean body temperature also resolved significantly ($p> 0.05$) at 2'n^{d} week and by 2 week 43.4%and by 1 month 89.7% patients became afebrile. The blood hemoglobin concentration improved significantly at V week of treatment ($p< 0.05$) and the mean improvements at 1" month and 2nd month were 0.58±0.25 gm/dl and 1.16±0.49 gm/dl respectively. These three acute phase response parameters were proved to be sensitive early markers of response to treatment. On contrast, ESR, body weight and anorexia were slower to resolve. ESR remained almost unchanged at 1s^{t} month and at 2 nd month of treatment values >30 mm in 1st hour was observed in 66.9% cases.

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No statistically significant differences for these parameters were observed between sputum smear positive and sputum smear negative patients ($p > 0.05$ for all parameters). In addition, in this study, association of older age, lower socioeconomic status, prolonged duration of fever, poorer nutritional status, and low initial hemoglobin and high initial ESR values produced delayed response to treatment.

Introduction:

Tuberculosis is at least as old as mankind, and the history of the disorder is intertwined inevitably with the history of civilization. The battle against TB is composed of (i) diagnosis (ii) treatment and follow up (iii) vaccination and (iv) prevention. Objective assessment of any response to treatment is an important part of management. In microbiologically confirmed cases, sputum microscopy and culture for mycobacterium tuberculosis are the primary tools for monitoring the response to drug treatment. But in addition to these, monitoring of parameters of acute phase response may provide a valuable means of making such an assessment. Moreover, a large number of PTB cases cannot be diagnosed micro biologically. In these cases anti-tubercular drugs are instituted on the basis of other supporting evidences like clinical history, radiological evidences, Mantoux test, pleural fluid study and pleural biopsy and so on. In such a case, objective assessment of any response to treatment is important and commonly used parameters of acute-phase response can be evaluated for successful resolution of PTB during the early course of treatment. The term 'acute-phase response' refers to diverse systemic effects that accompany inflammation. The response includes changes in plasma concentration of many proteins synthesized by liver, together with a wide range of physiological, biochemical and nutritional changes. Conditions that give rise to an acute phase response include infection, trauma, surgery, burns, tissue infarction, advance carcinoma and both immune and crystal mediated inflammatory disorders. Elements of acute phase response include acute phase proteins, anemia, ESR, body weight, fever, anorexia etc. Though these common acute phase response parameters have little diagnostic specificity, but serial assessment may reflect resolution of inflammatory disorders like pulmonary tuberculosis (Gabay and Kushner, 1999)[1].

Patients treated for PTB have an exponential decrease in mycobacterial burden during the early course of multi-drug treatment. This decrease is paralleled by similar reduction in plasma cytokines such as IL-6, which are key in the induction of the acute-phase response. Thus, in patients in responding to anti-tubercular treatment, similar reduction in acute-phase response might also be expected to occur. In this study the differential rates of resolution of six commonly used simple parameters of acute-phase response - (i) serum C-reactive protein concentration, (ii) blood hemoglobin concentration, (iii) ESR, (iv) body weight, and (v) anorexia were evaluated weekly for the first month and lastly at the end of the second month, and (vi) body temperature was recorded daily for the first two months of anti-tubercular drug treatment.

Materials and Methods:

It is a prospective sequential study.

The study was carried out in Department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka.

The study was conducted from January 2003 to December 2004.

Suspected cases of active pulmonary tuberculosis where both sputum smear positive and sputum smear negative patients who fulfilled the following inclusion and exclusion criteria were included in this study.

Initially 287 consecutive patients were included in the study. But during the study period 6 patients died, 4 patients developed drug induced complications, 3 patients were discharged on request and 2 patients were absconded. These 15 cases were excluded from the study and finally the total number of patients who completed the study was 272. Among them 145 were AFB excretor in their sputum and here in after referred to as 'SS +ve group' ($n = 145$) and 127 patients had no AFB in their sputum and here in after referred to as 'SS -ve group' ($n = 127$). The total patients who completed the study were referred to as 'total patients' ($n = 272$).

It was a consecutive sampling study.

Criteria for Selection of Patients. Criteria of inclusion

Clinical history suspected of active pulmonary tuberculosis with one or more of the following symptoms -

Fever, cough, chest pain, anorexia, hemoptysis, weight loss

Either patients with at least 2 sputum specimens positive for AFB out of 3 consecutive samples or 3 (three) sputum specimens negative for AFB and persisting symptoms after a course of antibiotics.

Pulmonary infiltration with or without cavity in chest radiograph.

Patients of ages 15-54 years.

Criteria of exclusion

Significantly disabled patients due to poor general condition.

Patient of PTB getting anti-tubercular drugs presently.

Patients having H/O taking anti-tubercular drugs previously.

Patient of PTB with associated major systemic diseases like CRF, DM, CLD, collagen disease, malignancy, cardiovascular disease, COPD, asthma etc.

Patients of PTB with blood hemoglobin concentration less than 8 gm/dl.

Patients who do not sign the contact form

Study Design

In the first phase of the survey a standard questionnaire proforma and patient's record form was designed with a view to collect patients who could serve study population. This was done with the patients coming to the Department of Respiratory Medicine of NIDCH from January 2004 to December 2004. Patients meeting the criteria for selection were enrolled in the study.

Written consents from all studied patients were obtained after discussion in details about the study procedure.

In each case information about the patient was obtained and recorded in the questionnaire proforma. The author himself filled up the questionnaires.

The accumulated questionnaires were analyzed to find out the patients who meet clinical inclusion and exclusion criteria to be cases. These patients will then be subjected to step 5.

Investigations before selecting patient were done and included the following-o

- o Blood for TC DC ESR Hb%
- o Blood for CRP
- o Sputum smear microscopy for AFB (consecutive 3 samples)
- o CXR (P/A view)
- o Blood sugar
- o Tuberculin test
- o Liver function test (Bilirubin, SGPT, Alk. Phosphatase).
- o Renal function test (blood urea, serum, creatinine).

The accumulated questionnaires and pretreatment laboratory results were analyzed. The patients who met the criteria for selection were enrolled in the study as total patients. Among them, patients who showed sputum positivity for AFB in at least 2 specimens out of 3 consecutive samples were included in SS +ve group. Those who were negative for AFB in all three sputum specimens were instituted a 10 days broad-spectrum antibiotic. If no clinical improvement occurred, they were included in SS -ve group. Then the pre-treatment (baseline) values of commonly used acute phase response parameters were recorded in patients both groups. These parameters are as follows-

Serum C-reactive protein (CRP) concentration

Blood hemoglobin (Hb) concentration

Erythrocyte sedimentation rate (ESR)

Body weight Fever

Anorexia

The enrolled patients then received directly observed short course chemotherapy in standard drug dosage in accordance with the guidelines of the National Tuberculosis Program 2003. No specific nutritional support, other than 10 mg Pyridoxine daily, was given to patients during the study period.

The parameters of acute phase response - body weight, blood hemoglobin concentration,

erythrocyte sedimentation rate, serum C-reactive protein concentration & anorexia were measured again weekly for the first month & then at the end of second month of therapy to assess their differential rate of resolution. To evaluate the pattern of resolution of fever, body temperature was recorded daily in study subjects for the first two months after start of therapy.

As the comparative index of response to treatment and resolution of acute phase phenomena chest radiograph and sputum microscopy for AFB (3 samples) were further tested on two occasions- at 1st month and 2nd month of treatment.

All data were recorded and processed in a predetermined proforma.

All the collected data were compiled and tabulated in a master sheet and analyzed statistically using the Statistical Package for Social science (SPSS) program, version 12.0, in computer. Chi square test, unpaired student's t test and paired student's t test were used to find out the differences of different variables. A two-tailed p value less than 0.05 was considered as significant.

Table-I

Age distribution of the study subjects

	Study subjects			
Age in years	SS+ve group	SS-ve group	Total patients	P value
<25	48 (33.1)	37 (29.1)	85 (31.3)	0.949**
25-34	38 (26.2)	28 (22.0)	66 (24.3)	
35-44	29 (20.0)	26 (20.6)	55 (20.1)	
45-54	30 (20.7)	36(283)	66 (24.3)	
Total	145 (53.3)	127 (46.7)	272 (100.0)	
Mean±SD	33.4±12.2	34.1±12.4	33.8±12.4	0.646

Table-II

Sex distribution of the study subjects.

	Study subjects			
Sex	SS+ve group	SS –ve group	Total patients	p value
Male	90(62.1)	78(61.4)	168(61.8)	0.912
Female	55(37.9)	49(38.6)	104(38.2)	
Total	145(53.3)	127(46.7)	272(100.0)	

Table-III

Smoking status of the study subjects.

Smoking status	Study subjects: Male (n=168)			Study subjects: Female (n=104)		
	SS +ve	SS -ve Group	p value group	SS +ve	SS -ve group	p value group
Never smoker	44 (48.9)	37 (47.4)	0.791*	52 (94.6)	43 (87.7)	0.314*
Ex-smoker	29 (32.2)	23 (29.5)	1 (1.8)	4(8.2)		
Current smoker	17 (18.9)	18 (23.1)	2 (3.6)	2(4.1)		
Total	90(100)	78(100)		55(100)	49(100)	

Table-IV

Nutritional status of the study subjects

Categories	SS+vegroup	8S 'vegroup	Total patients	p value
Severe Undernutrition	21(145)	13(10.2)	34(125)	0.706
Moderate undprnutrition	71(4&0)	S2(48.8))	133(48.S)	
Mild undeonutrition	42(29.0)	40(31.5)	82(30.1)	
Normal	11(7.5)	12(9.5)	23(8.5)	
Over weight	0(0.0)	0(0.0)	0(0.0)	
Total	145(53.3)	127(46.7)	272(100.0)	

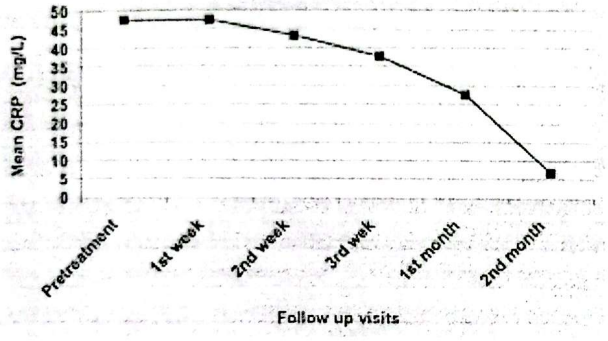

Fig.-1 : *Changes in mean blood CRP concentration in study subjects at different follow up visits.*

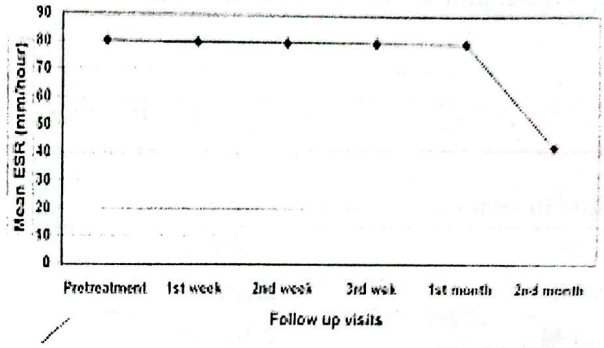

Fig.-2 : *Change in mean ESR in study subjects at different follow up visits.*

Table-V

Comparison of resolution of selected acute phase response parameters in study subjects at the end of 1st month of treatment

Acute Phase Response Parameters	Study subjects: Total patients (n=272)				P value
	SS+ve group (n=145)		SS-ve group (n=127)		
	Mean±SD		Mean±SD		
Fever (Body temperature in Celsius)	37.08±0.51		36.98±0.31		0.056*
Serum CRP (mg/L)	28.38±15.83		26.64±14.13		0.343* Concentration
Blood Hemoglobin Concentration (gm/dl)	10.13±0.97		10.28±1.09		0.239*
ESR (mm in 1st hr.)	79 37±26.57		80.48+26.26		0.753*
Body weight (kg)	40 75±5.52		41.62±5.55		0.195*
	No.	%	No.	%	
Anorexia					
Present	133	91.7	120	94.5	0.372**
Absent	12	8.3	7	5.5	

Discussion

The sociodemographic data of the study subjects were evaluated. Patients within 15-54 years of age were enrolled in this study. This particular age range was considered from the fact that in developing countries the majority of disease and death occurs among the most economically active segment of population: more than 75% among 15 to 54 years of age (The economic impact of tuberculosis, 2000). The mean age of the study subjects was 33.8±12.4 years ranging from 15-54 years. The mean age of patients of SS +ve patients was 33.4±12.2 years and that of SS -ve patients was 34.1±12.7 years and the highest proportion of the study subjects (31.3%) were below 25 years of age group. Analysis revealed that no statistically significant mean age difference was found between patients with sputum smear positive (SS +ve group) and sputum smear negative (SS -ve group) ($p>0.05$). This mean age of the patients was consistent with the findings of Ahsan (2004)[2] who worked with adult pulmonary tuberculosis patients at tertiary level in our country and the increased frequency of pulmonary tuberculosis patients in younger age group correlated with the global data.

