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Electrocardiogram Structural Changes between Chronic Obstructive Pulmonary Disease Severities in Adam Malik General Hospital Medan

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ABSTRACT

Introduction: Cardiovascular complications caused by chronic obstructive pulmonary disease (COPD) will change the normal function and the shape of the heart's anatomy. The purpose of this study to determine whether there was a relationship between the degree of severity of COPD and electrocardiogram (ECG) changes.

Methods: A cross-sectional analysis conduct on 80 subjects who fulfilled inclusion criteria at the outpatient cardiology clinic H. Adam Malik Hospital Medan. The subject was divided equally based on the severity of COPD and ECG examination was performed. Statistical analysis processed using multivariate with p>0,05 as statistical significance The correlation is presented as Pearson r values and new values are obtained by the ROC curve.

Results: The mean age was 57±13 years with males have a majority proportion (85%). P Pulmonale and RBBB were common in severe COPD (GOLD 3 p = 0.001, GOLD 4 p <0.001). P wave axis and the amplitude of the P wave was found to be significantly different (p <0.001) with a strong and moderate correlation (r = 0.706 and r = 0.577). P-axis values of more than 56.3 degrees and P-wave amplitudes of more than 0.15 mV had a sensitivity of 80-85% and specificity of 80% to differentiate more severe COPD.

Conclusion: ECG assessment can be used to differentiate severe COPD with a fairly good correlation. ECG assessment in COPD patients can be used as the initial modality for assessing severe COPD (GOLD 3 and GOLD 4) at H. Adam Malik Hospital Medan.

INTISARI

Latar belakang: Komplikasi kardiovaskular yang disebabkan oleh penyakit paru obstruktif kronik (PPOK) akan mempengaruhi fungsi dan struktur normal dari jantung. Studi ini bertujuan untuk mengetahui hubungan antara derajat keparahan PPOK dengan penanda perubahan struktur dan fungsi jantung dari penilaian elektrokardiogram (EKG).

Metode: Penelitian ini merupakan studi analitik potong lintang yang melibatkan 80 orang subjek yang memenuhi kriteria inklusi. Pemeriksaan EKG dilakukan berdasarkan derajat keparahan PPOK. Analisis data menggunakan analisis multivariat dilanjutkan dengan mencari menilai korelasi berdasarkan nilai *Pearson r* dengan nilai signifikansi p>0,05. Nilai baru didapatkan berdasarkan analisis nilai titik potong pada kurva ROC.

Hasil: Mayoritas subjek memiliki jenis kelamin laki-laki (85%) denganrerata usia 57±13 tahun. Penanda P pulmonal dan penanda RBBB lebih sering dijumpai pada PPOK berat (GOLD 3 p=0.001, GOLD 4 p<0,001). Nilai aksis gelombang P, amplitudo gelombang P dijumpai berbeda bermakna pada

setiap derajat PPOK (p<0,001) dengan korelasi kuat dan sedang (r=0,706 dan r=0,577). Nilai aksis gelombang P >56,3 derajat dan amplitudo gelombang P >0,15mV memiliki sensitifitas 80-85% dan spesifisitas 80% untuk membedakan derajat PPOK yang lebih berat.

Kesimpulan: Penilaian EKG dapat digunakan untuk membedakan derajat keparahan PPOK berat dengan korelasi yang cukup baik. Penilaian EKG pada pasien PPOK dapat menjadi modalitas awal untuk menilai PPOK berat (GOLD 4 dan GOLD 4) di RSUP H. Adam Malik Medan.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease that characterized by persistent and progressive air flow limitation. This is related to an excessive chronic inflammatory response to the airways and pulmonary parenchyma.[1] Global Initiative for Chronic Obstructive Lung Disease (GOLD) report that in 2010 as many as 384 million people or around 11.7% of the world's population weresuferred from COPD with mortality rate reach three million people each year.[2] COPD currently known has a role in worsening heart function. Despite from having the same risk factors as cardiovascular disease, COPD may directly cause cardiovascular complications. In contrast, cardiovascular abnormalities are undoubtedly contributors to morbidity and mortality in COPD patients.[3]

