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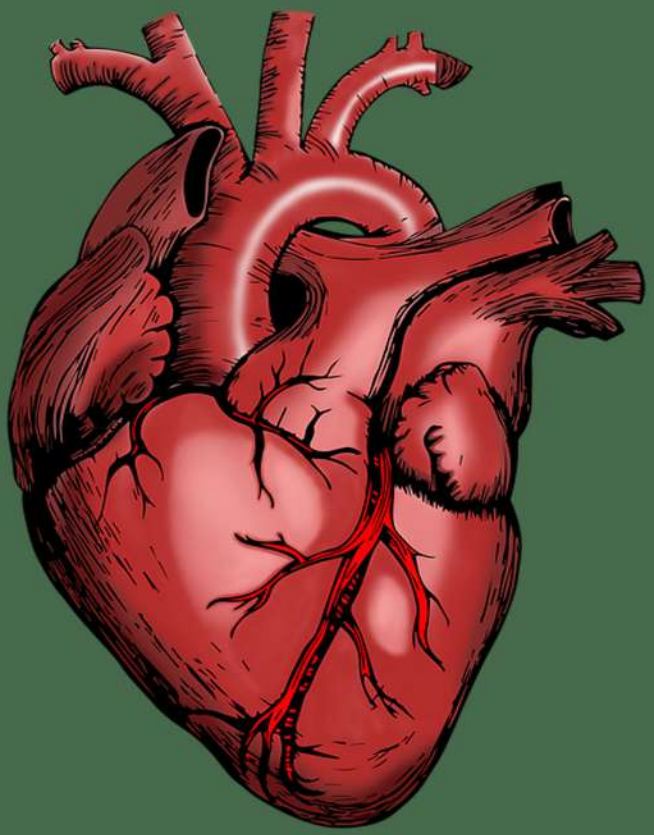

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Letter to the Editor

"The Moustache Sign": A Common Morphological Characteristic in Cardiovascular Disease Treatment

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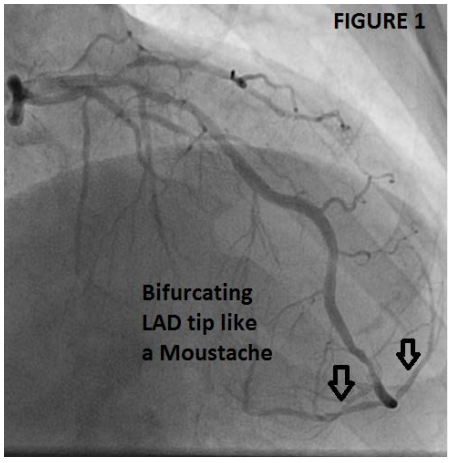
There are multiple eponymous medical signs in the field of cardiology. These "signs" refer to significant physical findings or observations made by the cardiologist while evaluating the patient. We hereby describe and summarize all the conditions in which "moustache sign", a commonly occurring observation, is seen in the field of cardiology. The importance of signs like these is that they help in earlier recognitionof the disease pathophysiology and in the management of patients.

Figure 1. *Left Coronary Angiogram Shows the Distal LAD Bifurcating (Marked with Arrows) Like a Moustache*



The first example is identification of the left anterior descending artery (LAD) on coronary angiography. The LAD bifurcates at the apex akin to a moustache or the bifid tail of a whale (Figure 1) and is variously described as "whale tail sign", "pitchfork sign" or "Moustache sign".[1] This feature helps us to identify this coronary artery in case of any anatomical confusion (may help identify Dual LAD morphology)[2] and is also used as the distal landmark while calculating the thrombolysis in myocardial infarction (TIMI) frame count.[3]

A second one is digitalis effect,the morphology of the QRS complex/ST segment in patients who have achieved therapeutic levels of digitalis in their circulation. This is variously described as either "slurred", "sagging" or "scooped" and resembling either a "reverse tick", "hockey stick" or "Salvador Dali's moustache" (Figure 2).[4] Salvador Dali was a Spanish surrealist who apart from his artwork famous is known for the unique style of his moustache (Figure 3).

Another observation is the stag's "antler sign" which refers to the upper lobe pulmonary venous diversion (cephalisation) in pulmonary venous hypertension or pulmonary edema as seen on frontal chest radiograph. This prominence of upper lobe pulmonary veins, resemble a stag's antlers. It is the earliest sign of pulmonary venous hypertension (grade 1 pulmonary edema). This sign is also known as "hands-up sign" or "inverted moustache sign" (Figure 4).[5]

Figure 2. *The ST Segment is Like a Moustache in Patient on Digitalis*

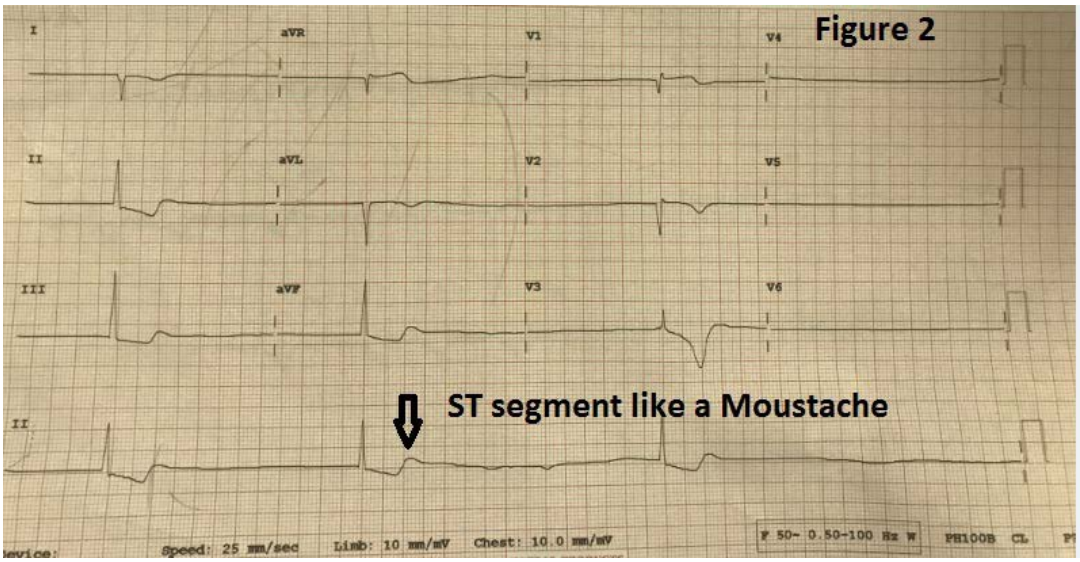
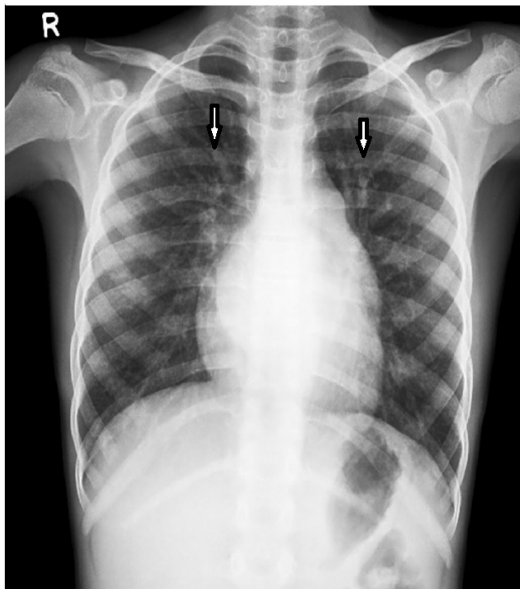


Figure 3. *Salvador Dali–a Spanish Surrealist*

Figure 4. *Chest X-ray Showing Cephalization of Upper Lobe Pulmonary Veins in Pulmonary Venous Hypertension in Both Lungs Akin to a Moustache*



And finally, partial anomalous pulmonary venous drainage with intact inter-atrial septum associated with mitral stenosis is rare. Differential pulmonary vascular distribution (plethora) on chest radiograph may lead to a "unilateral inverse moustache" sign and is a subtle clue for the presence of anomalous venous drainage.[6]

To conclude, this short review highlights the importance of 'The Moustache sign' and how its presence can be utilized in clinical cardiology practice.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Original Research

Changes on Electrocardiographic Patterns and Associated Factors among Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

Background
Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The lungs and the heart are so closely interrelated organs that diseases of the one results in impaired functioning of the other. COPD induced cardiovascular diseases (CVDs) are diagnosed by electrocardiogram (ECG) and other instruments. ECG is one of the basic diagnostic tools that uses in early screening of COPD associated systemic effect of CVDs. However, concomitant CVDs among COPD patients are not usually assessed by ECG in routine medical practice at the setup.