Analysis of the patients in respect to sex showed male predominance with a male: female ratio of 1.6:1 and there was no statistically significant sex difference in between the SS +ve patients and SS -ve patients ($p>0.05$). This finding correlated with the finding of Chowdhury (2001)[3] where male: female ratio was 1.4:1. The male preponderance may be explained by greater prevalence rate of male for pulmonary tuberculosis globally and differences in health care seeking behavior between men and women.

Smoking was not a common finding in our study. About two-thirds of the study subjects were never smoker (64.7%) though the proportions of ex-smoker and current smoker were higher in male than female in both SS +ve patients and SS -ve patients This finding was almost similar to the findings of Ahsan (2004) where 67% were non-smoker and also to that of Aziz et al. (2002)[4] where 85% were non-smoker.

In present study, most of the patients belonged to the near poor (45.6%) and poor (28.7%) socioeconomic groups with average monthly incomes Taka 3239- 6253 and Taka :_3238 respectively. This pattern of distribution of socioeconomic status of the study subjects was observed as people of near poor and poor groups are predisposed to malnutrition of several types that allow tuberculosis infection.

The clinical information related to the present study was analyzed in detail. Though body mass index (BMI) parameter does not indicate the corporal composition, it was performed to assess the nutritional profile of the study subjects since it gives an idea about the percentage of malnutrition in adults. Malnutrition based on the BMI as the anthropometrical parameter, most of our study patients (9 1.5%) belonged to undernutrition groups of varying severity and there was no statistically significant difference between sputum smear positive and sputum smear negative patients in term of nutritional profile ($p> 0.05$). This pattern of nutritional status of the study patients may be explained by poor immunity, allowing re-emergence of previous infections or even newer infections of tuberculosis. Our presenting findings in respect to nutritional status were in concordance with those established by Araujo et al. (2003)[5].

All the patients enrolled in our study presented with fever. In most cases the fever was low grade (84.9%), intermittent (73.8%), >1 month in duration (68.7%), associated with night sweat (68.8%) with evening rise of temperature (78.3%). The mean temperature on admission was 38.37±0.68°C and not associated with chill and rigor (80.9%). There was no statistically significant difference between the sputum smear positive and sputum smear negative patients by characteristics of fever ($p> 0.05$ for all variables). Similar distributions of patterns of fever in pulmonary tuberculosis patients were reported in previous studies (Ahsan, 2004), (Chowdhury, 2001).

On admission all the study subjects had the subjective complaints of anorexia and history of weight loss to a wide range (10-75%). The frequencies of these two complaints were a bit higher than those studies established at home (Chowdhury, 2001) and abroad (Aziz et al. 2002).

In this study we evaluated the selected laboratory parameters on admission related to the study. The

mean blood hemoglobin concentration, ESR and blood C-reactive protein concentration for the study subjects on admission prior to initiation of specific therapy were 9.62±1.03 gm/dl, 80.37±27.06 mm in 1st hour and 47.58±17.06 mg/L respectively. 46.7% patients had no acid-fast bacilli in their sputum and 53.3% showed sputum positivity ranging from scanty to 3+. There were no statistically significant differences between the sputum smear positive and sputum smear negative patients in respect to these parameters ($p>0.05$ for all parameters). The majority of sputum smear positive patients (53.1%) and sputum smear negative patients (56.6%) showed moderate lesions and minimal lesions respectively in their chest radiographs and the group difference by radiological involvement was statistically significant ($p<0.05$). The increasing radiological lesions in sputum smear positive patients might be due to increase bacillary load.

All these findings were more or less consistent with those established by Sezer et al. (2001)[6] of Turkey who reported mean hemoglobin 10.2±0.3gm/di, ESR 78±22 mm/hour and CRP 44.4±26.0 mg/L, by Immanuel et al. (1990)[7] of India where CRP was 7.2±6.2 mg/dl and by Aziz et al. (2002) of Pakistan where hemoglobin 11.01±1.77 gmldl and ESR 58.19 mm/hour were observed in their patients of pulmonary tuberculosis before starting specific anti-TB therapy. But regarding sputum positivity our finding differs from that published by WHO report 2004, country profile: Bangladesh[8] where sputum smear positive case detection rate was shown as 38%. The increased sputum positive case detection rate may be explained by referral of positive cases from different parts of the country to our National Institute, the tertiary referral center in the country.

Patients treated for pulmonary tuberculosis have an exponential reduction in mycobacterial burden during the first 2 months of multidrug bactericidal treatment (WHO report, 1979). This reduction is parallel by similar reductions in plasma cytokines such as IL-6, which are key in the induction of the acute phase response (Gabay and Kushner, 1999). In this study our main objective was to elucidate the initial resolution of six commonly used acute phase response parameters in pulmonary tuberculosis patients receiving anti-TB drugs. We found a significant resolution of fever (mean body temperature) and mean blood CRP concentration in 2 weeks and mean blood hemoglobin concentration in 3 weeks in our patients after initiation of short course chemotherapy, WHO category I regimen. In contrast, neither mean ESR nor mean body weight altered significantly until after 2 months of treatment. The subjective complaint of anorexia was also not improved significantly until the 2"° month.

Our study revealed that of 272 pulmonary tuberculosis cases (100%) who met the inclusion criteria presented with fever with the mean body temperature 38.37±0.68°C. At the end of 1st week of treatment, though the mean temperature had fall (38.34±0.88°C) it was not statistically significant ($p> 0.05$). At 2"d week of treatment, the mean body temperature became 37.85±0.99°C and the resolution of fever were statistically significant ($p< 0.05$). For our study, based on standard textbook recommendation, any patient with a temperature greater than 37.2°C was considered febrile. We were also convinced from our experience that patients were considered afebrile when their temperature remained normal for at least 48 hours without antipyretics. The cumulative percentage of afebrile patients after initiation of anti-tuberculosis drug therapy in present series was by 1 week 15.1 %, by 2 week 43.4%, by 3 week 81.6%, by 1 month 89.7% and by 2 months 100% patients. The earliest period of fall of fever was 5 days after start of chemotherapy.

Blood CRP concentration was elevated in all patients (100%) on admission (mean±SD: 47.58±17.06 mg/L). At the end of 1st week of treatment, though the blood CRP concentration decreased a little from the baseline value (mean difference±SD: 0.06±1.09 mg/L), it was not statistically significant ($p>0.05$). But at the end of 2"d week, the mean CRP concentration approached to a level of 43.30±18.46 mg/L with mean percent improvement 9% and the resolution was statistically significant ($p<0.05$). Subsequent follow up visits showed further rapid resolution at 1 month and 2 months with mean % improvement of about 40% and 85% respectively. IL-6, the principal cytokine that induces CRP synthesis, rapidly decreases in concentration in the blood of patients treated for pulmonary tuberculosis; furthermore, CRP itself has a very short half-life

in the circulation (Gabay et al. 1999). Hence, a rapid reduction in mean blood CRP concentration was observed in the patients treated in this study.

Suppression of blood hemoglobin concentration is common during inflammatory processes and is attributed to cytokine mediated reduction in erythropoietin secretion, reduced responsiveness of erythroid precursors to the hormone, and impaired mobilization of iron from macrophages (Means, 1995)[9]. In this study, an increase in hemoglobin was seen in the majority of patients by 2 weeks and the improvement was not statistically significant (p> 0.05). But an increase in hemoglobin over the baseline value (mean±SD: 9.62±1.03 vs. 9.94±0.99 gm/dl) was observed in all by 3 weeks of anti-tuberculosis treatment, reflecting a rapid restoration of hematopoiesis. This increment was proved statistically significant (p<0.05). Further improvements were observed in subsequent follow up visits and at 1st and 2nd month the mean percent improvement were about 6% and 12% respectively.

The erythrocyte sedimentation rate (ESR) determination is a simple and inexpensive laboratory test that is frequently ordered in clinical medicine. This test measures the rate at which erythrocytes fall through plasma, and is primarily affected by the concentration of fibrinogen in the blood (Deodhare, 2001)[10]. Prior to anti-tuberculosis treatment, ESR was elevated >30 mm/hour in 261 patients (96%). The mean percent improvement of ESR at 1 month was 0.07±7.39%, and the mean ESR at this time-point was almost similar to that at baseline (mean±SD: 80.37±27.06 vs. 79.89±26.39 mm/hour). The mean difference was not statistically significant (p> 0.05). Although the mean ESR decreased significantly from baseline during the 2nd month (80.37±27.06 vs. 43.02±21.01 mm/hour, p< 0.05) of treatment, values >30 mm/hour were observed in 66.9% cases at this time-point. The half-life of fibrinogen is much longer than that of many other acute phase proteins, including CRP, and this may partially explain the relatively slow fall in ESR that occurred among the patients in this study.

Weight loss has been attributed to the effects of cytokines, notably TNF-a, IL-1(3, IL-6, and IFN-y. During the 1s[t] month of treatment, at different follow up visits it was observed that body weight remained almost unchanged despite low BMI at diagnosis. Moreover, 8 patients lost their weights at first week and at the end of 1[6'] month of treatment the mean body weight was almost similar to that at pretreatment value (mean±SD: 41.13±5.55 vs. 41.15±5.54 Kg). The mean difference was not statistically significant (p> 0.05). At the end of 2nd month, the mean body weight increased by about 2.8% over baseline value and the rise was statistically significant (p> 0.05). Plasma IL-6 and IFN- y concentrations decrease rapidly during treatment of pulmonary tuberculosis, plasma TNF-á levels increase transiently early in treatment (Lawn et al. 1999)[11]. This transient rise in TNF-á may be associated with slow rise in body weight with ongoing anti-tuberculosis treatment observed in our study.

Anorexia has also been attributed to the effects of cytokines in inflammatory process. On admission our 264 patients (97.1%) presented with this subjective complaints and during the 1st month of treatment at different visits we observed a much slow insignificant (p> 0.05) resolution of this acute phase response phenomena among the study subjects. At the end of 2"" month, though the resolution was statistically significant (p< 0.05), about one-third patients (31.6%) still remained anorexic despite anti-TB treatment. The slower resolution and persistence beyond 2 months of this phenomenon in a large number of patients in the present study may be explained partially by the presence of anemia and the anorexic side effect of anti-tuberculosis drugs.

In the present study we compared the response to anti-TB drugs between the smear positive and smear negative pulmonary tuberculosis patients by observing the differential resolution of acute phase parameters. No significant group differences were observed in the resolution of fever, blood CRP concentration, blood hemoglobin concentration, ESR, body weight and anorexia at the end of 1st month and 2[nd] month of specific anti-tuberculosis treatment (p> 0.05 for all parameters at both time-points).