Cardiovascular complications included heart failure, progression of atherosclerotic, arrhythmias and pulmonary hypertension. Observational study found that as many as 42% of patients with mild COPD had cardiovascular disorders. Along with the progression of the disease, the probability of complications of pulmonary hypertension will increase in every degree of COPD. Previous studies have shown that pulmonary hypertension can determine the prognosis in COPD patients. Study by Oswald-Mammosser et.al. in 1995 it was successful in proving that the 5-year survival rate of COPD patients with mild pulmonary hypertension (20-30 mmHg) reached 50%, whereas for moderate pulmonary hypertension (30-50 mmHg) only reached 30% and 0% for pulmonary hypertension weight (> 50 mmHg).[4] Atrial fibrillation (AF) are often found in COPD population asa complication, with prevalence reaching 4.7% to 15% in stable COPD.[5]

An ECG examination is the easiest, simplest and most effective examination modality. Through ECG examination there is a high correlation between ECG changes in each degree of COPD and this shows the severity of the disease.[6]

All of ECG changes caused by COPD can describe the changes in heart structure and determine the prognosis.[7] ECG changes will be increasingly encountered along with the increase of COPD severity based on GOLD criteria.[6] ECG assessment in COPD patients is important, so that it can help the selection of appropriate therapy, assesement of prognosis and finally it can be used for secondary preventive measurements to improve patient quality of life.

Methods

Study Design

This cross-sectional study was conducted at the Haji Adam Malik Medan (HAM) General Hospital with permission from the Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara (FK USU)-HAM General Hospital from December 2018 to April 15th, 2019. The research subjects were male and female patients > 30 years old who had been diagnosed with COPD from the Outpatient Polyclinic of the Department of Pulmonology and Respiratory Medicine FK USU-HAM General Hospital. ECG examination is performed using BionetCardiotouch 3000, BiTech Medical Georgia.

Patients with clear evidence of bronchial asthma, lung cancer and pulmonary embolism were excluded from this study. Patients with coronary artery disease who have been previously diagnosed (history of angina, ischemic signs on electrocardiography, presence of left abnormality on left ventricle based on echocardiography or a documented history of heart attack), patients with significant heart valve disorders (stenosis/regurgitation of aortic valve, mitral valve stenosis/regurgitation, pulmonary valve stenosis and tricuspid valve stenosis) and congenital heart disease were also excluded from the study.

Data collection was carried out starting from clinical data consisting of disease history, initial physical examination, ECG, chest x-ray and spirometry results. The severity of COPD is determined by the GOLD criteria based on the results of spirometry. The degree of air flow resistance is classified as GOLD 1 (FEV1 ≥ 80% prediction), GOLD 2 (50% ≤ FEV1 <80% prediction), GOLD 3 (30% ≤ FEV1 <50% prediction) and GOLD 4 (FEV1 <30% prediction) coupled with a FEV1/FVC value (Forced Expiratory Volume in 1 Second / Forced Vital Capacity) < 0.70.

Electrocardiography is the process of recording electrical activity in the form of graphic recordings. An ECG is the result of recording the heart's electrical activity in the form of a graph on a recording paper. Graph of cardiac activity is described as a collection of waves (Figure 1) and measurement of values on an electrocardiogram is carried out using a calibrated digital verniercaliper.