Objective
The present study aimed to explore and detect changes of ECG pattern, and determine the associated risk factors among COPD patients.

Materials and Methods
The study was conducted among COPD patients visiting chest clinic of Jimma Medical Center (JMC), Southwest Ethiopia; from May 18 to August 18, 2017 G.C. A hospital based cross-sectional study was conducted among 80 COPD patients; and investigations for 12 lead resting supine ECG as well as measurements of other variables were performed. The results of ECG patterns and other variables were entered into Epidata (3.1) and exported to statistical package for the social sciences (SPSS) 20 for further analysis.

Results
Eighty COPD patients were enrolled in the study and the prevalence of abnormal ECG was 83.75% where arrhythmia accounted for 50%, atrial enlargement 48.8%, myocardial infarction (MI) 41.3%, axis deviation 35%, other ECG abnormalities (poor R-wave progression and low QRS amplitude) 35% and ventricular hypertrophy 15%. The identified associated factors with the abnormal ECG were less monthly income, smoking, hypoxia, male gender and severity of COPD with their specific adjusted odds ratio (AOR) and 95% CI of 2.1(1.6-7.9), 2.2(1.5-8.6), 2.9(1.2-6.9), 3.1(1.5-23) and 3.2(2.0-8.4) respectively.

Conclusion
Routine ECG investigation should be performed at the setup to initiate early management of CVDs comorbidity for better prognosis among COPD as abnormal ECG is inevitable among them.

Keywords
ECG pattern; Minnesota ECG criteria; COPD; Six minute walk distance test (6MWDT); Associated factors.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease with some significant extra pulmonary effects that is characterized by a progressive/persistent airflow limitation, associated with an abnormal inflammatory response of the lung and airways to noxious particles or gases which

is not usually fully reversible.[1]

The risk factor for COPD results from a gene-environment interaction; related in more complex ways by which one risk factor influences another factor.[2] Even though, cigarette smoking is the most commonly encountered risk factor for COPD, there are also many identified risk factors of COPD like the genetic deficiency of alpha-1 antitrypsin (AAT),[3,4] frequent exposure to occupational dusts and chemicals (vapors, irritants, and fumes),[5-7] indoor air pollutions (wood, animal dung, crop residues, and charcoal) by burning as biomass fuel in confined spaces especially among women living in rural parts and outdoor air pollutions (fossil fuel combustion and motor vehicle emissions) in industrialized countries.[8-12]

Following triggers from different risk factors there is a characteristic pattern of inflammation in the lungs of COPD patients (increased numbers of neutrophils, macrophages and CD8+ lymphocytes)[13]; results in abnormal inflammatory response that induce parenchymal tissue destruction and impairs defense mechanisms due to imbalance between released inflammatory mediators and anti-inflammatory mediators from inflammatory cells,[14,15] and/or with an amplified effect of oxidative stress over anti-oxidative and an excess of proteases against anti-proteases in the lung.[16] Pathophysiological changes as characteristic of the disease are manifested in both pulmonary and as well as extra pulmonary/systemic effects. Pulmonary pathophysiology includes mucus hyper secretion, airflow limitation and air trapping (leading to hyperinflation), gas exchange abnormalities, pulmonary hypertension and corpulmonale.[17,18] Systemic/extra pulmonary effects of COPD, particularly in patients with severe disease include skeletal muscle wasting,[19] risk of cardiovascular diseases (CVDs),[20] anemia,[21] osteoporosis[22] and other systemic effects[23-25] (diabetes, sleep-disorders, glaucoma, depression and etc.) with a major impact on survival and prognosis of COPD patients.

The CVDs developed among COPD patients as systemic effect can be diagnosed by different instruments including electrocardiogram (ECG). ECG is the graphic records of time-varying bio-electric potential generated by the electrical activity of heart which used to measure and monitor the structural and functional activity of the heart for its ease of usage and non-invasiveness. The ECG changes observed among heart of COPD patients are high amplitude of P wave, vertical P wave axis, vertical QRS axis, prolonged PR and QT interval as cardiac markers of CVDs suggesting abnormal ECG (arrhythmia, axis deviation, heart chamber enlargement and hypertrophy).[26]

Even though, mechanism of COPD induced development of CVDs evidenced with abnormal ECG is complex and unclear; their correlation was expected *via* the effect of abnormal systemic inflammatory response[27,28] resulting in progression of pathologic atherosclerosis, biological (hypoxemia, endothelial dysfunction, increased platelet activation, arterial stiffness) with the mutual classical risk factors[1] (smoking, pollution, free radicals and aging) that ends in pulmonary vascular dysfunction, pulmonary hypertension, right and left heart dysfunction and arrhythmia. The anatomical and physiological similarity of two vital organs also affect each other[29] and may be adverse effects of drugs used to treat COPD can directly induce cardiac problems with acute exacerbation of COPD.[30]

In general, there were very limited studies that determine the factors associated with ECG changes than exploring the magnitude of various ECG findings. The identified factors for ECG changes were amount of systemic C-reactive proteins (CRP) as markers of inflammation, hypoxia, duration and severity of COPD which was exacerbated by mutual risk factors smoking and aging.[26-33]

Thus, the current study aimed to explore and detect changes of ECG pattern by using the 12 lead ECG which is not routinely performed especially in developing countries including Ethiopia and the study area due to economic constraints and determine the associated risk factors among COPD patients.

MATERIALS AND METHODS

Study Design and Setting

The study was conducted at JMC, located in Oromia regional state, at southwest Ethiopia which is one of the largest teaching referral hospitals in the country, providing the health service at inpatient and outpatient level for the catchment area of 15 million populations in dwelling in the southwest of the country. The health service is delivered by specialists, medical residents, medical interns and other health professionals. The study was conducted from May 18 to August 18, 2017 G.C among COPD patients attending chest clinic of JMC employing a hospital based cross-sectional study design.

Participants and Recruitment

The study populations were all COPD patients attending chest clinic of JMC who were available during data collection period. The sample size was determined based on the total annual number of COPD patients attending chest clinic of JMC. According to the data used in the study conducted for assessment of osteoporosis and associated factors among COPD patients, the hospital had a total of 100 COPD patients in the year 2013/14 G.C. By considering this annual flow of the cases as a target population, the total sample size of 80 patients was obtained by using Yamane Taro, 1967 equation [$n=N/(1+Ne^2)$], where n-sample size, N-target population (100) and e-level of precision (0.05).[34]

Data Collection (Instrument and Technique)

The data was collected by trained Diploma Nurses employed from the chest and cardiac clinic of JMC. Data collectors were briefly oriented about the objectives and purpose of the study to respondents and took informed verbal and written consent prior

to data collection. Then, face-to-face interview was conducted using structured questionnaires to assess COPD related and socio-demographic variables.

Body mass index (BMI) was computed from client's height and weight measured with validated tape meter and weight scale at standing position.

Six minute walk distance test (6MWDT) was obtained by measuring the total distance the patient walked/covered in meter within six minutes to evaluate the severity of the disease as the indicator of exercise tolerance capacity of the COPD patients.