In this study we also observed the association of selected sociodemographic, clinical and laboratory parameters with the resolution of acute phase response phenomenon in our pulmonary tuberculosis patients receiving anti-TB drugs. Here

we used fever as representative of acute phase response because of its quick resolution following initiation of chemotherapy and also for its easy recording procedure. We choose 2 week because many physicians assume that the duration of fever after initiation of modern chemotherapy is brief. We found significant association of age groups, socioeconomic status, nutritional status and duration of fever at presentation with the resolution of acute phase response ($p > 0.05$ for all parameters). Similar significant associations ($p > 0.05$) were observed with pretreatment hemoglobin and ESR values. We also found no significant association ($p < 0.05$) gender, smoking status, bacillary loads in sputum, and extent of radiological involvement with the resolution of acute phase response during the course of anti-TB drug treatment, These findings suggested us the link of slower treatment response in pulmonary tuberculosis patients to the followings: i) elderly patients, ii) lower socioeconomic status, iii) poorer nutritional status, iv) prolonged duration of fever, v) low pretreatment hemoglobin level, and vi) high pretreatment ESR level. The slower response in elderly patients may be explained by decline immune status in this group. Similarly slower response in patients with poor nutritional status may be explained by poor immunity and people of lower socioeconomic status have an increased propensity of having malnutrition. The association of slower treatment response with prolonged duration of fever, low pretreatment hemoglobin level and high pretreatment ESR level may be partially explained by far advancement of the illness with these clinicopathological changes.

In this study, as the comparative index of response to treatment and resolution of acute phase response phenomena chest radiograph and sputum microscopy for AFB (3 samples) were further tested on two follow up visits- at 1 st month and 2nd month of treatment. We found sputum conversion rate 44.1% at 1st month and 91.7% at 2nd month of treatment among the sputum smear positive group. All patients (n = 272) irrespective of sputum status also showed statistically significant improvement in resolution of radiological lesions at 1st month and 2nd month of treatment.

The study concluded that among the commonly used acute phase response parameters fever, blood CRP concentration and blood hemoglobin concentration resolved significantly earlier than other parameters like ESR, body weight anorexia in pulmonary tuberculosis patients receiving anti-TB treatment. This study also showed no significant differences in differential resolution of these parameters between sputum positive and sputum smear negative patients. It also suggested the significant association of age groups, socioeconomic status, nutritional status, duration of fever and initial hemoglobin and ESR levels with the resolution of acute phase response phenomena.

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REVIEW ARTICLES

Cor-Pulmonale-A Review

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Introduction:

Cor-pulmonale is one of the common disabling disease worlds wide of varying aetiologies. The common causes are COPD, restrictive lung diseases, chronic thromboembolic disease and primary pulmonary hypertension. These diseases account for 80% to 90% of all causes of cor pulmonale in the adults in the United States[1].

Certainly hypertension, coronary artery disease and cardiomyopathies account for a majority of cases of heart failure in the adult; thereafter cor-pulmonale rivals valvular heart disease in number of congestive heart failure. However the incidence of the cor pulmonale has increased over the last decade because of urbanization and environmental pollution[2].

COPD associated with right ventricular enlargement was first described in the early 1800s and the term cor-pulmonale was first used in 1931[1]. With the development of modern medical technology there is a great revolution in the field of aetiopathogenesis, diagnosis and treatment *of* cor-pulmonale including successful heart lung transplantation. So, the aim *of* this review is to present the recent information on cor pulmonale with special emphasis on aetiopathogenesis, modern non-invasive investigations and treatment.

Definition

"Cor-pulmonale" is a synonym for pulmonary heart disease. Both terms are now being used to signify right ventricular enlargement from disorders that affect either the structure or function of the lungs[13].

Now, it is defined as right ventricular enlargement with or without failure, eventually failure due to parenchymal disease of lung, pulmonary vascular diseases, chest wall diseases and any cause of hypoventilation[3].

Cor-pulmonale may be acute or chronic, depending on the underlying pulmonary disorder. In acute cor-pulmonale, as after massive pulmonary embolization, dilatation is the basis for the cardiac enlargement. Conversely, in chronic cor-pulmonale, as may occur after repeated embolization of the lungs, hypertrophy generally predominates unless heart failure supervenes to add an element of dilatation.

Aetiology And Pathogenesis:

Aetiology

There are many causes of cor-pulmonale. Any disease that affects ventilatory mechanics, gas exchange, or the vascular bed either directly, through intrapulmonary events, or indirectly, via its effect on ventilatory control or the neuromuscular apparatus of respiration, may cause cor-pulmonale[10]. A list of the various disease categories commonly associated with cor-pulmonale, along with some specific examples of each process, is presented in table-no. I.

Table-I

Aetiologies of Cor-pulmonale

1. Diseases affecting air passages of the lung and alveoli
   - a. Chronic obstructive pulmonary diseases
   - b. Cystic fibrosis
   - c. Congenital developmental defects
   - d. Infiltrative or granulomatous diseases
     - i) Idiopathic pulmonary fibrosis
     - ii) Sarcoidosis
     - iii) Pneumoconiosis
     - iv) Scleroderma
     - v) Mixed connective tissue disease
     - vi) Systemic Lupus Erythematosus
     - vii) Rheumatoid arthritis
     - viii) Polymyositis
     - ix) Eosinophilic granuloma
     - x) Malignant infiltration
     - xi) Radiation

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e. Upper airways obstruction
f. Pulmonary resection
g. High altitude disease

2. Disease affecting thoracic cage movement
   a. Kyphoscoliosis.
   b. Thoracoplasty
   c. Pleural fibrosis
   d. Neuromuscular weakness
   e. Sleep apnea syndrome
   f. Idiopathic hypoventilation
3. Diseases affecting the pulmonary vasculature
   a. Primary disease of the arterial wall
      i) Primary pulmonary hypertension
      ii) Granulomatous pulmonary arteritis
      iii) Toxin-induced pulmonary hypertension
         • Aminorex fumarate
         • Intravenous drug abuse
      iv) Chronic liver disease
      v) Peripheral pulmonic stenosis
   b. Thrombotic disorders
      i) Sickle cell disease
      ii) Pulmonary microthrombi
   c. Embolic disorders
      i) Thromboembolism
      ii) Tumor embolism
      iii) Amniotic fluid embolism
      iv) Schistosomiasis
4. Pressures on pulmonary arteries by mediastinal tumors, aneurysms, granulomata, or fibrosis.

Pathogenesis

Common factors in all cases of cor pulmonale are increased pulmonary vascular resistance (PVR) and pulmonary hypertension that causes abnormalities in right ventricular structure and function. Normal mean pulmonary artery pressure (PAP) is about 12 to 17 mmHg; PAP greater than 20 mmHg is pulmonary hypertension[15]. The effective cross-sectional area of pulmonary vascular bed must be reduced by more than 50% before any change in PAP can be detected at rest, but a higher pressure will be required to increase blood flow[s.15] Obliterative vascular diseases increase PAP by vascular occlusion, while diffuse interstitial diseases act primarily by compression and obliteration of small vessels. It is now well established, however, that arteriolar constriction is the most common cause of pulmonary hypertension[15].

The pathogenic sequence of cor-pulmonale is unknown and probably a number of mechanisms interact to produce pulmonary hypertension. Any theory regarding the development of cor pulmonale must take into account the effects of the anatomical loss of vessels, i.e. anatomical restriction of the pulmonary vascular bed, pulmonary arteriolar constriction, increased blood viscosity and increased blood flow, although their relative roles have not been, clearly defined. However the pathogenic mechanism varies depending on the underlying causes.

Clinical Features:

Diagnosis of cor pulmonale is difficult because early symptoms and signs are nonspecific'. There is often a long delay between onset of disease and ultimate diagnosis of cor-pulmonale, which must begin with recognition of a severe pulmonary disorder. Overt right heart failure is a late manifestation of chronic cor pulmonale and need not be present either to entertain or to establish diagnosis of cor pulmonale[3,6]. The clinical manifestations and criteria of diagnosis on which the clinical recognition of cor pulmonale in life depends are mentioned in the following sections which include

(1) Clinical picture of cor pulmonale secondary to pulmonary diseases with special reference to chronic bronchitis and emphysema.

(2) Clinical feature of right ventricular hypertrophy and failure.

(3) Clinical feature of cor pulmonale secondary to vascular diseases

The signs and symptoms of underlying pulmonary disease often modify clinical manifestation of chronic cor pulmonale. Diseases that affect the pulmonary parenchyma, the intrathroacic airways, or both account for the vast majority of cases of cor pulmonale. Complete discussion of all causes of cor-pulmonale is not with in the scope of this review but some features of common types of disease will be described.

Chronic Obstructive Pulmonary Disease (COPD):

COPD, by far the most common form of pulmonary parenchymal disease responsible for chronic pulmonary hypertension, consists of chronic bronchitis, emphysema, and bronchial asthma.

However, atopic asthma does not produce chronic cor pulmonale[8] and intrinsic or nonatopic asthma is often a variant of chronic bronchitis; in this discussion, COPD refers only to chronic bronchitis and emphysema exclusively.

Symptoms:

Chronic bronchitis: The characteristic symptoms of chronic bronchitis are cough, sputum, wheeze and breathlessness. This is almost confined to smokers and much more common in men than in women over the age of 40 years. At the onset, the symptoms may be so trivial that remain unnoticed. In the patients developing chronic bronchitis, the cough gradually becomes more continuous and productive; it then occurs during the day as well as in the morning and may keep him awake at night, although spontaneous cough appears to be at least partly suppressed at night in these patients 3'6. At a relatively early stage the patient's cough is usually susceptible to fog or to cold, damp weather, and wheeze and dyspnoea may also be under these conditions, confining the patient indoors. Wheeze, which was confined to the acute attacks, may become chronic throughout the winter; later, wheeze and dyspnoea may persist throughout the year.

The sputum in between attack is usually mucoid, grey or black due to residua of cigarette smoking or atmospheric pollution; later on sputum may be purulent or mucopurulent in between attacks.

Emphysema

At the pure emphysema end of the spectrum is a group of patients in whom cough, sputum and wheeze appear to be relatively unimportant and the principal disability breathlessness. There is history of severe progressive dyspnoea sometimes starting after some apparently mild infection. Within a relatively short period of time the patient becomes a respiratory invalid and may die within a few years, usually from respiratory failure without cor pulmonale, except sometimes terminally. Some of these patients reffered to as pink and puffing manage to maintain a healthy $Pa0^{2,3}$ and normal PaCO2 by hyperventilation until at late stage of their disease.

Mixed chronic bronchitis and emphysema:

By far the most common form of the disease, both clinically and pathologically, is that where bronchitis with airways obstruction and emphysema co-exist and where cough and sputum are prominent features.

Cor Pulmonale with heart failure:

In these later stages of chronic bronchitis and emphysema, when the patient is already dyspnoic, is liable to develop right-sided heart failure exacerbations. There appears to be a spectrum of constitutional responsiveness to the stimulus of hypoxia[3,9]. Those most sensitive to the hypoxic stimulus will develop pulmonary hypertension and eventually right heart failure at an earlier stage. Presentation of such patients of cor pulmonale with heart failure include increasing dyspnoea; paroxysmal cough, occasionally with syncope; and fluid retention with oedema and sometimes ascites. Physical findings of these patients are mentioned below.

Physical Signs:

The physical signs of patients with cor pulmonale fall into three groups:

(1) Those related to airway narrowing

(2) Those related to the blood gas disturbance and

(3) Those related to right ventricular dysfunction, However, here physical signs are described in general. General condition:

In the early stages of the disease the general condition may be good but those with advanced disease may become emaciated. In the later stages the patient may be cyanosed, even between exacerbations, but those with pure emphysema may not be cyanosed even though very dyspneic.

The chest:

In the later stages of the disease the chest is often barrel-shaped with kyphosis, increased anteroposterior diameter, horizontal ribs, prominent sternal angle and wide sub costal angle and presence of tracheal tug with reduced cricosternal distance.

Movement of the chest wall restricted and may largely be confined to the upper thorax. The patient may have to use his accessory muscles of respiration, the scalene and sternomastoid muscles. A rise in jugular venous pressure may be seen on expiration. In this advanced stages the costal margin may even, paradoxically, be drawn

inwards on inspiration, owing to the pull of the low, flattened diaphragm. The most important finding on percussion is the obliteration of hepatic and cardiac dullness, indicating hyper inflated lungs or emphysema. Elsewhere the note may be hyper-resonant.

Breath sounds may have a prolonged expiratory phase or be uniformly diminished. The most frequent finding on auscultation is of wheezes, which are most often expiratory but may be inspiratory as well. They are usually widespread but may be most marked at the base of the lungs. High-pitched early inspiratory crackles may often be heard at the mouth, when airflow obstruction is severe, and there may sometimes be fine inspiratory crepitations audible at the bases

The cardiovascular system:

Pulse: In chronic obstructive pulmonary disease, an abnormal pulse, "pulsus paradoxus" may be found.