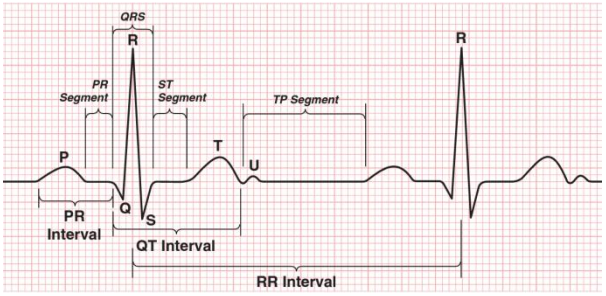

Figure 1. Structural wave of an electrocardiogram.[8]

Statistical Analysis

Processing and analysis of statistical data using statistical computer devices 'Statistical Package for Social Science '/ SPSS version 22-23, (IBM United States). The Pearson Chi Square test was used to compare the unpaired categorical variables between groups on independent and dependent variables. If requirements of Chi Square test are not met, then the Fisher test is used.[9]

Anova test was used to compare the numerical variables of more than 2 groups with Post-hoc analysis using LSD and Bonferroni. To assess clinical relationships, a comparative test was performed by dividing the severity group into 2 large groups (Light-Moderate and Severe).[10]

Decision making in the categorical analytical test is taken by comparing asymp. significance value of Chi Square test output with critical value by 0.05 (with type I error rate = 5%). If the asymp. significancy value is found <0.05 then there is a relationship between variables.

New value of the parameter obtained from the cutoff by using the ROC curve. It can be provided when AUC value is > 80%. The new value also determined by considering the best sensitivity and specificity for this study.

Results

Baseline Characteristics

In this study, 80 patients with COPD were obtained who had met the inclusion and exclusion criteria. The subject is divided into 20 people for each GOLD group. From the total of COPD subjects, 68 people (85%) were men. 44 people (55%) had a long smoking period of more than 20 years.

Table 1 shows the basic demographics of the study subjects which compared between smoking history, hemodynamic status, spirometry and baseline echocardiographic results in each COPD group.

From the table, it was found that subjects with GOLD 3 and GOLD 4 had older age averages compared to subjects with milder COPD severity (p <0.001). There were no significant differences in the variables of height, weight, blood pressure and pulse among the subject groups. (p> 0.05)

The average FEV1 for all subjects was 51% and this predictive value declined in line with the increasing severity of COPD disease. The same thing was found in the predictive values of FVC and FEV1 / FVC subjects of this study. History of smoking was found significantly differ between the COPD group. Most of subjects (85% and 100%) from GOLD 3 and 4 groups had a smoking history of more than 20 years.

Table 1.
Baseline Characteristics

VARIABLE	TOTAL N = 80	GOLD 1 N = 20	GOLD 2 N = 20	GOLD 3 N = 20	GOLD 4 N = 20	*P value*
Male (N,%)	68 (85)	15 (75)	15 (75)	19 (95)	19 (95)	0,26
Age (Years)	57. ± 13	45 ± 12	56 ± 15	65 ± 9	62 ± 8	<0,001
Body Weight (Kg)	60 ± 11	62 ± 9	59 ± 8	60 ± 11	58 ± 14	0,69
Body Height (cm)	160 ± 6	162 ± 5	162 ± 5	160 ± 4	158 ± 7	0,18
Systolic BP(mmHg)	123 ± 14	122 ± 7	123 ± 15	130 ± 17	122 ± 14	0,28
Diastolic BP (mmHg)	77 ± 8	78 ± 5	72 ± 7	79 ± 10	78 ± 7	0,02
Smoking duration (N,%)						
< 20 years	36 (45)	17 (85)	16 (80)	3 (15)	0 (0)	<0,001
>20 years	44 (55)	3 (15)	4 (20)	17 (85)	20 (100)	
Heart Rate (times/minute)	77 ± 11	77 ± 7	77 ± 11	74 ± 11	81 ± 12	0,29
FEV_1 (%)	51 ± 24	81 ± 0.9	65 ± 8	39 ± 6	20 ± 6	<0,001
FVC (%)	57 ± 23	83 ± 8	68 ± 14	51 ± 11	28 ± 8	<0,001
FEV_1 / FVC (%)	72 ± 17	68 ± 15	67 ± 9	63 ± 11	56 ± 18	<0,001
RV Linear Dimension (mm)	37 ± 5	32 ± 4	33 ± 3	39 ± 4	42 ± 4	<0,001
TAPSE (mm)	20 ± 3	21 ± 1	22 ± 2	20 ± 3	18 ± 6	<0,001
LV Systolic funct. (%EF)	63 ± 6	65 ± 4	65 ± 6	59 ± 7	61 ± 5	0,002
MPAP (mmHg)	26 ± 6	20 ± 2	22 ± 2	30 ± 5	31 ± 4	<0,001