Dynamic pulmonary function test was carried out to diagnose and grade severity of COPD based on post bronchodilator result of forced expiratory volume in one second (FEV1) % predicted, forced vital capacity (FVC) and (FEV1/FVC) ratio as per the guideline of Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] by using dry digital spirometry (Care Fusion, Germany).

Hypoxic status was measured by digital pulse oximeter (Lifebo, Germany) indicating percentage of SPO_2 by placing the probe on non-polished/bare finger of the clients.

Finally the patients underwent ECG investigation after other variables (anthropometry and COPD related) were measured. Standard 12-lead supine resting ECG (NIHON KOHDEN Cardiofax S) was used with machine calibrated on 1 mV for a 10 mm (0.1 mV/mm) at speed of 25 mm/s, where each small box and large box represents 0.04 sec and 0.2 sec respectively. 10 electrodes (4 limb electrodes at right and left arms & legs +6 chest electrodes (V1-V6)) were placed on clients' arms, legs and chest after orientation and gel applied, yielding a total of 12 leads that measures the potential difference of movement of electrical activity of the heart.

Each ECG paper was visually analyzed for recording errors, manually interpreted by investigator in liaison with the cardiologist and classified according to the Minnesota coding criteria, merged and thematised to different main and sub-categories.

Data Processing and Analysis

Data was checked, categorized, coded and entered into EpiData version 3.1 after template formed and finally exported to SPSS version 20 for further analysis. Descriptive statistics like frequencies, percentages, mean and standard deviations were used to describe the findings. In bivariate analysis, simple-crosstab/chi–square test and binary logistic regression were conducted to explore the association between ECG pattern status& the associated factors. Those variables with p-value <0.25 were taken as a candidate for the final model. In multivariate analysis, the confounders were controlled and adjusted to odds ratio (AOR) with 95% confidence interval (CI) to express the strength of the association between ECG pattern and p-value less than 0.05 was considered as statistically significant.

ETHICAL CLEARANCE

Implementation of the proposal was carried out after getting approval letter from the ethical clearance committee/ethical review board of Jimma University (IRB/699/2017). An official letter of collaboration and permission request to chest and cardiac clinic of JMC was obtained from Department of Physiology and Internal Medicine prior to study conduction. Informed verbal and written consent was taken from the respondents/clients after explaining the objectives and purpose of the study. The participants were assured that they have full right to participate or withdraw from the study and the collected data/information were kept confidentially. Any abnormal finding of the ECG pattern was required consultation of physicians of chest clinic for further interventions.

Operational Definitions

- Hypoxia is refers to result of SPO_2 less than 90% post 6MWDT.[35]
- Severity of COPD was categorized by using the result of six minute walk distance test (6MWDT) which is the total distance covered/walked in meter within six minutes by taking the initial and last result of saturation pressure of oxygen (SPO_2) with Pulse oximetry. Based on distance covered within six minutes, the severity of COPD can be classified as mild (≥350 m), moderate (250-349 m), severe (150-249 m) and very severe (≤149 m).[36]
- Abnormal ECG–refers to any change deviated from normal sinus ECG based on Minnesota ECG coding criteria.[37]

RESULTS

Results of Socio-demographic and Economic Status of COPD Patients

Out of the total sampled 80 COPD patients attending chest clinic of JMC from May 18 to August 18, 2017 G.C, the mean age was 55.1 (±13.66) that ranges from 26-90 years by which majority of them (32.5%) belongs to interval of 51-60 years. Majority of the analyzed 80 COPD patients were males (53.8%), married (85%), farmers (38.7%), not attend formal education (63.8%), Oromo (73.8%), Muslims (56.3%), dwellers of rural (53.8%) and had monthly income of less than 2000 ETB (63.75%) (Table 1).

Results of Anthropometric Measurements of COPD Patients

The (mean,±SD) of height, weight and BMI of the sampled and analyzed 80 COPD patients were (1.64±0.089 meter, 53.5±10.55 kg and 19.98±3.43 kg/m^2) respectively (Table 2).

Table 1. *Socio-demographic and Economic Status of COPD Patients Attending Chest Clinic of JMC from May 18 to August 18, 2017 G.C, n=80*

Variables	Categories	Frequency	Percentage (%)
Age in years	<30	4	5.0
	31-40	9	11.3
	41-50	18	22.5
	51-60	26	32.5
	61-70	15	18.6
	71-80	5	6.3
	>81	3	3.8
	Total	80	100.0
Sex	Male	43	53.8
	Female	37	46.2
	Total	80	100.0
Marital status	Unmarried	3	3.8
	Married	68	85.0
	Widowed	7	8.7
	Divorced	2	2.5
	Total	80	100.0
Occupation	Gov't employee	13	16.2
	Private	5	6.3
	House wife	28	35.0
	Farmer	31	38.7
	Other	3	3.8
	Total	80	100.0
Educational status	No formal educ.	51	63.8
	Primary school	20	25
	Secondary school	3	3.8
	College & above	6	6.7
	Total	80	100.0
Ethnicity	Oromo	59	73.8
	Amhara	8	10.0
	Dawuro	6	7.5
	Others	7	8.7
	Total	80	100.0
Religious status	Orthodox	22	27.5
	Muslim	45	56.3
	Protestant	11	13.8
	Others	2	2.5
	Total	80	100.0
Residence	Urban	37	46.2
	Rural	43	53.8
	Total	80	100.0
Monthly Income in ETB	<2000	51	63.75
	>2000	29	36.25
	Total	80	100.0

In ethnicity others refers to Tigre (2), Wolaita (3) and Kefa (1), ETB-Ethiopian birr/ national curreny, currently exchange for 1 dollar=27 ETB

Table 2. *Results of Variables Related with COPD among COPD Patients Attending Chest Clinic of JMC from May 18 to August 18, 2017 G.C, n=80*

Variables	Categories	Frequency	Percentage (%)
Smoking Status	Smoke cigarette	51	63.75
	Non smokers	29	36.25
	Total	80	100.0
Exposure to Biomass	Exposed	48	60.0
	Not exposed	32	40.0
	Total	80	100.00
Results of 6MWD in Meter	350-750	11	13.8
	250-349	17	21.2
	150-249	22	27.5
	<149	30	37.5
	Total	80	100.0
Duration of the Illness	<5 years	57	71.25
	>5 years	23	28.75
	Total	80	100.00
Hypoxia status (Result of SPO_2 post 6MWDT)	>90%	20	25.0
	<90%	60	75.0
	Total	80	100.0

Results of Variables Related with COPD

Among the total observed 80 COPD patients during 3 month study period, majority of the COPD patients were smokers (63.75%), also exposed to non-smoking risk factors/biomass exposure (60%), and walked a distance of less than 149 meter (37.5%) within six minutes. Majority of the patients were classified to stage 4/ very severe category of COPD (37.5%) based on the result of 6MWDT who were developed the disease within five years (71.25%) and hypoxic based on the result of their SPO_2 percentage less than 90(75%).

Results of ECG patterns among COPD patients

Out of the total analyzed and interpreted ECG papers from the sampled 80 COPD patients by investigator in liaison with the cardiologist, about 67 patients had abnormal ECG pattern (83.75%) while a few 13 patients had normal sinus ECG pattern (16.25%). Among the abnormal ECG pattern categorized based on the Minnesota coding criteria; arrhythmia accounted for (50%), atrial enlargement (48.8%), Myocardial infarction (MI)/coronary artery diseases (CADs) (41.3%), axis deviation (35%), other abnormalities (35%) like (poor progression of R-wave and low QRS amplitude), and ventricular hypertrophy (15%) were observed as one patient may have more than one types of abnormal ECG. Among arrhythmias as one types of abnormal ECG, different sub types were evaluated as per the Minnesota coding criteria. From this, sinus origin arrhythmia, conduction block, ectopic arrhythmia and pre excitation syndrome (PES)/Wolf Parkinson syndrome (WPWS) were interpreted with frequency of 30%, 23.8%, 17.5% and 2.5% respectively. The results of sub types of arrhythmias were listed under Table 3 in detail.