Neck Veins: In corpulmonale with heart failure the jugular venous pressure is raised on inspiration with prominent 'a' and 'v' waves and giant 'a' wave may be found with functional tricuspid regurgitation.

Precordium: The apex beat may be difficult to identify and cardiac dullness may be lost due to emphysema or hyperinflation of lungs. The characteristic heave, of right ventricular hypertrophy may be palpable to the left of the lower sternum or in the sub costal angle but is often obscured by lung inflation. Because of the inflated overlying lung it may be difficult to hear the heart sounds except in the epigastrium. The second sound may be loud, especially in the second and third left intercostal spaces, when the pulmonary arterial pressure is raised, but may be soft or absent in emphysema[4,1].

There may be a right sided gallop rhythm with the third sound audible in the fourth intercostal space to the left of the sternum or in the epigastrium, with the cardiac failure of cor pulmonary there may be evidence of functional tricuspid incompetence with a diastolic gallop rhythm.

Abdomen: When the diaphragm is low, the liver may be palpable several fingers below the costal margin; with right heart failure there may be tender hepatomegaly, and pulsatile liver when tricuspid regurgitation co-exists. Ascites occur in advanced cases.

Oedema: Oedema will only be present in right-sided heart failure. It is mainly present in the dependent parts of the body.

Optic fundi: Venous engorgement may be seen in severe right-sided heart failure. Occasionally, gross carbon dioxide retention may cause papilloedema, usually thorough raised cerebrospinal fluid pressure.

Other physical findings:

Beyond the above-mentioned findings if the patient develops acute respiratory failure, cyanosis, confusion, hyper kinetic circulation may also be found. The classical signs of hypercapnea, bounding pulse, flapping tremor, palmar erythema, and papilloedema, may occur but they are inconstant and unreliable.

Investigation:

The revolutionary changes in the field of cor-pulmonale is because of the development of modern non-invasive investigation facilities such as colour Doppler, imaging techniques. Brief description of investigations is given bellow.

Haematology:

The white cell count may be raised in acute exacerbation. Polycythaemia is relatively uncommon and closely related to the degree of chronic hypoxaemia between exacerbation.

Radiology:

Radiological examinations of chest wall show the evidence of the primary disease. In COPD, the postero-anterior chest radiography may show no abnormality but more frequently the distention of the lungs result in flattened diaphragm above which the posterior portion of the 11^{th} or even 12^{th} rib may be visible. The heart may appear long and thin and the hilar vessels may be compressed with enlargement of the proximal parts of the pulmonary artery. Peripheral vascular shadows may be thinned, straightened or lost as vessels are deranged or destroyed by advancing emphysema[3,4]. On the lateral film over distension may be shown by a large retrosternal air space.

Sometimes emphysematous bullae are identified by fine hair-like margins and lack of vascular shadow, with anatomic restriction of the vascular bed, signs of pulmonary artery, right ventricular and right atrial enlargement are usually evident.

Electrocardiogram:

The aetiology of cor pulmonale is an important factor in the effectiveness of electrocardiogram to diagnose right ventricular hypertrophy. Patients with COPD have major structural and physiological changes of the lungs and chest that place serious limitations on the use of the ECG, including a flattened diaphragm, hyper extended lungs, and barrel chest deformities.

Electrocardiographic changes in cor-pulmonale

(a) *ECG criteria for cor pulmonale without Obstructive Disease of the airways**

1. Right axis deviation with a mean QRS axis to the right of +1 100
2. R/S amplitude ratio in V_1 >l.
3. R/S amplitude ratio in V_6 <1
4. Clock wise rotation of the electrical axis.
5. P-pulmonale pattern.
6. S Q3 or S1 S_2 S_3 pattern.
7. Normal voltage QRS.

(b) ECG *criteria for cor pulmonale with Obstructive Disease of the airways+*

1. Isoelectric P-wave in lead I or right axis deviation of the p vector.
2. P-pulmonale pattern (an increase in P-wave amplitude in II, III, aVF.)
3. Tendency for right axis deviation of the QRS.
4. R/S amplitude ratio in V_6 <1.
5. Low voltage QRS.
6. S1 Q3 or S_1 S_2S_3 pattern.
7. Incomplete (and rarely complete) right bundle branch block
8. R/s amplitude ratio in V_1 >I.
9. Marked clockwise rotation of the electrical axis.
10. Occasional large Q-wave or QS in the inferior or midprecordial leads, suggesting healed myocardial infarction.

Echocardiography in cor pulmonale and pulmonary hypertension

Echocardiography has been used among other non-invasive techniques, to assess right ventricular hypertrophy and/or dilatation, right ventricular function and the degree of pulmonary hypertension. Measurement of right ventricular wall thickness and end-diastolic internal diameter by M-mode echocardiography have been used to assess right ventricular hypertrophy and have shown good correlation with necropsy data although neither was a sensitive indicator of right ventricular hypertrophy[4,5]. The major problem associated with the technique of M-mode echocardiography is that of unsuccessful or incomplete visualization of the right- sided cardiac structures, especially in patients with COPD. In recent years, the new technique of Doppler echocardiography has provided a novel noninvasive means to characterize blood flow in cardiac chambers and vessels by assessing is timing, direction and velocity.

Respiratory Function Tests:

The main disturbances of respiratory function that may lead to cor pulmonale can be diagnosed by three main groups of tests:

a) Tests of ventilatory function and lung volume determination

b) Tests of alveolo-capillary gas exchange

c) Measurement of arterial blood gas[8]

By measuring the lung volumes, capacities, and arterial blood gas analysis, we can assess the type of lung disease causing chronic cor pulmonale or we can consider other non-parenchymal pulmonary cause of cor-pulmonale.

Dynamic lung volumes-the FEV_1 and FVC.

A more commonly used index of increased airways resistance or airways obstruction is the "forced expiratory volume in first second (FEV,) and its ratio to the "forced vital capacity" (FVC). The later is the volume expired with the greatest force and speed from total lung capacity and the former of the volume expired in one second during the same manoeuvre. The FEV, is usually above 70% of the FVC and a reduction in this ratio signifies airways obstruction, the degree of which is related to the absolute value of FEV, (the obstructive pattern).

Airways obstruction is usually reversible to some extent following administration of a beta-adrenergic bronchodilator aerosol, increases of greater than 20% in FEV, favoring a diagnosis of asthma rather than COPD. In restrictive lung diseases, the FEV, and FVC are reduced in parallel (restrictive pattern).

Arterial blood gas analysis

In virtually, all cases of pulmonary heart diseases are hypoxemic. Carbon dioxide retention is usual in COPD and in those disorders in which the movement of the thoracic cage and respiratory muscles are impaired. With cor-pulmonale, arterial PO_2 will be less than 55 to 60 mmHg, certainly with exercise and during sleep and, probably, at rest due to ventilation perfusion inequality. Arterial PCO2, greater than 50 mmHg indicates either net or general alveolar hypoventilation.

Imaging techniques in cor-pulmonale in addition to chest x-ray

Besides chest x-ray, imaging techniques include the ventilation perfusion lung scan, MRI and pulmonary angiography. Some of these techniques have limitation in patients with cor-pulmonale secondary to COPD, where as they are almost uniformnly helpful in obliterative pulmonary artery hypertension.

The major interest in 'ventilation perfusion lung scan' and 'MRI' is the possibility of separating patients with chronic thromboembolic disease from those with primary pulmonary hypertension.

Cardiac Catheterization:

It is necessary for the precise measurement of the pulmonary artery pressure, the calculation of pulmonary vascular resistance, and the response to oxygen and vasodilators. It is sometimes indicated to exclude congenital and left heart diseases and in some instances, to carry out angiography to confirm the nature of the pulmonary vascular obstruction.

Lung Biopsy:

Lung biopsy can be useful in showing vasculitis in some types of specific pulmonary vascular disease such as the collagen vascular diseases, rheumatoid arthritis and wegener's granulomatosis[5].

Treatment:

Treatment of cor pulmonale requires multidimensional approach as it is not a primary disease; rather secondary effect of an underlying disease. The major objectives of the therapeutic programmed include attempts at:

- Treatment of the underlying disease
- Reversal of the effects of cor pulmonale
- Patient education

Treatment of cor pulmonale can be considered under headings depending on the aetiopathogenesis. Whatever the approach, the aims of treatment are to decrease pulmonary hypertension, prevention or treatment of heart failure, control of acute exacerbations and prevention of further deterioration.

Treatment of Chronic Obstructive Pulmonary Disease and Cor-Pulmonale

Treatment of COPD and cor pulmonale can be discussed under the headings of the long-term management of the patient and the short-term management of acute exacerbations.

Long-Term Management

Long-term management of COPD with cor pulmonale includes general aspect of management, protection against infection, drug treatment and long-term oxygen therapy. General management includes avoidance of smoking, atmospheric pollution.

Smoking

The most important step, which can be taken to prevent the progression of chronic bronchitis, is to persuade the individual patient to give up smoking. If smoking is given up in the early stages of the disease there is good evidence that both symptoms and lung function may be improve, 349.10. or in older men, that lung function falls with increasing age only at the rate of non-smokers. In more advanced disease there may be little improvement in function, but cough improves whatever the stages of the disease

Atmospheric pollution

This has greatly decreased in Britain and many other developed countries. Sometimes a change from a dirty or polluted occupation or a change in dwelling place may be justified. In foggy weather it is wise, if practicable, to stay indoors.

Protection against infection:
Vaccine protection against S. Pneumoniae or influenzae

The current 23 valent pneumococcal vaccine is recommended for patients of 55 to 70 years old with chronic disease of the heart, lungs, or liver or with diabetes'.

Bronchodilators
The main bronchodilators used in the therapy of the various phases of COPD are 1) theophylline compound, 2) B_2 agonists and 3) anticholinergic agents. Their use was reviewed recently in a publication 1 and brief discussion particularly on especial points are given, bellow

(a) *Theophylline compounds*
Short and long-acting preparations of theophylline are used universally in the continued management of COPD, though compliance is often poor, toxicity possible, and monitoring serum levels has increased the cost. Newer xanthine derivatives, such as enprophylline, which are more potent and slightly less toxic, await evaluation.

(b) *Beta-adrenergic agonists*
Inhaled and oral beta-agonists have been used with or without theophylline in the treatment of stable and unstable COPD for over 30 years. The inhaled route is preferred as being less prone to side effects[67], but the effective dose varies in individuals from two to six puffs four times a day.

(c) *Anticholinergic agents:*
The introduction of ipratropium bromide, a quaternary salt of atropine, has made anticholinergic therapy more acceptable and does not affect mucociliary clearance, urinary flow, or intraocular tension. Now a day's tiotropium has shown promising effect. There is also combination of beta adrenergic agonist and anticholinergic drugs.

Bronchodilator therapy in COPD is essential to control symptoms and to improve short-term function. The effect on long-term prognosis and on cor pulmonale is not known.

Corticosteroids:
Early studies of corticisteroids in COPD were confusing and inconsistent. This was largely the result of imprecise diagnostic criteria for chronic bronchitis, emphysema and asthma and to questions about the significance of an FEV_1 response of greater than 20% to a Bronchodilator. The long-term use of corticosteroids in chronic bronchitis and emphysema is usually given in step III, IV and frequent exacerbations.

Digoxin:
Interest was shown early in the effect of digoxin in congestive heart failure with emphysema and other chronic disease of the lungs. But it is found rather to cause detrimental effects.

Diuretics and Atrial Natriuretic Factor:
Extra vascular lung water increases during exacerbations of cor-pulmonale with oedema in COPD, and decreases after remission of the venous congestive state. Regardless of the multiple mechanisms in the accumulation of the extra vascular lung water in hypercapnic cor-pulmonale, "5.c' reduction in the quantity of extra vascular lung water and oedema may be therapeutic, bearing in mind that too great a reduction compromise cardiac Output.

Atrial natriuretic factor has no beneficial effect.