ECG markers for impaired function and right heart structure (Table 2) show that the Pulmonary P and RBBB markers have a significant difference (p = 0.001 and p <0.001) in each degree of COPD. At mild degrees of COPD (GOLD 1 & 2), there was no abnormal pathological ECG marker.

Table 2.
Correlation between COPD Severity and Pathological ECG Markers of the Right Heart

VARIABLE	GOLD 1 N = 20	GOLD 2 N = 20	GOLD 3 N = 20	GOLD 4 N = 20	*P Fischer's*	*r Pearson*
P Pulmonale (N,%)						
Present	0 (0)	0 (0)	2 (10)	7 (35)	0,001	0,407
None	20 (100)	20 (100)	18 (90)	13 (65)		
RAD (N,%)						
Present	0 (0)	0 (0)	1 (5)	4 (20)	0,051	0,300
None	20 (100)	20 (100)	19 (95)	16 (80)		
RVH *sekollow* (N,%)						
Present	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A
None	20 (100)	20 (100)	20 (100)	20 (100)		
RBBB (N,%)						
Present	0 (0)	0 (0)	5 (25)	13 (65)	<0,001	0,589
None	20 (100)	20 (100)	15 (75)	7 (35)		
Low Voltage (N,%)						
Present	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A
None	20 (100)	20 (100)	20 (100)	20 (100)		
RV Strain (N,%)						
Present	0 (0)	0 (0)	0 (0)	0 (0)	N/A	N/A
None	20 (100)	20 (100)	20 (100)	20 (100)		

In GOLD 3 the frequency of RBBB markers was found in 5 subjects (25%), Pulmonary P markers 2 subjects (10%) and RAD markers as many as 1 subject (5%). In GOLD 4, frequency of RBBB, P Pulmonary and RAD markers was found more frequently, 13 subjects (65%), 7 subjects (35%) and 4 subjects (20%) respectively.

There was a moderate correlation between the RBBB marker and the COPD degree (Pearson r value 0.589). Lower correlations were found in the Pulmonary P Marker (Pearson r value 0.407) as seen in Table 2.

Tabel 3.
Correlation between COPD Severity and Pathological ECG findings

VARIABLE	TOTAL N = 80	GOLD 1 N = 20	GOLD 2 N = 20	GOLD 3 N = 20	GOLD 4 N = 20	*P Value*
P wave Axis (degree)	58,0 ± 17	39,6 ± 5	51,3 ± 10	63,4 ± 16	77,8 ± 9	<0,001
P wave Amplitude in Lead II (mV)	0,16 ± 0,06	0,10 ±0,02	0,14 ±0,04	0,17 ±0,06	0,22 ±0,06	<0,001
QRS Axis (degree)	46,8 ± 41	54,0 ± 13	32,3 ± 45	40,8 ± 41	60,4 ± 51	0,128
QT interval (ms)	423 ± 37	395 ± 18	419 ± 28	430 ± 39	446 ± 42	<0,001

The pathological ECG findings in COPD showed significant differences in the P wave axis in each GOLD degree (p <0.001) as shown in Table 3. The mean P wave Axis in this study was 58±17 degrees. The rotation of P wave axis to the inferior direction was also found at the same time increasing the degree of COPD where the highest value was found in GOLD 4 (77.8±9 degrees).