Table 3. *Results of ECG patterns among COPD patients attending chest clinic of JMC from May 18 to August 18, 2017 G.C, n=80*

Variables	Categories	Frequency	Percentage (%)
General ECG pattern	Normal	13	16.25
	Abnormal	67	83.75
	Total	80	100.00
Abnormal ECGs			
1. Arrhythmia 40 (50%)	Sinus origin (SOA)	24	30.0
	Sinus tachycardia (ST)	7	8.8
	Sinus bradycardia (SB)	13	16.3
	Sinus arrhythmia (SA)	4	5.0
	Ectopic (EA)	16	20.0
	Atrial flutter (Af)	1	1.3
	Atrial fibrillation (AF)	5	6.3
	Multi focal atrial tachyc.(MAT)	1	1.3
	Premature atrial contr.(PAC)	3	3.8
	Premature ventr. Contr.(PVC)	6	7.5
	Conduction block (CBA)	19	23.8
	AVB	1	1.3
	BBB	14	17.5
	CRBBB/complete	3	3.8
	IRBBB/incomplete	6	7.5
	CLBBB/complete	4	5.0
	ILBBB/incomplete	1	1.3
	Hemi fasicular block (HFB)	4	5.0
	LAHFB	2	2.5
	LPHFB	2	2.5
	PES or WPWS	2	2.5
2. Axis deviation (AD) 28 (35%)	RAD	11	13.5
	LAD	15	18.8
	EAD/Indefinite	2	2.5
3. Atrial enlargement (AE) 39 (48.8%)	RAE/ P-Pulmonale	23	28.8
	LAE	9	11.3
	BAE/ biatrialenlargt	7	8.8
4. Ventr. Hypertrophy (VH) 12 (15%)	RVH	5	6.3
	LVH	7	8.8
5. Myocardial infaction (MI)/ CADs 33 (41.3%)	Qwave abnormality	3	3.8
	ST-Twave changes	23	28.8
	Prolonged QTc interval	7	8.8
6. Other abnormality 28 (35%)	Poor Rwave progression	12	15.0
	Low QRS amplitude	16	20.0

One patient may have more than one abnormal ECG, AVB-Atrioventricular block, BBB-Bundle branch block, CBBB-Complete bundle branch block (right-R and left-L), IBBB-Incomplete bundle branch block (right and left), PES-Preexcitation syndrome, WPWS-Wolf Parkinson white syndrome, RAD-Right axis deviation, LAD-Left axis deviation, EAD-Extreme axis deviation, RAE-Right atrial enlargement, LAE-Left atrial enlargement, BAE-Biatrial enlargement, RVH-Right ventricular hypertrophy, LVH-Left ventricular hypertrophy.

Another interpreted abnormal ECG was axis deviation which was seen among 28 COPD patients (35%) from which LAD responsible for 18.8%, RAD 13.8%, and EAD 2.5% as interpreted by the hexaxial reference system.

The ECG also diagnosis enlargement and hypertrophy of heart champers as RAE accounted for 28.8%, LAE 11.3% and bi atrial enlargement/BAE contributed 8.8% from the total 48.8% of atrial enlargement while RVH and LVH responsible for 6.3% and 5.8% respectively to ventricular hypertrophy.MI/ CADs (ST-T-wave changes 28.8%, prolonged QTc interval 8.8% and Q-wave abnormality 3.8%) and other ECG abnormalities (low QRS amplitude 20% and poor R-wave progression 15%) were also observed.

Changes on ECG pattern and factors associated with ECG changes

Among evaluated 80 ECG papers of COPD patients, the prevalence of abnormal ECG pattern was 83.75% where the

high prevalence was observed among urban dwellers 32.4%, rural 51.3%, male 48.8%, smokers 60%, Muslims 48.8%, Oromo 63.8%, farmers 37.5% and also it was higher among COPD patients with age less than the mean/<55 years 50%, who had no formal education 55%, who engaged 72.5%, who earned less than 2000 ETB 58.75%, among underweight patients 50% and among patients with SPO_2 level less than ninety/hypoxic (70%).

Table 4. *ECG Pattern Changes and Associated Factors by Bivariate Logistic Regression and chi square/ X^2 test among COPD Patients Attending Chest Clinic of JMC from May 18 to August 18, 2017 G.C, n=80*

Dichotomous Variables	Categories	Status of ECG pattern			COR(95% CI)	X^2	*p*-value
		Normal	Abnormal	Total			
Residence	Urban	11(13.8)	26(32.4)	37(46.2)	1	9.2	0.008 *
	Rural	2(2.5)	41(51.3)	43(53.8)	8.6(1.8-42)		
	Total	13(16.25)	67(83.75)	80(100.00)			
Sex	Male	4(5.0)	39(48.8)	43(53.8)	3.1(1.8-11)	3.3	0.079 *
	Female	9(11.2)	28(35.0)	37(46.2)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Age in years	>55	2(2.5)	40(50.0)	42(52.5)	8.1(1.6-39)	8.6	0.009 *
	<55	11(13.8)	27(33.7)	38(47.5)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Educational Status	No formal educ	7(8.7)	44(55.0)	51(63.8)	1.6(0.5-50)	0.66	0.42
	Others (educated)	6(7.5)	23(28.7)	29(36.2)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Religious stat	Muslim	6(7.5)	39(48.8)	45(56.3)	1.6(0.5-5.36)	0.64	0.425
	Others	7(8.7)	28(35.0)	35(43.7)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Ethnicity	Oromo	8(10.0)	51(63.8)	59(73.8)	1.9(0.57-6.9)	1.2	0.28
	Others	5(6.2)	16(20.0)	21(26.2)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Occupation	Farmer	1(1.3)	30(37.5)	31(38.8)	1	6.3	0.033 *
	Others	12(15.0)	37(46.2)	49(61.2)	0.1(0.013-0.84)		
	Total	13(16.25)	67(83.75)	80(100.00)			
Marital status	Married	10(12.5)	58(72.5)	68(85.0)	1	0.79	0.379
	Others	3(3.8)	9(11.2)	12(15.0)	0.5(0.1-2.2)		
	Total	13(16.25)	67(83.75)	80(100.00)			
Monthly income (EBR)	<2000	4(5.0)	47(58.75)	51(63.75)	8(2-28)	3	0.003 *
	>2000	9(11.25)	20(25.0)	29(36.25)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Severity of BMI	Under weight	5(6.25)	40(50.0)	45(56.25)	5.5(1.7-44)	3	0.113 *
	Others	8(10.0)	27(33.75)	35(43.75)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Smoking status	Smoke	3(3.8)	48(60.0)	51(63.75)	8.4(2-33)	11	0.003 *
	Not smoke	10(12.5)	19(23.75)	29(36.25)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Exposure to biomass	Exposed	2(2.5)	46(57.5)	48(60.0)	12(2.5-59)	12	0.002 *
	Not exposed	11(13.75)	21(26.25)	32(40.0)	1		
	Total	13(16.25)	67(83.75)	80(100.00)			
Severity of COPD	Mild	7(8.75)	4(5.0)	11(13.75)	1	15	0.000 *
	Others	6(7.5)	63(78.75)	69(86.25)	18(4-81)		
	Total	13(16.25)	67(83.75)	80(100.00)			
Duration of disease	<5 years	12(15.0)	45(56.25)	57(71.25)	1	4.1	0.099 *
	>5 years	1(1.3)	22(27.5)	23(28.75)	5.8(1.7-48)		
	Total	13(16.25)	67(83.75)	80(100.00)			
Hypoxia (SPO_2 level)	>90%	9(11.2)	11(13.8)	20(25.0)	1	14	0.000 *
	<90%	4(5.0)	56(70.0)	60(75.0)	11.4(2.3-43)		
	Total	13(16.25)	67(83.75)	80(100.00)			