Polycythemia and Phlebotomy:
It is often stated that increased viscosity is a contributory factor in the pulmonary hypertension of COPD. Polycythemia may decrease cardiac output and oxygen transport and be disadvantageous.

Expectorants and Mucolytic Agents
Expectorants have nearly always failed to show an effect when used in controlled trials, although some patients do value them.

Oxygen Therapy
Recent studies have suggested that prognosis in COPD may be better related to haemodynamic variables, oxygen delivery, and mixed venous oxygen tension. As a result, the hypothesis may be stated that in cor-pulmonale increased cardiac output and pulmonary vascular resistance determine tissue oxygen delivery and prognosis. Augmented cardiac output appears to be an adaptation found in some patients who otherwise would have a decrease in oxygen transport and a failure of this adaptation may lead to death. If breathing oxygen leads to a fall in cardiac output,

it may be counterproductive and measures to increases output (vasodilators) may be more important. This viewpoint is enhanced by the knowledge that long-term oxygen therapy may not result in a fall in pulmonary arterial pressure, but lead only to a failure of progression of pulmonary hypertension.

Selection Criteria For Long-Term Oxygen Therapy[14]

Pre-requisite:

Patient must stop smoking.

FEV1 - Less than 1.5 Litre Arterial blood gas in clinically stable patient on optimal medical therapy on at least two occasions 3 weeks apart.

Indication of L TOT.

1. Documentation of PaO2 less than or equal to 7.3 kPa (55 mm Hg) or oxygen saturation at or bellow 88% with or without hypercapnea.
2. A $Pa0_2$ between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or $Sa0_2$ 89% if there is evidence of pulmonary hypertension, polycythemia (hematocrit more than 55%), peripheral oedema or nocturnal hypoxaemia.

The medical standard for long-term oxygen therapy should be at least 15 hrs/day with ambulatory capability, with the exception of patients not capable or desirous of mobility, patients requiring oxygen only during sleep, or patient requiring oxygen during ambulation.

The physician must prescribe the oxygen source, delivery device, and flow rate needed to relieve hypoxaemia. Short-term oxygen therapy for dyspnoea without hypoxaemia has been dismissed as unphysiologic, but this may be in error and should be reassessed'.

Vasodilator Therapy:

While the beneficial effects of oxygen therapy may include vasodilatation of the pulmonary vasculature, the degree and significance of this is in doubt[1,6,7]. Consequently, many investigators have failed to show any beneficial effects.

Physiotherapy:

There is some evidence that slow, deep diaphragmatic breathing with exhalatior against purse lips does help to relax breathing and improve the ratio of alveolar tc dead space ventilation '5 and certainly many patients do spontaneously adopt this pattern of breathing. Postural drainage may be of value in certain patients with a good deal of sputum, and if performed in the morning after a bronchodilator may help to clear the bronchi[1,11].

Respiratory Stimulants:

The role of respiratory stimulant drugs remains to be clarified. But they have o definite role in acute exacerbation.

Social Aspect:

COPD often interferes severely with employment and social life, especially it unskilled workers. Difficulties of getting to work, the number of stairs to be climate in a tenement or flat, unsuitable work, loneliness and isolation all contribute to the sum of suffering. Some of these difficulties can be addressed by a social worker, Possible community approaches to this grave problem has been outlined in reports[12].

Management of acute exacerbation:

Acute exacerbation of COPD vary from a mild increase of cough and sputum without general upset or much increase in dyspnoea, to a severe and prostrating illness, perhaps with accompanying bronchopneumonia and cardiac failure.

Chemotherapy:

In the absence of clinical or radiological evidence of pneumonia, H. *influenzae Strep.pneumoniae and moraxella cataralis* are the most common causes of exacerbations. As a consequence, bacteriological examination of sputum seldom influences management[13]. Co-amoxiclar three times daily[13] or erythromycin 500 mg four times daily are suitable antibiotics.

Prevention of acute bacterial relapse by the use of long-term antibiotic prophylaxis has not been shown to be of positive value[1,13], and no such study has demonstrated any long-term effect on function or prognosis.

Oxygen Therapy and the Management of Respiratory Failure:

In any severe exacerbation of chronic bronchitis, the attainment of adequate oxygenation is one of the first aims of therapy. This depends on maintaining an adequate airway an appropriate

supply of oxygen. In many patients with hypercapnia the respiratory center has lost its normal sensitivity to CO_2 and the patient is dependent on his hypoxic drive to maintain ventilation. Overenthusiastic oxygenation there fore may be dangerous and the aim should be to provide an inspired oxygen concentration, which maintains PaO2 at or just above 8 kPa (60 mm Hg) by careful monitoring of arterial blood gas tensions. Sedatives, especially opiates, which further depress the drive to ventilation, should be avoided[14].

Bronchodilator Drugs

Beta-adrenergic drugs and anticholinergic drugs by nebulizer are valuable in alleviating airways obstruction. In the very wheezy patients aminophylline 0.25-0.5 gm given slowly i.v. is often useful not only for its bronchodilator effect but also in acting as a respiratory stimulant. The place of corticosteroid therapy in acute exacerbation is not clear but occasional patients with intractable wheeze appear only to respond when corticosteroid therapy is introduced.

Treatment of Cor-Pulmonale:

Cor pulmonale complicating an acute exacerbation of chronic bronchitis and emphysema usually responds to diuretic therapy and routine management of acute exacerbation. There is no evidence that digitalis therapy is of any value in this situation.

Patient Education Programs:

The success of a continuing care program for COPD with cor pulmonale depends heavily on comprehensive patient education[14]. A chronic pulmonary patient must be instructed in respiratory anatomy and then encouraged to develop an understanding of his disease process. He must be carefully educated in the early signs and symptoms of acute exacerbations of his disease in order to prevent the occurrence of acute respiratory failure and further functional deterioration. A family member should also be instructed and a co-operative understanding between family, patient, nurse-therapist and physician should be established. Booklets explaining chronic respiratory insufficiency that include illustrations of aerosol inhalation and breathing and postural drainage techniques are highly effective. The physician must schedule time for orientation and education sessions. Elements of the care program should be outlined and reviewed by the physician and patients at these meetings.

Prevention:

Cigarette smoking The association noted between cigarette smoking and bronchitis makes even more urgent the need for a campaign to control the modern pandemic of cigarette smoking. Health education may be most usefully concentrated, however, on dissuading children and adolescents from taking up smoking.

Atmospheric conditions

Programmes for the study and control of all forms of air pollution are to be strongly encouraged, and in areas where industrialization is preceding the avoidance of air pollution by careful sitting of factories and disposal of their effluents is of prime importance to the public healt[15].

Infection

Experience of the effect of repeated infections on the progress of this disease suggests that all measures designed to prevent respiratory infections and their complications should be considered1[6].

Working Conditions

In general, the same comments apply to the conditions of work. In addition, however, there are the specific hazards of a dusty environment. Many of these have already been recognized and dust suppression measures introduced. There remains the need for continuing scrutiny of respiratory morbidity according to occupation in order to detect previously unsuspected sources of bronchial irritation in chemical and other disorders17.

Prevention of cardiac failure in cor pulmonale

The prevention of cardiac complications of pulmonary disease is primarily a question of treating the causative conditions. Methods directed more specifically to the cardiovascular system may, however, reduce the right ventricular work and delay cardiac failure[18].

Prognosis:

The prognosis for a patient with cor pulmonale is inextricably linked to that of the underlying

pulmonary disease or disorder. In essence, the circulatory disorders are potentially reversible if the initiating mechanisms can be brought under control. The prognosis of cor pulmonale secondary to COPD are affected by the case mix studied. Long-term continuous oxygen therapy may have resulted in some overall extension of life in severe instances of hypoxaemic respiratory failure resulting from COPD, but this may not be reflected in overall mortality figures since the extension of the life is modest.

Invasively, mean pulmonary arterial pressure has been related to survival, which is significantly worse if greater than 20 mm Hg. Pulmonary arterial pressure is negatively correlated with the degree of resting hypoxaemia. The development of cor-pulmonale is likely as FEV_1, declines toward and below 1 liter and the PaO_2 falls below 60 mm Hg. It is important to realize that survival is better correlated with NO_2, rather than with pulmonary arterial pressure or right ventricular ejection fraction

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Management of Asthma: Current Therapies & New Option

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Introduction:

The prevalence of asthma is increasing worldwide at an alarming rate. Although current asthma therapies particularly inhaled steroids, have greatly helped to treat patients with asthma, an important number of patients require additional therapy and an increasing number of new medications are there. Many researchers are currently working on the development of such medications & this article summarizes the various treatment options available now for different types of asthma, highlights some of their limitations and outlines directions which may improve the management of asthma in the future. Asthma is characterized by variable airflow obstruction, airway hyper-responsiveness and chronic airway inflammation. It is a common disease that can cause considerable morbidity & a significant mortality. Recent national & international asthma management guidelines recommend a stepwise approach, with treatment increased until asthma control is achieved & stepped down once control has been maintained for several months[1,2].

Pharmacological treatment for Asthma of varying severity

- Mild intermittent asthma
  Short acting B2 agonists
- Mild persistent asthma
  Add low dose inhaled corticosteroids
- Moderate persistent asthma: Select one of the following options
  - Low dose inhaled corticosteroids plus long acting β2 agonist
  - Higher dose inhaled corticosteroids
  - Low dose inhaled corticosteroid plus leukotriene antagonist
  - Low dose inhaled corticosteroid plus oral Theophylline
- Severe persistent asthma
  - High dose inhaled corticosteroids plus one or more of the following:
  - Long acting â2 agonist
  - Leukotriene antagonist Oral Theophylline
  - Oral β_2 agonist
  - Add oral corticosteroids if control still not achieved
  - Consider corticosteroid-sparing agents.

Mild Intermittent Asthma

As required short acting â2 agonists Salbutamol (brand name Ventolin) is one of the commonest reliever drugs i.e. for the relief of asthma symptoms. They are also useful in preventing symptoms of exercise induced asthma when given before the start of exercise and are important in the treatment of acute severe asthma. Their mechanism of action is thought to occur primarily by the relaxation of airway smooth muscle cells, but they also increase mucocilliary anti-inflammatory activity. Although sympathomimetic agents, short acting 02 agonists have side effects when inhaled but tremor, palpitations & tachycardia can occur with high doses. Studies have shown that their regular use provides no additional benefit 4'5 & may even be harmful. Furthermore, individual patients requirements for short acting B2 agonists provides a useful guide to the need for a step-up in treatment; current guidelines suggest that if they are used on a daily basis for symptom control than regular anti-inflammatory agents are indicated. Tolerance to the effects of short acting B2 agonist can occur particularly to the protection against bronchoconstriction induced indirect challenges'

Mild Persistent Asthma

Low dose inhaled corticosteroids:

Corticosteroids are currently the most effective anti-inflammatory agents for the treatment of

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asthma & inhaled corticosteroids are currently recommended for all patients with persistent asthma who require short acting â$_2$ agonists more than once per day.' or those with intermittent asthma who experience severe exacerbations.[2] Studies have consistently shown that treatment with regular inhaled corticosteroids results in significant improvements in airway inflammation in asthma, an effect demonstrated on bronchial biopsies[7]. Furthermore, there is evidence that corticosteroid treatment is not helpful in the absence of eosinophilic airway inflammtion[8]. In conjunction with these improvements in airway inflammation, inhaled corticosteroids improve symptoms,' health status') airway hyper-responsiveness and lung function[9] and reduce asthma exacerbations[12]. There is also epidemiological evidence from cohort and case control studies showing that regular low dose inhaled corticosteroids reduce both hospital admissions[13] and asthma deaths[14].

Side effects of inhaled Corticosteroids:

At low doses, up to 800 microgram daily of Beclomethasone dipropionate or Budesonide or 500 microgram daily of Fluticasone, systemic side effects are not usually significant, but do become an issue at doses beyond this. Dysphonia commonly occurs due to deposition of inhaled corticosteroid particles locally in the oropharynx15 and oral candidiasis may also develop[16]. Systemic side effects include bruising & atrophy of the skin[17]. & reduced bone mineral density[18]. Suppression of the adrenocortical axis can occur but this is not usually clinically significant[19]. These systemic effects occur partly due to gastrointestinal absorption of swallowed particles &partly due to systemic absorption via the airways. The use of spacer devices, dry powder mechanisms[7], mouth rinsing after inhaler use minimize adverse effects[20,21]. 'Drugs with high first pass metabolism in the liver such as Budesonide & Fluticasone have fewer systemic side effects than Beclomethasone[20, 22] but at high doses systemic absorption through the buccal & airway mucosa is an important consideration.