The amplitude of P waves was also found to be significantly different (p <0.001) with the mean P amplitude in this study was 0.16±0.06 mV. The values were above the average at GOLD 3 and GOLD 4 (0.17±0.06 mV and 0.22±0.06 mV). Prolongation of the QT interval was also found to be significantly different (p <0.001) with the mean value of the QT interval (423±37 ms). The QT interval value is found to be longer at GOLD 4 (446±42 ms).

Data analysis was continued by grouping the severity of COPD into 2 large groups, namely mild-moderate COPD and severe COPD (Table 4 and Table 5). P Pulmonary markers and RBBB markers had a significant difference between the two COPD groups (p = 0.002 and p <0.001). The correlative test of these two variables showed that the correlation of the RBBB marker was higher than that of the Pulmonary P marker (Pearson r =0.539 vs. r=0.356).

Tabel 4.
Correlation between COPD Severity by Categories and Pathological ECG Markers of the Right Heart

VARIABLE	COPD MILD-MOD N = 40	COPD SEVERE N = 40	*P Fischer's*	*R Pearson*
P Pulmonale (N,%)				
Present	0 (0)	9 (22,5)	0,002	0,356
None	40 (100)	31 (77,5)		
RAD (N,%)				
Present	0 (0)	5 (12,5)	0,055	0,258
None	40 (100)	35 (87,5)		
RVH *sokollow* (N,%)				
Present	0 (0)	0 (0)	N/A	N/A
None	40 (100)	40 (100)		
RBBB (N,%)				
Present	0 (0)	18 (45)	<0,001	0,539
None	40 (100)	22 (55)		
Low Voltage (N,%)				
Present	0 (0)	1 (2,5)	1	N/A
None	40 (100)	39 (97,5)		
RV Strain (N,%)				
Present	0 (0)	0 (0)	N/A	N/A
None	40 (100)	40 (100)		

Bivariate analysis performed on pathological ECG findings in the mild and moderate COPD group also showed consistent results (Table 5). The P wave Axis, the P wave amplitude in leads II and the QT interval shows a significant difference in value (p <0.001). The correlative test shows that Axis Wave P has a strong correlation with the degree group COPD (Pearson r 0.706), then followed by the amplitude of the P wave in leads II and QT intervals with the middle degree of correlation (Pearson r 0.577 and 0.415).

Tabel 5.
Correlation between COPD Severity by Categories and Pathological ECG findings

VARIABLE	COPD MILD-MOD N = 40	COPD SEVERE N = 40	*P Fischer's*	*r Pearson*
P wave Axis (degree)	45,4 ± 10	70,6 ± 15	<0,001	0,706
P wave Amplitude in Lead II (mV)	0,12 ± 0,04	0,20 ± 0,06	<0,001	0,577
QRS Axis (degree)	43,1 ± 35	50,6 ± 47	0,091	0,421
QT interval (ms)	407 ± 26	438 ± 41	<0,001	0,415

This study obtained a new cut-point value for axis P wave of 56.3 degrees and P-wave amplitude was 1.5mm (0.15mV). Both of these cut-off values are considered to provide a fairly good value of sensitivity and specificity in this study (Table 6).

Table 6.
New cutofffor P Wave Axis and P Wave Amplitude

Variable	Cut-Off	Sens (%)	Spes (%)	AUC	Asymp. Sig
P wave Axis (degree)	56,3	85	80	91.5%	<0.001
P wave Amplitude in Lead II (mm)	1,5	80	80	84,2%	<0,001

Discussion

Based on the demographic data obtained in this study, the majority of the subjects were male with range of age in the 5th to 7th decades. Subjects with GOLD 3 and GOLD 4, has higher frequency of men than subjects in GOLD 1 and GOLD 2 (38 vs 30 subjects) with age about 7th decade. The ratio of male and female as a whole subject is 5.66: 1. This is in line with previous studies conducted by Jatav et al, where the frequency of male subjects was greater than that of women (comparison ratio = 6.14: 1) and the average age of subjects was 63.2 years (7th decade).[6]