**-candidate variables for multivariate analysis (p-value<0.25), others in dichotomous variables were expressed in Table 1 in detail.*

Table 5. *ECG Pattern Changes and Associated Factors by Multivariate Logistic Regression among COPD Patients Attending Chest Clinic of JMC from May 18 to August 18, 2017 G.C, n=80*

Dichotomous Variables	Categories	Status of ECG pattern		AOR(95% CI)	*p*-value *≤0.05
		Normal	Abnormal		
Residence	Urban	11(13.8)	26(32.4)	1	0.274
	Rural	2(2.5)	41(51.3)	2.4(0.08-7.45)	
Sex	Male	4(5.0)	39(48.8)	3.1(1.5-23)	0.027 *
	Female	9(11.2)	28(35.0)	1	
Age in years	>55	2(2.5)	40(50.0)	2.4(0.1-4.1)	0.527
	<55	11(13.8)	27(33.7)	1	
Occupation	Farmer	1(1.3)	30(37.5)	0.2(0.1-3.6)	0.106
	Others	12(15.0)	37(46.2)	1	
Monthly income (EBR)	<2000	4(5.0)	47(58.75)	2.1(1.6-7.9)	0.047*
	>2000	9(11.25)	20(25.0)	1	
Severity of BMI	Under weight	5(6.25)	40(50.0)	0.7(0.06-8.4)	0.802
	Others	8(10.0)	27(33.75)	1	
Smoking history	Yes	3(3.8)	48(60.0)	2.2(1.5-8.6)	0.046 *
	No	10(12.5)	19(23.75)	1	
Nonsmoking exposure status	Yes	2(2.5)	46(57.5)	1.8(0.1-8)	0.124
	No	11(13.75)	21(26.25)	1	
Severity of COPD	Mild	7(8.75)	4(5.0)	1	0.021 *
	Others	6(7.5)	63(78.75)	3.2(2-8.4)	
Duration of disease	<5 years	12(15.0)	45(56.25)	1	0.345
	>5 years	1(1.3)	22(27.5)	4.8(1.8-12.9)	
Hypoxia (SPO_2 level)	>90	9(11.2)	11(13.8)	1	0.037 *
	<90	4(5.0)	56(70.0)	2.9(1.2-6.9)	

**-statistically significant variable (p-value<0.05), others value was known from Table 1.*

In the bivariate analysis, the candidate variables having *p*-value<0.25 were selected for the final model. Accordingly about eleven variables (residence, sex, age, occupation, monthly income, severity of BMI, smoking status, status of exposure to nonsmoking risks, severity of COPD based on 6MWDT results, duration of the illness and hypoxia status) were identified as the expected factors associated with the development of abnormal ECGs with their specific chi square, COR with 95% CI and *p*-values also explained in Table 4 in details.

Further, multivariate analysis (binary logistic regression with enter methods) were used to identify the main predictor variables by controlling the confounders with AOR and showed by dichotomous variables.

Finally the five variables (sex, monthly income, smoking history, severity of COPD and hypoxia) with *p*-value less than 0.05 fitted the final model with AOR (95% CI) and identified as the associated factors with abnormal ECG pattern among COPD patients.

By making all other variables constant; the likelihood of developing abnormal ECG pattern among COPD patient was 3.1 times among males than females, 2.1 times among those who earned less than 2000 ETB than earned more than 2000 ETB, 2.2 times among smokers than nonsmokers, 3.2 times among other stages of COPD than mild stage and 2.9 times among hypoxic patients (SPO_2 less than 90) than more than 90 (Table 5).

DISCUSSION

Among 80 COPD patients assessed, their mean age was greater than 50 years (55.1±13.66) which is also in line with other studies that revealed the mean age of more than 50 years from minimum mean 52.56±11 to maximum mean 59±7[12,38-41] while majority of the patients (32.5%) classified at interval of 51-60 years which is also in harmony with the study of Banker H who reported that majority of patients (35%) were grouped in this age interval.[42] The male dominance (53.8%) observed in the present study is in agreement with other studies.[12,36,38,40-62] But the odd female dominance (54.2%) was observed among COPD patients conducted in India.[38] The frequency of underweight BMI category (56.25%) was dominant over other groups as it is in harmony with study of Tariku et al[22] but the pattern of severity of COPD was against the study of Tariku et al[22] because different approach of severity classification was used while the prevalence of COPD by its stages was matched with the study conducted by Lokendra et al[41] where the frequency of patients were increased through the stages from mild to very severe (13.8%-37.5%) and (12%-36%) in the present study and Lokendra et al study respectively.[41] The dominance of smokers (63.75%) than nonsmokers was also in line

with other studies as it confirms that majority of COPD patients (50-80%) were smokers.[1]

Abnormal ECG pattern was interpreted among 67(83.75%) of COPD patients which is consistent with other studies[32,36,41,46,48,58-62] that reported the prevalence of abnormal ECG among COPD patients >50% ranges 50%[46,62]-81.5%.[60] But, the prevalence of abnormal ECG <50% was only reported by study of Agarwal R (35.7%).[49]

Based on Minnesota ECG coding criteria for classification, the observed abnormal ECG were:

1. Arrhythmia (50%) due to global hypoxia in COPD patients manifested in high alveolar wall resistance, alveolar, and capillary destruction and air trapping that result in under ventilated/alveolar hypoxia which is compensated by vascular remodeling (hypoxia induced pulmonary vasoconstriction (HIPVC), intimal hyperplasia, smooth muscle hypertrophy/ hyperplasia, endothelial cell dysfunction and loss of the pulmonary capillary bed) resulting in pulmonary hypertension that increases work load on the heart reflected as arrhythmia.

2. Heart chamber enlargement (atrial enlargement 48.8% like RAE/P-pulmonale 28.8% and ventricular hypertrophy 15%) due to HIPVC as compensatory of alveolar hypoxia in COPD patients resulting in pulmonary hypertension with increased burden of heart to overcome pulmonary pressures ends with chamber enlargement specially on the right side the heart; seen on ECG as p-pulmonale.

3. Axis deviation 35% due to hyperinflation and hyper expansion of the lungs of COPD patients that compresses the heart and pushes diaphragm downwards and resulting in the heart to be elongated, and vertically oriented and rotated clockwise in the transverse plane as the heart has fixed attachments to the great vessels. This causes displacement of the right ventricle anteriorly and the left ventricle posteriorly.

4. Signs of MI/CADs (41.3%) also observed on ECG secondary to global hypoxia among COPD patients.

5. Low QRS amplitude 20% and poor progression of R-wave 15% due to dampening effect/insulating effect of hyper inflated lungs and lowered position of the heart (tubular) with respect to electrodes.

The determined associated factors with abnormal ECG by their specific AOR with 95% CI were:

1. Hypoxia/SPO_2 level less than 90% post 6MWDT with [AOR 2.9(1.2-6.9)] as it induces pulmonary vasoconstriction as compensatory mechanism and further increases work load of heart results in abnormal ECG like p-pulmonale, RVH, axis deviation and MI/CADs. This is in line with study conducted by Shah V et al as the hypoxia is the independent risk factor in inducing abnormal ECG especially atrial fibrillation with [AOR 1.76(1.64-1.89)].[33]

2. Severity of COPD: by making the mild stage of COPD reference, other stages are 3.2 more likely to develop abnormal ECG/AOR 3.2(2.0-8.4) as it is consistent with the study conducted by Sin & Man with [AOR 2.18(1.46-3.27)] and Nilson U et al with [AOR 1.89 (1.2-2.99)].[27,31] This is mainly due to the exacerbation of the disease resulting in systemic comorbidities including CVDs as evidenced by ECG.