Cromones

The cromones sodium cromoglycate & nedocromil sodium both given by inhalation, have been used as controller therapies in mild persistent asthma[2]. Their mechanism of action is not fully understood, although they are believed to suppress IgE mediated inflammatory responses & may inhibit inflammatory cells.[23] Sodium cromoglycate has been shown to reduce symptoms, and exacerbation frequency[24] and nedocromil sodium to improve symptoms, lung functions & airway responsiveness[25]. Overall, however, they appear to be rather less effective than low doe inhaled corticosteroid.[26] The use of these agents in adults has therefore largely been superseded by the introduction of low doses of inhaled steroid for the majority of patients with persistent asthma.

Moderate Persistent Asthma

An important number of patients with asthma treated low dose inhaled corticosteroids have sufficient symptoms to justify an increase in treatment. The clinician is faced with an increasing number of treatment options for this important group of patients.

Long acting β_2 agonists:

Long acting â$_2$ agonists (Salmeterol & Formeterol) are currently generally recommended as the first choice for patients who have symptoms that persist despite regular inhaled corticosteroids. Salmeterol is a partial agonist of the â2 receptor while Formeterol is a full agonist. Both appear to have similar clinical effects, but Formoterol has a more rapid onset of action[2]. Side effects of tachycardia, tremor, muscle cramps are rarely a problem unless given in high doses. Tolerance to the effects of long acting â2 agonists with loss of bronchodilator activity after the subsequent administration of both short & long acting 7 T 30. R2 agonists, has been reported[29-30]. As with short acting â2 agonists, these agents work primarily via the relaxation of airway smooth muscle, with additional effects on mast cells & vascular permeability, but without significant anti-inflammatory activity[31]. This lack of anti-inflammatory activity precludes their use as first line agents in asthma[32].

Increasing the dose of inhaled Corticosteroids

There is increasing evidence that asthma exacerbation is associated with eosinophilic airway inflammation[33,34] & the benefits of the high doses of inhaled corticosteroids on exacerbation

frequency are therefore likely to reflect dose related anti-inflammatory effects. While low doses of inhaled corticosteroids are therefore probably appropriate for the majority of patients, higher doses of these drugs may be indicated in some patients who experience frequent severe exacerbation of asthma or who have persistent airway inflammation.

Leukotriene antagonists:

Montelukast & Zafirlukast are both effective cysteinyl leukotriene receptor antagonists capable of markebly inhibiting exercise induced bronchoconstriction[35,35,36] & the early & late response to inhaled allergen[37,38]. When added to as required â$_2$ agonist, clinical trials have been shown to improvement in lung function. function[39,40] reduction in the need for rescue bronchodilators[41,42] & some evidence of a reduction in eosinophilic airway inflammation[43]. The relative effectiveness of leukotriene antagonists compared with long acting â2 agonists as add on therapy also remains unclear & need further investigations. Although some studies have shown that the addition of leukotriene antagonists[45,46] cause improvements in symptoms & lung function providing additional anti - inflammatory effects that long acting â$_2$ agonist do not[47,48].

Theophylline:

Theophylline has been used for many years in relatively high doses as a bronchodilator, but due to adverse effects it has been reserved for use in patients with more severe asthma. Gastrointestinal upset is particularly common[49] but tachycardia & arrhythmia can also occur and measurement with high dose treatment[2]. It is suggested that long acting â2 agonists are more effective than theophylline in patients taking low doses of inhaled corticosteroid & result in fewer side effects[50].

Severe Persistent Asthma

A proportion of patients will have persistent symptoms despite appropriate treatment for moderate persistent asthma. While representing a relatively small minority these patients experience much morbidity, consume significant healthcare resources, & are probably best managed in specialist settings. Once the diagnosis is continued, current guidelines advocate a step-up in treatment usually with high doses of inhaled corticosteroids in combinations with long acting â2 agonists, leukotriene antagonists, theophylline, oral â2 agonists or a combination of these agents. Additional therapy should be instituted on a trial basis & discontinued if there is no objective evidence of benefit[10]. Occasionally high doses of inhaled â2 agonists are needed for optimum symptom control. Though these may be administered via a nebuliser, metered dose inhalers used in combination with spacer devices have been shown to be equally effective even during acute exacerbations[52].

Oral Corticosteroid & corticosteroid sparing agents:

A further group of patients have severe persistent asthma that remains difficult to control despite the measures outlined above. In these circumstances treatments with oral corticosteroids usually in the form of Prednisolone, may be required to minimize symptoms & prevent severe asthma exacerbation. Other corticosteroid sparing agents include Methotrexate, Gold & Cyclosporin. Although there is some evidence that these agents have steroid sparing effects in asthma[53,54,55] each have their own safety concerns & their use should be continued to specialist units.

Non pharmacological & alternative therapies in Asthma Smoking Cessation:

Cigarette smoking in adults with asthma is associated with an accelerated decline in lung function[56] increased symptom severity & exacerbation frequency[57], and an impaired response to inhaled corticosteroids.[58] Appropriate advice should therefore be given to all patients with asthma who smoke and pharmacological treatments such as nicotine replacement therapy or buproprion should also be considered.

Allergen advice:

The exposure of patients with atopic asthma to the allergens that they are sensitized to has been shown to increase asthma symptoms & airway hyper-responsiveness & to cause bronch-oconstnction[59].

Studies of allergen control measures in infancy have shown reduction in respiratory symptoms[60,61].

Immunotherapy:

It appears to be particularly useful in allergic rhinitis but has also been shown to improve symptoms & airway responsiveness in patients with allergic asthma.

Future Developments in the management of Asthma

It is likely that new therapies will become available over the next 5-10 years.The new developments of drugs of asthma are likely to play a key role.

Anti IgE monoclonal antibody:

IgE has an important role in the development of allergic disease in atopic subjects &suppression of IgE is therefore a potential target in the management of atopic asthma. A monoclonal anti-IgE antibody, Omalilzumab which blocks the interaction of IgE with mast cells & basophils, has been developed. It resulted in improved symptom control[63], fever exacerbation & greater reductions in inhaled corticosteroids doses with no apparent adverse effects[64,65]. It therefore appears to be a potentially useful anti-inflammatory agent in patients with atopic asthma.

Monoclonal antibody to interleukin-5

Since eosinophils are a characteristic pathological feature of asthma inhibition of interleukin-5 represents another potential treatment.

Humanized recombinant interleukin-12

interleukin-12 is another potential treatment for asthma. It is a macrophage-derived cytokine that is able to suppress eosinophilic inflammation via modulation of T lymphocyte[66].

interleukin-4 receptor antagonists:

interleukin-4 is another key cytokine in the development of airway inflammation that has been targeted in the search for nivel asthma therapies. A nebulised soluble interleukin-4 receptor, which acts as an interleukin-4 antagonist, is under investigation. Initial studies have shown that this drug is well tolerated & may reverse the deterioration in symptoms & lung function that occur after withdrawal of inhaled corticosteroids[67].

Conclusion:

Inhaled corticosteroids remain the cornerstone of treatment for patients with chronic asthma. While they effectively improve eosinophilic airway inflammation & lung function & control asthma symptoms in most patients, a number will require additional therapy. There is currently a range of effective additional treatments available for these patients. To rationalize the future management of asthma it will be important to target treatments to those patients, who are most likely to respond by identifying individual treatment goals and carefully assessing the likely underlying pathophysiology.

There are many new asthma drugs in development, as well as research into improving current drugs and drug delivery devices. Unfortunately many of these drugs will not be useful and the useful ones may not be available for some time. However, it is hoped that current and future patient with asthma will have better control of their condition due to the research being carried out.

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Chest & Heart Journal
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CASE REPORTS

Cystic Fibrosis: Report on Two Cases Diagnosed by Using Improvised Technique of Sweat Collection and Review of Literatures

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Col Azhar Uddin Ahmed, AKM Razzaque

Abstract:

This paper reports two cases of cystic fibrosis where diagnosis was confirmed by doing sweat chloride test. Sweat was collected by an improvised technique and was found very effective in collecting sufficient amount of sweat for analyzing electrolytes specially chloride. The first case was a 5 months old baby who had history of recurrent respiratory tract infection (RTI) and failure to thrive (FTT). After exclusion of other common causes like tuberculosis (TB) and Congenital Heart Disease (CHD), cystic fibrosis was suspected. The second case was a five and half years old boy who had history of various types of infectious diseases like malaria, tubercular pericarditis, otitis media and recurrent sinusitis since early infancy. Inspite of getting specific treatment of all kind of infections, he was admitted to hospital repeatedly for RTI. Lastly cystic fibrosis was suspected. In both cases sweat was collected by using aluminium foil and room temperature was increased by using room heater and warmer. From aluminium foil and skin, sweat was sucked into a syringe and than transferred to a test tube and send for analysis to biochemical laboratory immediately.

[Chest & Heart Journal 2005; 29(1) : 65-70]

Introduction:

Cystic fibrosis (CF) is an inherited multi system disorder characterized by chronic obstruction and infection of airways and by maldigestion and its consequences'. Dysfunction of the exocrine glands is the predominant pathogenetic feature and is responsible for a broad, variable, and sometime confusing array of presenting manifestations and complications. The diagnosis of cystic fibrosis has been based for many years on a positive quantitative sweat test in conjunction with history either of chronic pulmonary obstructive disease or exocrine pancreatic deficiency or a positive family history. Sweat test by using pilocarpine lantophoresis is not available in our counnry[3] But these two cases of cystic fibrosis were diagnosed in paediatric Cardiology Unit of Combined Military Hospital (CMH) Dhaka by using a very effective alternative method of sweat collection. Previously another case was diagnosed in Dhaka Shishu Hospital where polythene bag was used for sweat collection4. We found our method as more easy and practical than the method used before. This method will help the paediatricians to diagnose Cystic fibrosis in our country in those patients where there is diagnostic dilemma.

Case-1

Rumi, 5 months old baby girl, daughter of consanguineous parents was admitted to CMH Dhaka on 5th August 2002 with history of recurrent respiratory tract infection and failure to thrive. She had history of hospital admission 3 time earlier and was diagnosed as bronchiolitis on two

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occasions and persistent pneumonia on third occasion. Echocardiography excluded cardiac lesions. She had history of neonatal jaundice and delayed passage of meconeum after her birth. Other causes of persistent pneumonia like Tuberculosis (TB), Whooping Cough were excluded. As patient's condition was not improving, cystic fibrosis was suspected and sweat chloride test advised. Sweat collection technique will be described, later.

Sweat chloride level was 146 mmol/L, which was much higher than cystic fibrosis level. The patient was treated with antibiotics, which could cover pseudomonous specially (ceftazidime), chest physiotherapy was given and nutrition was maintained by nasogastric feeding. The baby was discharged after two weeks with antibiotics. Genetic counseling was done. This patient expired 3 months after diagnosis with pneumonia and respiratory failure.

Case -II

Juel, five and half years old boy got admission to CMH Dhaka on 1st January 2004 with the complaints of irregular high grade fever and discharge from both ear for 7 days. He had history of tubercular pericarditis with pericardial effusion and was treated with antitubercular drug from February 2002 to February 2003. He had history of pericardiocentesis several times in first 2 months of treatment. This child had history of malaria at the age of 9 months. He also had febrile convulsion on three occasions from 3 years of age. He had history of otitis media and sinusitis on several occasions since 2 years of age.

After 6 months of completion of Antitubercular therapy (February 2003) he developed fever and cough and pulmonary tuberculosis was suspected again. This time parent discontinued medicine after 3 months, as they were not convinced with this diagnosis. Lastly he got admission to CMH Dhaka, as he was not improving

This time he had high-grade irregular fever with convulsion on two occasions and had respiratory distress also. Chest X-ray showed patchy opacities and antitubercular therapy (ATT) advised again with diagnosis of drug resistant tuberculosis.

But patient's condition was deteriorating, and CXR after one months of 5 drug Antitubarcular Therapy (ATT) showed bronchiectatic changes with milliary shadows. CT scan of chest also showed bronchiectatic change. His aural swab for culture and sensitivity showed growth of pseudomonous Aeruginosa. So clinically cystic fibrosis was suspected and sweat chloride test was advised. Sweat was collected in an improvised way like previous one and diagnosis was confirmed with this test. Symptomatic treatment and genetic counseling was done Pneumococcal vaccine was advised. Patient was discharged after one month. He is still under follow up.

Sweat Collection: Materials used

1. Aluminium foil
2. Intravenous fluid : baby saline
3. Syringe : 10 ml
4. Baby cot
5. Room heater or baby warming unit
6. Test tube

Intravenous line was established first. All clothing's were removed. Skin of the patient was cleaned with distilled water & dried. Patient was wrapped with aluminum foil from neck to toe in such a manner that there was no chance of heat loss. Patient was kept in supine position on the cot and I. V. fluid started. One heater was kept under the cot and another at the side. Warmer was on from the top. Room temperature was recorded. At the temp of 35^0 C patient started sweating and temp was increased to 38^0C. Patient had profuse head and forehead sweating. Heaters were off first and foil was removed from the body. Sweat collected in the foil and skin was sucked in 10-ml syringe immediately and transferred to a test tube. Sample sent to laboratory for test.

Summary of two cases:

Parameters	Case -I	Case -II
Clinical feature	Recurrent respiratory tract infection	Recurrent fever, sinusitis, otitis media. H/O tuberculosis and RTI
Consanguinity	Present	Absent
Failure to thrive (FTT)	Present	Present
Wt	4.6k	14 kg
Age	5 months	5 ½ years
CXR	Patchy opacities	Patchy opacities bronchiectatic change, collapse consolidation of left lower lobe
Anti mycobacterial	Negative	Negative antibody
Hb%	14	m /dl 12.8 gm/dl
ESR	20 mm in 1st hour	10 mm in 1st hour
Sputum C/S	No growth	No growth
HIV antibody	Negative	Negative
Serum immuno lobulin	Within normal limit	
I gG	6,03 G/L	9.08 G/L
I gG	0.62 G/L	0.785 G/L
IgA	1.54 G/L	2.206 G/L
Ear swab C/S	No Growth	Pseudomonous aeruginosa
Sweat chloride level:		
Patient	146 mol/L	75 mmol/L
Normal range	5-35 mmol/L	5-35 mmol/L
Cystic fibrosis range	60-200 mmol/L	60-200 mmol/L
Serum electrolytes:		
Na+	141 mmol/L	144 mmol/L
K+	4-6 mmon	4 mmol/L
$C1^{1-}$	101 mmol/L	101 mmol/L
MT test	5 mm	5mm
Echocardiogram	NAD	NAD
Treatment	Chest physiotherapy, Antibiotics with pseudomonous coverage, Bronchodilators, Nutritional support and Genetic counseling	Chest physiotherapy, Antibiotics with pseudounonous and staphylococcal coverage, Bronchodilators, Mucolytics, Nutritional support and Genetic counseling
Follow up	Expried after 3 months of diagnosis	Stable at present

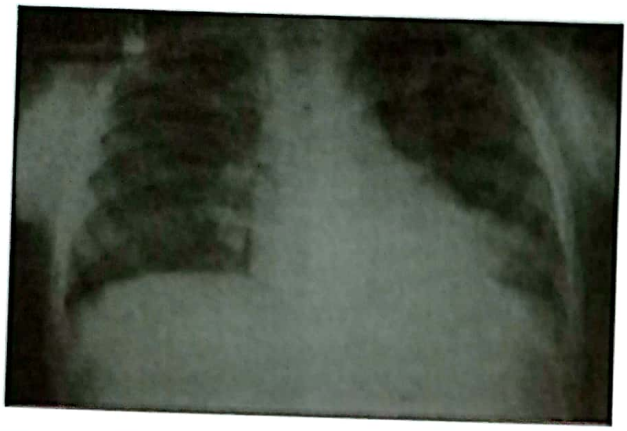

Fig.-1 : *X-ray chest of case 1, showing patchy opacities*

Fig.-2 : *This photograph is showing technique of sweat collection*

Discussion:

Cystic fibrosis (CF) results in damage to organs containing secretary epithelial cells, such as Lungs, intestine, pancreas, liver and vas deferens. CF results from mutation in the gene that encode cystic fibrosis transmembrane conductance regulator (CFTR). This gene is located in the long arm of chromosocure 7 and it encodes a protein that function as a chloride channel regulated by cyclic AMP, in the apical membrane of secretory epithelial cells[5]. The defects in Ion transport from mutation affect the osmotic flow of water across the epithelium and result in thickened secretions, which are not properly cleared out. Incidence of CF is approximately 1:2,500 and 1:17,000 live birth in white and black populations of the United States. The world wide incidence varies from 1:620 in some area to 1:90,000 in other area[2]. This disease is rare in our subcontinent. Incidence study is not available in our country, as sweat chloride test is not performed here to diagnose these cases.

This disease cause chronic infection which is limited to the respiratory tract[6]. Chronic bronchiolitis and bronchiectasis are the first lung manifestations followed by bronchiolectasis and bronchi ectasis. The predilection of CF airways for staphylococcus aureus and pseudomonous aeruginosa is incompletly understood. pseudomonous aeruginosa is responsible for 90% death of CF patient[7]. Our first case had history of recurrent bronchiolitis and the 2nd case had history of recurrent pneumonia, sinusitis and otitis media. Second case had isolation of pseudomonous, aeruginosa from ear Swab. This patient ultimately developed bronchiectasis. As lung disease progresses, exercise intolarance, shortness of breath and failure to gain weight are noted. Finally, cor pulmonale, respiratory failure, and death supervene our first case had shortness of breath, Failure to thrive and she died from respiratory failure after 3 months of diagnosis.

Intestinal symptoms are less common. A newborn may manifest as meconicum illeus[8], More than 85 % of children show evidence of maldigestion for exocrine pancreatic in-sufficiency. Other gastrointestinal manifestations are distal intestinal obstruction (10-20%), Intususception (1-5%)) rectal prolaps etc[9]. Our first case had history of delayed passage of meconium and neonatal jaundice but no other intestinal symptoms were present in this case or in the 2nd case.

Diagnosis based on positive sweat chloride test, positive family history and presence of one or more of typical clinical feature [2]. Sweat chloride test is sometime normal in some cystic fibrosis patients[10]. These are atypical phenotype (2%) and diagnosis can be confirmed by the identification of a CF causing mutation in each CFTR allelle or in vivo demonstration of CFTR dysfunction by nasal potential difference study[10]. Neonatal biochemical screening is best to diagnose the cases in earliest possible time[12]. Screening can be done by serum immunoreactive trypsin assay.

Mutational analysis of CETR gene showed deletion of a phenylalanine residue at codon - 508 (F-508). Prenatal diagnosis can also be one by amniotic fluid analysis and chorionic villus biopsy. Our patients had strong clinical findings and positive sweat chloride tests. In one case culture of aural swab was positive for pseudomonous aeruginosa which also helped in diagnosis as a co-association. Positive cough swab is a strong prediction of sputum culture. So cough swab should be tested for all cystic fibrosis cases[13].

Since the identification of the gene (CFTR), more than 100 mutations have been discovered[14]. This gene has role in on transport, mucus rheology and inflammation. So therapeutic measures are being investigated in an attempt to overcome these abnormalities.

Recombinant human DNase is benefitial in many patients and the use of antiinflammatory agents such as steroids, ibuprophan and macrolides have potential role. Mucolytic therapy also has some role in cystic fibrosis patients[15].

A comparative study was conducted in respiratory unit of Great Ormond Hospital, London, UK to show the efficacy of hypertonic saline nebulizer and daily or alternate day human deoxyribnuclease (rh DNase) in children with cystic fibrosis[16]. This study concluded that hypertonic saline, delivered by jet nebulizer is not as effective as daily rh DNase[16].

Role of cationic lipid: PDNA complexes for the treatment of cystic fibrosis is still under trial[15] . A two year randomized, placebo control trial of dornase alfa in young patient, revealed that dornase alfa maintains lung function and reduces the risk of exacerbation over a 96-weeks period[17]. Endoscopic sinus surgery of cystic fibrosis patients also improved lung function and reduce the need for hospitalization in every cases[18]. Frequency of lung transplantation in cystic fibrosis patients has risen in past decades because of clean cut survival benefit[19]. Some preventive measure like pneumococcal immunization in CF patient is also recommended[20]. In our two cases nutritional supplementation, chest physiotherapy, antibiotics, bronchodilators, steroids were the main stay of therapy. Genetic counseling was also done and prognosis was elaborated to the patients. One of them had expired and 2nd case is still under follow up.

Conclusion

The median estimated life expectancy of children with cystic fibrosis (CF) born in 1980's is 40 years which represents a doubling in the last 20 years and a nearly half of the patient are now adults in developing country. Whilst gene therapy and other new treatment such as bilateral living lobar lung donation give our patient optimism for the future, it is important to remember that the increase in survival is a result of good physiotherapy, nutrition, aggressive antibiotic use and an increase in our under standing of the disease. Advance treatment is not available in our country. In this two cases we have tried to improve their survival by giving nutritional and other symptomatic supports. Though one had expired other one might have chance of advance treatment in future because days are not far away when treatment will be available in our country.

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Pulmonary Agenesis : A Case Report

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Abstract:

Unilateral pulmonary agenesis is a very rare case radiologically simulating pulmonary collapse. A 22 years old young unmarried lady presented with the complaints of recurrent left sided chest pain with exertional dyspnoea for last 2 years. She did not have any haemoptysis, cough, fever or weight loss. She noticed that 2 years back he suffered from fever and cough lasting for 3 weeks. At that time she was treated by a qualified physician and told by the physician that she had a major problem in her left lung as stated in x-ray chest. Since then she began to suffer from above complaints. However patient was evaluated thoroughly and investigated with bronchoscopy and CT Scan of the chest. Ultimately the patient was diagnosed as a case of unilateral pulmonary agenesis. After confirmation of diagnosis patient was explained everything and surprisingly patient improved dramatically.

[Chest & Heart Journal 2005; 29(1) : 71-73]

Introduction:

Agenesis of the lung refers to complete absence of the carina, the main bronchus, the lung and the pulmonary vasculature of the affected side[1]. It may be bilateral or unilateral. Congenital bilateral pulmonary agenesis follows failure of the primitive lung buds to develop and is uniformly fatal. Unilateral pulmonary agenesis is a rare anomaly, occurring once in every 10000 to 15000 autopsies. More than 50% of patients with unilateral pulmonary agenesis are associated with other congenital anomalies particularly cardiac anomalies. In the absence of cardiac anomalies the clinical feature in unilateral pulmonary agenesis may vary from no symptoms to severe respiratory distress, usually precipitated by infection of the remaining lung.

Case summary:

A 22 years old young unmarried lady presented with the complaints of recurrent left sided chest pain with exertional dyspnoea for last 2 years. She did not have any haemoptysis, cough, fever or weight loss. She noticed that 2 years back he suffered from fever and cough lasting for 3 weeks. At that time she was treated by a qualified physician and told by the physician that she had a major problem in her left lung as stated in x-ray chest. Since then she began to suffer from above complaints. However she did not have any history of childhood pneumonia or pulmonary tuberculosis or of contact of any tubercular patients. She also did not have any history of foreign body inhalation. On examination , patient was well built with good nutrition having mild drooping of left shoulder and mildly depressed left chest. All others parameter of general examination were within normal limit. On examination of the respiratory system , the movement of the chest was symmetrical, trachea shifted to the left and apex beat was also shifted to the left. Percussion note was dull on the left side. On auscultation heart sound was clearly audible in all the area of the left chest with diminished breath sound of vesicular in nature.