3. Smoking [AOR 2.2(1.5-8.6)] as a mutual risk factor for COPD and CVDs also in harmony with study conducted by Shah V et al as one of the determined risk factor [AOR 2.2(1.5-3.1)] for the development of abnormal ECG indicating CVDs due to COPD systemic comorbidity.[33]

4. Gender male [AOR 3.1(1.5-23)] is another identified risk factor for development abnormal ECG among COPD patients because all the male patients were exposed to smoking and they were relatively elders (the two mutual risk factors (smoking and aging)). This is also in agrrementwith study conducted by Larssen MS et al who revealed that being male was risk for developing abnormal ECG with [AOR 1.864(0.39-3.57)].[26]

5. COPD patients with low monthly income less than 2000 ETB are also the risk factor for abnormal ECG among COPD patients by [AOR 2.1(1.6-7.9)] but it was not determined among other reviewed studies. Because low socioeconomic status is multi component factor for poverty and malnutrition affecting birth weight that impairs growth, maturation & development of vital organs and as well as frequent exposures to respiratory infection that later develops CVDs.

In nutshell, the present study revealed higher prevalence of abnormal ECG than any previous studies. The possible justification for this difference might be absence of routine screening for systemic comorbidities including CVDs in the setting and the treatmentis also limited to the primary compliant of the patients (COPD).

STUDY LIMITATION

The present study is limited to a small sample size, thus further research is needed with inclusion of more patients, preferably at multicenter level to validate our findings.

CONCLUSION

Among 80 COPD patients enrolled in the present study, maximum numbers of patients were in the age range of 51-60 years, with high prevalence among males, with low economic status, living in rural areas, farmers, smokers and underweight. The prevalence of abnormal ECG was 83.75%. As the classification was based on Minnesota ECG coding criteria, the identified abnormal ECG were: arrhythmia 50%, atrial enlargement 48.8%, MI/CADs 41.3%, axis deviation 35%, other ECG abnormalities (poor R-wave progression and low QRS amplitude) 35% and ventricular hypertrophy 15% .

The identified associated risk factors with the abnormal ECG were hypoxia, sex, low monthly income, smoking history and severity of COPD.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Malignant Restenosis and Progression of Disease in Psoriatic Patients Undergoing Coronary Interventions: Is it the Koebner's Phenomena to Blame?

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ABSTRACT

Severe psoriasis is associated with an enhanced risk of cardiovascular (CV) diseases. The potential impact of psoriasis on the prognosis following coronary revascularization (percutaneous coronary intervention (PCI) or surgical) is not well studied and sparse data available in literature points towards a grim long-term prognosis. The following two cases highlight this phenomenon. We also discuss the plausible reasons responsible for the poor prognosis and propose some possible mechanisms for the same.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disorder affecting about 1-3% of the population worldwide. It is now considered a systemic disease affecting several body systems rather than a disorder characterized by skin and joint manifestations. Not only is the prevalence of established traditional cardiovascular (CV) risk factors higher in patients with severe psoriasis they also exhibit increased rates of myocardial infarction, atrial fibrillation, coronary revascularization, stroke, CV death, and overall mortality, suggesting a potential role of shared pathways in both psoriasis and atherosclerosis.[1] However, whether psoriasis also poses as a significant risk factor for repeated coronary interventions remains, largely unexplored. Only one study[2] has looked at the impact of psoriasis on post-percutaneous coronary intervention (PCI) prognosis and results have raised several valid concerns that this disease may pose in patients undergoing PCI.

We came across two patients who underwent repeated coronary interventions (surgical/percutaneous) due to recurrent restenosis. One thing common between the two was the presence of severe psoriasis. The following discussion looks at the patient profiles and the plausible mechanisms and role of psoriasis in perpetuating this malignant restenosis.

CASE REPORT

Case 1

A 68-years-old lady normotensive, non-diabetic and a known case of severe psoriasis presented with unstable angina. She had suffered an anteroseptal myocardial infarction (MI) a year ago. She underwent coronary angiography which revealed 100% ostial left anterior descending artery (LAD) occlusion and significant left main coronary artery (LMCA) and proximal left circumflex disease (LCx). Following a stress thallium study which revealed no significant reversible ischemia in the LAD territory, she underwent percutaneous transluminal coronary angioplasty (PTCA) and stenting from LMCA to LCX using a 4X 23 mm vision stent (Abbot Vascular, Santa Clara, CA, USA). She was also on methotrexate and phototherapy for her psoriatic skin lesions. The patient had clinically documented Koebner's phenomena. She presented 3-months later with recurrence of angina and a check angiogram

revealed 90% in-stent restenosis (ISR) in the proximal part of the LMCA stent. This time she underwent repeat angioplasty and stenting from LMCA to LCX using a 4X 28 mm Xience V stent (Abbot Vascular, Santa Clara, CA, USA). Eight months later she once again had recurrence of angina and an angiogram revealed 90% LMCA in-stent restenosis following which PTCA with drug-eluting balloon (SeQuent Please, B. Braun, Berlin, Germany) to LMCA was done. One month later the patient had sudden cardiac death at home.

Case 2

A 76-years-old gentleman known diabetic, hypertensive with psoriasis and psoriatic arthropathy presented with angina in June 2001. Coronary angiography (CAG) was performed revealing double vessel disease following which he underwent PTCA and stent to LAD using a Tetra 3X13 mm bare metal stent (Guidant Corporation, Santa Clara, CA, USA) and balloon angioplasty to posterior descending artery (PDA). He had recurrence of angina in September 2001 and then underwent coronary artery bypass grafting (CABG) (Left Internal Mammary Artery-LIMA to LAD, Saphenous venous graft-respiratory syncytial virus glycoprotein (RSVG) to diagonal 1 and radial artery to right coronary artery-RCA). Four months later in view of angina a repeat angiogram was carried out which revealed occluded left internal mammary artery (LIMA) and radial grafts, and underwent redo coronary artery bypass grafting (CABG) using venous grafts. The fact that the sites of occlusion of these grafts were the distal anastomotic sites the possibility of this being a surgical technical complication cannot be negated totally with certainty. In August 2004, CAG done, for recurrence of angina revealed blocked SVG grafts, normal LMCA, LAD 80% instent restenosis, D1 90% ostial disease, LCx 50% proximal lesion and PDA 100% occlusion. He subsequently was on medical management with partial relief. Following an angiogram in January 2006 he underwent PTCA and stent to LAD using Cypher select 3.5X28 mm stent and plain balloon angioplasty to D1. This was then followed by plain balloon angioplasty to LAD in June 2008 as LAD revealed 100% ISR (the procedure performed as patient had rest angina). At this time diffuse disease in LAD was noted distal to the stent and hence a check shoot one month later was planned, which revealed 100% LAD occlusion. He subsequently was put on optimal medical therapy however succumbed following stroke related complications in 2016.

DISCUSSION

The normal healing response of the arterial injury following coronary stenting comprises of two main processes, the formation of new intima and reendothelialization of the injured vessel surface.[3,4] The earliest reaction following deployment of bare-metal stent is vessel injury which results in formation of platelet-rich thrombus. At the same time acute inflammatory cell infiltrate occurs within the thrombus and the adjoining vessel wall. This is followed by macrophage infiltration which induces cytokine and growth factor release. The growth factors lead to smooth muscle proliferation and migration. These processes in the animal models occur within 14 to 21-days. Simultaneously, matrix deposition occupies approximately 50% of the neo-intimal growth by 28-days in animals, whereas in man this process takes 6-9-months. Thereafter the neo-intima begins to regress as it gets replaced by type 1 collagen.[3,4] Finally there is endothelialization of the injured vessel. At this stage endothelial cells repopulate the luminal surface thus forming a protective barrier against thrombus formation.

When this healing response gets exaggerated it leads to restenosis which is a major limitation with coronary stenting requiring patients to undergo repeated revascularization procedures or even surgery. It is proposed that restenosis is a multi-factorial process caused by a number of overlapping processes, such as neo-intimal hyperplasia due to increased inflammation, increased smooth muscle cell proliferation, and/or increased extracellular matrix deposition.[3,4]

What is unique to Psoriasis? In a Danish study,[2] which looked at the prognosis after PCI in psoriatic patients found that there was a non-significant trend (p=0.23) for increased repeat revascularization rates in patients with psoriasis compared to patients without psoriasis. The incidence rates (IRs) were 66.9 (CI 65.6-68.3), 71.3 (CI 62.2-81.6), and 75.0 (CI 57.7-97.5), for patients without psoriasis, with mild psoriasis, and with severe psoriasis, respectively. The corresponding adjusted HRs were 1.05 (CI 0.89-1.22) and 1.14 (CI 0.85-1.52) for mild and severe psoriasis. Inflammation has also been suggested to contribute to post-PCI complications including restenosis, in-stent thrombosis and mortality. Very limited data are available, however, on the impact of inflammatory diseases on the prognosis after PCI. A small study of patients with systemic lupus erythematosus demonstrated a worse 1-year outcome compared to controls while a very small study of patients with rheumatoid arthritis found no differences between groups.[4,5]

Apart from being an immune-mediated disease characterized by a heightened inflammatory state which could lead to enhanced and exaggerated inflammatory reaction to vessel injury psoriatic patient's exhibits unique phenomena called Koebner's phenomenon. This is characterized by development of new skin lesions wherever trauma occurs in uninvolved areas. Trauma caused by friction and lacerations are known to induce this phenomena.[6] The Koebner's response is more likely to occur when psoriasis is unstable or flaring and less likely with quiescent or resolving psoriasis. More severe injury may result in more extensive lesions. Histopathology of such lesions also reveals an exaggerated immune response.[6] We strongly feel that in the presence of an already heightened inflammatory condition the vessel trauma caused by the intervention induces a Koebner's like response in the vessel wall (due to trauma at site of intervention) and leads to an exaggerated inflammatory state with subsequent higher rates of restenosis. However, this phenomena needs to be proven histo-pathologically and at the present time is a postulation.

It also highlights the need for a proper history taking by the cardiac sciences team so that such subsets can be identified and counseled accordingly.

CONCLUSION

Autoimmune inflammatory disorders as psoriasis are associated with increased risk of adverse cardiovascular events. Interventional cardiac therapies in such patients might also be fraught with higher failure rates in the long-term due to enhanced rate of restenosis secondary to a hyper-intense inflammatory reaction. Although not proven, Koebner's phenomena like response at sites of trauma (secondary to intervention) in the coronaries may act as a triggering factor.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

Pulmonary Artery Hypertension in Children Living with Sickle Cell Anaemia

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ABSTRACT

Pulmonary artery hypertension (PAH) ultimately leads to straining of the right ventricle and increases the risk of heart failure in affected patients. Its clinical presentation is similar to that of many other diseases thus delaying the diagnosis until the disease is far advanced. It remains one of the leading causes of death in adults with sickle cell anaemia (SCA) worldwide. It confers a high risk of death with two-year mortality rates as high as 40-50% even at modest elevation of pulmonary artery pressure. Median survival age after detection of the disease is said to be 25.6-months. Early detection of elevated pulmonary artery pressure in childhood and appropriate intervention by optimization of anti-haemolytic therapy may prevent the progression of this complication. The current writes up is a review of literatures on pulmonary artery hypertension among children with sickle cell anaemia. This will give information which will aid early diagnosis and treatment of pulmonary artery hypertension among children with sickle cell anaemia. This will ultimately improve the quality of life of children with sickle cell anaemia and reduce morbidity and mortality from the disease in adults and children living with sickle cell anaemia.

Keywords
Sickle cell anaemia; Pulmonary artery hypertension; Children.

INTRODUCTION AND EPIDEMIOLOGY

Pulmonary artery hypertension (PAH) once considered a rare complication of sickle cell disease (SCD) occurs in approximately one-third of adults with SCD.[1,2] Much less is known about its prevalence and natural history in children worldwide.[1,3,4] Pashankar et al[5] conducted the first prospective study in the USA. The study comprised of 75 children all older than six years (mean age range of 9.41-years) and also found a prevalence of 30%. This is similar to the adult findings.[1,2]

Contrary to the study conducted by Pashankar et al,[5] Minniti et al,[6] in another prospective, multicenter study also in the USA conducted a study on 310 SCD patients aged three to twenty years and found a prevalence of 11% (one case seen in a three-year-old patient with SCD) quite similar to that found in another study conducted by Gordeuk et al[7] wherein a prospective longitudinal study of 160 subjects aged three to twenty years, a prevalence of 14.1% was found. They both concluded that the incidence of PAH begins very early in life (as early as the third year of life) in patients with SCD and increases with age.

However, the result of some small screening studies,[1] a combination of prospective[1,5,8] and retrospective studies,[3,9-13] an aggregation of screening results from over 600 children with SCD in the USA showed a prevalence of 35% nearly identical to 32% in the summarized screening experience in adults with SCD.[1]

In West Africa, where the burden of sickle cell disease is highest, Aliyu et al[14] conducted a subgroup analysis in Zaira, Nigeria, on 208 consecutive SCD patients, aged ten to 52-years in steady-state to determine the prevalence of pulmonary artery hypertension and found a prevalence of 25%. This finding is low compared to the first prospective study conducted by Pashankar et al[5] in the US despite adequate laboratory data showing an increase in hemolysis in subjects in the Nigerian study subjects. The researchers concluded that a relatively lower prevalence found in the study could be due a reduction in the older age bracket (>

35-years) of patients used in the Nigerian study (7%) as compared to (46%) in the US based study. This they attributed to the possibly reduced life expectancy of SCD patients in West Africa compared to the American cohort. In a more recent study, conducted in Nigeria by Dosunmu et al[15] the Lagos State University Teaching hospital (LASUTH), Ikeja, Nigeria on 56 patients with sickle cell anaemia older than 14-years with mean age range (22±6-years) the researchers found a prevalence of 3.6% which is much lower than the US based study. The researchers concluded that the very low prevalence of PAH in subjects studied could be due to the very small sample size used compared to the US based study as well as reduced life expectancy of SCD patients in Nigeria.

Ambrusko et al[11] reviewed out-patient echocardiography of 44 adolescents and found a prevalence of pulmonary hypertension of 26.2%. Qureshi et al[12] did a case comparison of echocardiograms on patients with sickle cell disease and healthy controls and found a prevalence of 16%. However, these studies were retrospective and only eligible patients were recruited thereby introducing bias into their study.

It is obvious from the above that socioeconomic factors may strongly influence the varying prevalence rates of pulmonary artery hypertension worldwide.[16] Even though the prevalence of PAH may increase with age generally in developed countries as seen in the US based studies the contrary maybe for our environment where the life expectancy of patients with SCD is reduced.

PHYSIOLOGY OF PULMONARY ARTERY PRESSURE

The lungs receive cardiac output with each stroke volume. The pulmonary circulation is normally a high flow, low resistance system that carries blood into the pulmonary microcirculation.[17] Pulmonary artery pressure is a measure of blood pressure found in the pulmonary artery. The normal values for mean pulmonary artery pressure ranges from 8-20 mmHg.[18]

Pulmonary artery hypertension is said to begin when this mean pulmonary artery pressure exceeds 25 mmHg at rest and 30 mmHg during exercise. This definition applies to both adults and children except during infancy.[18,19]

There are other causes of an elevated pulmonary artery pressure some of which are listed below:

- Congenital heart diseases associated increased pulmonary blood flow i.e those with left to right shunting of blood at the atrial, ventricular or great vessel level such as ventricular septal defect, atrial septal defect, atrioventricular septal defect and patent ductus arteriosus.[18,20]

- Pulmonary causes which could be idiopathic as seen in primary pulmonary hypertension. Other pulmonary causes include: Obstructive lung disease such as chronic obstructive pulmonary airway disease (COPD)[15,18,20] and restrictive lung disease such as emphysema.[21] Pneumonia, pulmonary hypoplasia associated with congenital diaphragmatic hernia or renal dysplasia, peripheral pulmonary stenosis.[18,20]