Chest skiagram of the patient revealed complete homogenous opacification of left hemi-thorax with shifting of trachea to the left and elevation of the left dome of the diaphragm with "rib crowding as well as compensatory hyperinflation of the right lung. Bronchoscopy revealed blunting of the carina with distortion of the left principal bronchus with non-visualization of distal left bronchial trees. CT Scan of the chest showed that there was absence of left lung with left bronchial tree suggesting left

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sided pulmonary agenesis. After confirmation of diagnosis patient was explained everything and surprisingly patient improved dramatically.

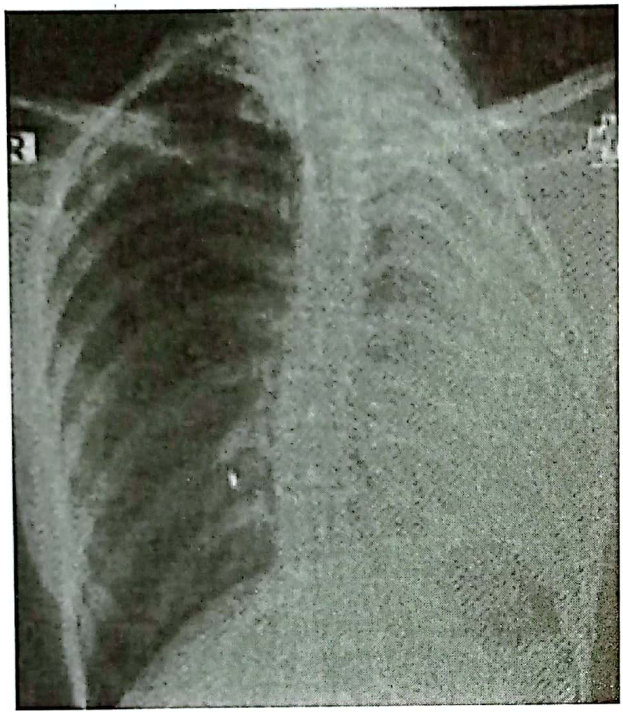

Fig-1 : *X-ray chest of a case of pulmonary agenesis showing homogenous opacification of left hemithorax associated with ribs crowding, elevation of left dome of diaphragm and pooling of the mediastinum and herniation of the compensatory emphysematous right lung.*

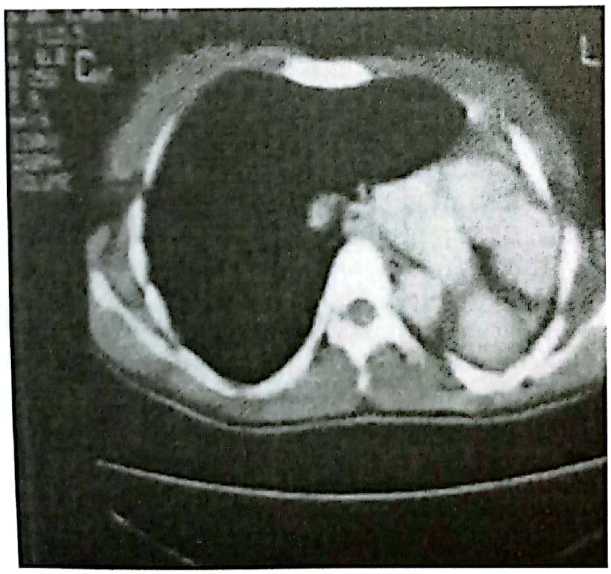

Fig.-2 : *CT Scan of the chest showing absence of left lung.*

Discussion:

Growth and development of the lung can be divided into intrauterine and postnatal stage, with birth representing one point in the continuum[2]. The intrauterine stage can be divided into an embryonic, pseudo-glandular, canalicular and terminal sac stage. The embryonic stage extends from postovulatory period to 5th week of gestation. During this stage trachea and lung buds are split off from the foregut by the esophagotracheal septum. Distally the left lung bud develops into two main bronchi and two lobes; right bud forms three main bronchi and three lobes[3]. At the end of 5th weeks to 16th weeks of gestation mark the glandular stage and in this period all conducting system are developed and lined by columnar or cuboidal epithelium as well as development of cartilage and tracheobronchial gland. Canalicular stage extends from the end of 16th weeks to 25th weeks of gestation which represents early stage of acinar airway. Terminal sac stage lasts until birth representing saccular proliferation, progressive vascularization and organization of surrounding mesenchyme[4]. Normal postnatal growth representing tracheobronchial remodeling extends upto 4 years of life.

Congenital anomalies of the lung represent a spectrum of closely related abnormalities that arise during an early stage of embryonic foregut maturation. Underdevelopment of lung tissue is classified by Schneider into three groups. Agenesis of the lung refers to complete absence of the carina, the main bronchus, the lung and the pulmonary vasculature of the affected side[1]. Aplasia occurs when the carina and a rudimentary main bronchus are present but the pulmonary vessels and the alveolar tissue are absent. Hypoplasia occur when an illform bronchus is capped by poorly developed alveolar tissue forming a fleshy but unlobulated structure lying in the mediatinum.

Congenital unilateral pulmonary agenesis is usually associated with other congenital anomalies particularly cardiac anomalies. Recent evidence suggest that unilateral pulmonary agenesis may be related to a basic chromosomal abnormality s. The average life expectancy with this lesion is shortened to 6 years for right sided and to 16 years for the left sided agenesis, largely as a result of associated congenital anomalies[6] . In the absence

of cardiac anomalies, however, infant who survive 5 years can expect an almost normal life span. Pulmonary agenesis is distributed equally between the right and left sides and is more common in males. The existence of embryonic pulmonary tissue is important for the growth and vascularization of the pulmonary arteries, because agenesis and aplasia are, for practical and developmental purposes the same; there is no lung tissue or ipsilateral pulmonary artery. Cyanosis or respiratory distress in the infant usually indicates a co-existing congenital cardiac lesion. In the absence of cardiac anomalies the clinical feature in unilateral pulmonary agenesis and aplasia may vary from no symptoms to severe respiratory distress, usually precipitated by infection of the remaining lung. In early life physical findings are not very pronounced except the evidence of mediastinal pooling because in utero the single lung expands to fill the entire chest, leading to normal chest wall development and there is no associated diaphragmatic elevation or narrowing of the intercostals space. But with increasing age the feature of pulmonary collapse is usually evident. So to diagnose a unilateral pulmonary agenesis in adult clinical suspicion is a must and it is usually confirmed by CT Scan of the chest.

Regarding management, no specific surgical therapy is necessary for agenesis unless there are associated cardiac or chest wall deformities.

Conclusion:

Pulmonary agenesis is a very rare condition and it is usually asymptomatic if not associated with any congenital cardiac anomalies. But unilateral pulmonary agenesis radiologically mimics pulmonary collaypse. So suspicion of pulmonary agenesis in a case of incidentally diagnosed pulmonary collapse is very crucial because pulmonary agenesis does not need any specific surgical therapy.

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Case Report: MCTD Presenting as ILD

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Introduction

MCTD is an overlap syndrome characterized by combinations of clinical features of SLE, SSC, polymyositis and rheumatoid arthritis, and the presence of very high titres of circulating autoantibodies to neuclear RNP antigen. This antibody in high titre, now referred to as anti-v1 RNP; has been a justification on for considering MCTD as a distinct clinical entity. MCTD has been challenged as a distinct disorder by those whom consider it as a subset of SLE or SCLERODERMA. Other prefers to classify MCTD as an undifferentiated connective tissue disease. MCTD occurs world wide, and in all races. The peak onset of disease is in the second and third decades, but MCTD is seen in children and the elderly. Women are predominantly affected. The pathogenic mechanism in MCTD reflect the disorders making up this syndrome.

Case report

Mrs. Sarifun Nesa, married Muslim female of forty, Housewife blessed with one son,normotensive, non- diabetic hailing from Dhaka was admitted in NIDCH with progressive thickening of skin of face & both limbs for 3 years, dry cough for 2 years,multiple joint pain including small & large joints with bodyache - 1 year; irregular low grade evening rise of temperature for 6 months & progressive shortness of breath for 6 months. She noticed color change of fingers on exposure to cold.

No haemoptysis or contact with TB patient. She was given antikoch's this april; at chankharpul TB clinic; but discontinued the drug one month later due to drug intolerance. She is ex- smoker, 5 packyear, no arsenicosis in the family or locality. No history of ankle edema, chest pain or lymphadenopathy. Never took OCP or worked with vibrating tools.

On Examination

Build is below average, nutrition -poor. Early clubbing of fingers & toes.

Pulse 80/min regular, BP-130/80 mm of Hg, vitiligo on neck head & leg. Thikening of skin of face, skin below elbow & knee. Face is smooth, shiny; with microstomia and pert-oral puckering. Loss of forehead wrinkling with multiple telangiectasia. Oral ulceration present. Hand, leg skin smooth, shiny, tight. Tenderness over small joints of hands. Respiratory system examination reveal resting tachypnea; bilateral end inspiratory crepitation in basal area unaltered by coughing or posture change. Proximal myopathy in the upper and lower limbs.

Laboratory findings:

Routine blood examination showed normal total count. ESR-100 mm in first hour, Hb -12.7 gm Ml. Fasting blood sugar- 72 mg MI. CXR P/A view showed bilateral mid & lower zone reticulonoidular shadow. C' ANCA negative, RA factor-positive, Anti - Scl 70 - Negative. High titre of autoantibody to neuclear RNP, Tuberculin test-Negative. Sputum - 3 Sample ;Negative, kidney function test-Normal. ECG& ECHO - Normal, Spirometry- mixed pattern. Barium swallow esophagus - normal. Bronchoscopy - No endobronchial lesion seen, Inflamation noticed. BAL-polymorph-25% Lymphocytes-20% Macrophage-55%. HRCT - features suggestive of ILD.

Skin biopsy showed- skin without subcutis. In one area the epidermis reveals blunting of the rete ridges. In some area the dermis reveal thickening and increased collagenation with peri vascular infiltration of lymphocytes. The skin adnexae is absent in this zone. The deeper margin of the dermis could not be ascertained. The adjacent

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dermis reveal rudimentary skin adnexae (early scleroderma).

Treatment:

The patient was prescribed steroid along with cyclophosphamide. The patient gradually showed improvement and after few weeks was discharged with advice for follow up monthly. She was well in her first follow up visit.

Discussion

Approximately 85% of patients of MCTD have pulmonary involvement, which is often asymptomatic. Apart from involvement of the parenchyma, it also causes disease of the pleura, diaphragm and chest wall muscles. Fibrosing alveolitis is a recognized complication of MCTD.The clinical features are usually indistinguishable from cryptogenic fibrosing alveolitis and response to immunosuppressive drugs is similarly unpredictable. Here lung parenchyma involve in a diffuse manner by cellular infiltrate and also there is deposition of extra cellular matrix in the acini.

The duration of disease may sometimes be difficult to ascertain in the early stage particularly. Gradually progressive shortness of breath on exertion may be the only symptom and hence the patient may not present clinically until there is quite extensive lung pathology, but in the background of systemic connective tissue disorder diagnosis not so difficult. Diagnostic approach can be done as

Phase-1 & Phase-2

Phase-1 - Clinical history
Clinical examination
Chest radiography
Pulmonary function test
Selective blood test

Phase-2 - High resolution CT
BAL
Lung biopsy

Physical examination often unrewarding. Showers of bilateral end inspiratory crackles are typical which are unaltered by coughing or posture. Signs of pulmonary hypertension may be present; which is the most common cause of death. In blood test RNP is the most important in MCTD diagnosis'. Regarding Chest X-ray ; Five important features should be noted which give important diagnostic clues are

- Size of the lungs
- Distribution of the nodules
- Size and shape of the nodules
- Presence of confluent shadows
- Pleural disease or lymphadenopathy.

Pulmonary function test commonly shows restrictive ventilatory pattern. High resolution CT scan is extremely valuable in detecting early interstitial lung disease and assessing the extent and type of involvement[2]. Bronchoalveolar lavage is not often of diagnostic value in MCTD[3]. Open lung biopsy confirm the ILD, & biopsy should be done before the treatment is initiated. Prognosis is poor in MCTD involving the lung, presenting as ILD. Steroid & immunosuppressive drug is the mainstay of treatment but prognosis is poor in MCTD involving the lung.

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