- Hereditary hemolytic anaemia such as: SCD,[1,5,13,14,18,19,21] Thalassemia,[1,5,16] Hereditary spherocytosis,[5] Paroxysmal nocturnal haemoglobinuria.[5]

- Hepatic disease such as cirrhosis and portal hypertension.[18,20]

- Collagen vascular diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.[20]

- Granulomatous disease such as sarcoidosis.[20]

THE PATHOGENESIS OF PULMONARY ARTERY HYPERTENSION IN SICKLE CELL ANAEMIA

The pathogenesis of pulmonary hypertension in sickle cell anaemia (SCA) as suggested by many studies is likely to be multifactorial.[1,5,6,13] Proposed mechanisms include haemolysis-induced endothelial dysfunction[5,14] chronic hypoxemias,[22] asplenia, parenchymal and intravascular sequestration of sickled erythrocytes, iron overload and inflammation.[1]

The role of haemolysis in the development of pulmonary hypertension has been described by many authors.[5,23,24] Haemolysis results in the release of haemoglobin and the enzyme erythrocyte arginase from red blood cells both increasing consumption and decreasing production of nitric oxide (NO). NO is a critical regulator of vasodilatation and vascular homeostasis whose inactivation produces vasoconstriction and proliferative vasculopathy. Minniti et al,[6] in the United States of America found a significant correlation between markers of haemolysis such as lactate dehydrogenase (LDH), aspartate aminotransferase and bilirubin concentration, reticulocyte count suggesting haemolysis plays a strong role in the pathogenesis of pulmonary artery pressure. There was however, no significant relationship found between anaemia and elevated pulmonary artery pressure.[6] This finding was in contrast to that of Pashankar et al[5] where subjects who had elevated pulmonary artery pressure had significantly higher reticulocyte count when compared with unaffected patients. Although, no significant relationship was found between elevated pulmonary artery pressure and some markers of haemolysis (anaemia, bilirubin levels and LDH) was found. In addition, they found that thrombocytosis was significantly associated with elevated pulmonary artery pressure, a finding they attributed to functional asplenia. Hence, they concluded that the pathophysiology of PAH in SCD is most likely multifactorial with haemolysis being just one of the causes in SCD.

Functional asplenia, a clinical condition which occurs in SCA patients, has also been linked to the incidence of pulmonary hypertension.[5] It is speculated that loss of splenic function in patients with SCD increases circulation of platelet-derived mediators, senescent and abnormal erythrocytes in circulation promoting pulmonary microthrombosis and red cell adhesion to endothelium hence leading to PAH.[5]

In Zaira, Nigeria, Aliyu et al[14] found that white blood cell count, platelet count and reticulocyte counts of patients with sickle

cell disease were not significantly associated with an increase in tricuspid regurgitant velocity (TRV) while lactate dehydrogenase was found to have significant associations with an elevated TRV. Hence, they concluded that haemolysis played a major role in the cause of PAH in SCD patients.

This finding in the Aliyu et al[14] study could be attributed to the fact that the subjects recruited for the study were largely those who had been attending regular clinic. Hence, many are treated appropriately and promptly when an infection arises. The above studies show that haemolysis,[5,6,14] a clinical feature seen in patients with SCD, play a strong role in the aetiopathogenesis of PAH among patients with SCD, but beyond haemolysis, other features such as thrombocytosis resulting from functional asplenia seen in them, also play a role.

CLINICAL PRESENTATION OF PULMONARY ARTERY HYPERTENSION

Pulmonary artery hypertension usually progresses unnoticed.[5] The symptoms of PAH in children are variable with symptomatology depending on the aetiology and severity of disease as well as age of the patient. Symptoms may be nonspecific and may include poor appetite and poor growth in infants while older children may present with nausea, vomiting, lethargy or over syncope.[18] The most common presenting symptom for pulmonary hypertension in SCD is worsening of dyspnoea on exertion.[1] This may wrongly have attributed by clinicians to anaemia and cardiopulmonary evaluation may be delayed. Signs elicited in affected patients include; digital clubbing,[1] On cardiac examination a loud P_2 may be heard an ejection systolic murmur loudest in the pulmonary area also referred to as the Graham Steell murmur,[20] as the disease progresses signs of right-sided heart failure such as an elevated jugular venous pressure (JVP), hepatomegaly, ascites, pedal and peripheral oedema may be seen.

DIAGNOSIS OF PULMONARY ARTERY HYPERTENSION

The gold standard for determining pulmonary artery pressure (PAP) is by cardiac catheterization. However, this procedure is highly invasive and not suitable for screening purposes.[5,21] Doppler echocardiography is however very sensitive and non-invasive.[4,8] The use of echocardiography to estimate pulmonary artery systolic pressures has been well validated in patients with SCD, and non-invasive assessment correlates well with measurement of pulmonary artery pressures by right heart catheterization.[25,26] An optimal view of TRV is obtained during echocardiography by taking multiple measurements of TRV on multiple views (apical 4 chamber, parasternal short axis, parasternal long axis). An average of these measurements is then taken as the estimated TRV to ensure accuracy. The pulmonary artery systolic pressure is then estimated using the modified Bernoulli equation.[18]

MANAGEMENT OF PULMONARY ARTERY HYPERTENSION

It is likely that maximization of standard treatment in patients with SCD particularly targeted at reduction of haemolysis would be beneficial since haemolysis has been found to be a major cause of PAH.

There are currently several Food and Drug Administration (FDA) approved drugs for the treatment of pulmonary hypertension but there are few studies on the efficacy of these drugs.[5] Kato et al[1] reported that the use of phosphodiesterase-5-inhibitor sildenafil reduces pulmonary pressure and improves cardiopulmonary performance in patients with thalassemia and SCD who have already developed pulmonary artery hypertension. This was demonstrated in their study by an increase in the 6-minute walk distance on fifteen patients with SCD who had PAH after. Twelve of the patients were found to have an increase in the 6-minute walk distance after chronic use of sildenafil.[1,27] There are well-documented beneficial effects of therapy with prostanoids (epoprostenol, treprostinil, iloprost, beraprost).[14,28] Endothelin (ET) antagonists (bosentan and sitaxsentan) and possibly phosphodiesterase-5 inhibitors sildenafil) in patients with traditional forms of pulmonary arterial hypertension. There are no long-term data on the specific treatment of pulmonary hypertension in SCD and the choice of agents at this juncture is largely empirical.

Hydroxyurea, an antisickling drug which also increases the fetal haemoglobin, is known to help reduce haemolysis but has not been found to significantly impact on the mortality of SCD related pulmonary artery hypertension.[5]

EFFECT OF SICKLE CELL ANAEMIA ON PULMONARY ARTERY PRESSURE

Sickle cell anaemia is an independent cause of PAH[15] Minniti et al[6] reported that a greater than 2 standard deviation (SD) increase in haemolyticindex was associated with a 4.5 fold increase of elevated TRV and an oxygen saturation of ≤98% was associated with a 3.2 fold rise of TRV.

Among patients with SCA who develop pulmonary artery hypertension early in life, it is suspected that between the ages of twenty to fifty years more extensive vascular smooth muscle hyperplasia would have occurred with luminal narrowing that may not respond to therapeutic maneuvers to reduce haemolysis. In advanced cases, irregular, chronically activated endothelium may have accrued *in situ* thrombosis and plexogenic changes that dramatically increase pulmonary vascular resistance. It is speculated that in such advanced stages prevention of haemolysis by transfusion may be ineffective and only pharmacological treatment

PAP=Mean Right Atrial pressure (a constant of 5 mm Hg)+Bernoulli derived TRV (4V2)

can improve pulmonary pressure but gradual progression of the disease is still likely.[5]

THE EFFECT OF PULMONARY ARTERY PRESSURE ON SICKLE CELL ANAEMIA

Pulmonary artery hypertension has been found to drastically reduce the life expectancy of patients with SCA. Two-year mortality rate is known to be as high as 40-50%.[13,22,23,27]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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