Demographic data did not found any significant differences in anthropometric data and hemodynamic data. This shows that anthropometric factors have no influence on the severity of COPD. If seen from the mean body weight (BW) and height, subjects with GOLD 4 have a lower value than other subjects (BW 58±14 kg vs. 60±11 kg and height 158±7 cm vs. 160±6 cm). This is in accordance with a study conducted by Larssen et.al. which states that patients with severe COPD have a tendency to experience cachexia.[7]

From this study, it can be observed that groups of subjects with more severe degrees of COPD had more than 20 years of smoking history. Previous studies state that the longer the duration of exposure to cigarette smoke will be the more severe the severity of COPD.[11,12,13]

From basic echocardiographic data, it appears that there is a change in the structure and function of the right heart along with the increase in COPD severity. There was an increment of the right ventricle dimension as indicated by widening of linear RV diameters. Significant differences were found in linear RV diameters between degrees of COPD ($p < 0.001$). This is consistent with data from a previous study conducted by Chaudhari et al. where the right ventricular dilatation was found more frequently in severe COPD.[14]

Disturbances of right ventricular function were also found in this study which was characterized by a decrement of TAPSE. This study found the lowest TAPSE value on subjects with GOLD 4 (18±6 mm). In addition, there was an increase in pressure facing by the right ventricle (RV afterload) along with the severity of CO PD. It also describes an increase in pressure at the level of the pulmonary artery. The increase in RV afterload in this study was described by the mean pulmonary artery pressure value (MPAP). It was found that the MPAP value for each GOLD group had a significant difference. This indicated an increment in pulmonary artery resistance in cases of severe COPD (30±5 mmHg and 31±4 mmHg).

From the ECG, the Pulmonary P and RBBB markers were found quite frequent at the heavier COPD severity with a moderate correlation. This is in accordance with the study ofJatav and Chaudhari.[6,14] (Table 7)

Tabel 7. Incidence of P Pulmonary and RBBB markers in the comparison study

ECG STUDY	Total Subject	Pulmonary P		RBBB sign	
		Mild COPD	Severe COPD	Mild COPD	Severe COPD
Jatav (2017)	100	8%	37%	1%	14%
Chaudhari (2018)	100	0%	48%	0%	8%
Present (2019)	80	0%	11,3%	0%	22,5%

In this study the incidence of RBBB markers has different frequency between mild and severe COPD degrees, this may be due to the characteristics of subjects found in subjects with mild COPD and severe COPD having a far distant FEV1 value which clearly illustrates the degree of COPD disparity

The study also found that classic pulmonary P markers were found with a low frequency in patients with severe COPD of 11.3%. This may be because the pulmonary P marker is considered to have better sensitivity and specificity for the diagnosis of CPC in COPD. Pulmonary P markers can also detect the occurrence of dilatation of the right atrium, where the two conditions are markers of the degree of COPD. Therefore, the amplitude of P waves is considered to help distinguish severity in COPD patients, but a new value is needed to increase the sensitivity of the parameters.

In addition, the incidence of RBBB was also found to be quite high in the moderate and severe COPD group. This illustrates structural and functional changes of the right heart caused by an increase in pulmonary artery resistance. In this study, structural changes were demonstrated by increment the value of the linear dimension of the right ventricle, whereas impaired right ventricular function was proven by a decreased TAPSE. Impairment of right heart function was also caused by the increase in right ventricular load which was assessed by an increase in MPAP value. This significant difference in MPAP values was found between each degree of COPD. This is in accordance with the Warnier Study which found that the incidence of RBBB in COPD patients occurred due to an increase in pressure in the right ventricle.[15]

Correlative analysis of the P wave axis in mild and severe COPD groups, significantly gave a different results with good correlation. This further reinforces the evidence that the severity of COPD will cause changes in the structure and axis of the P wave on the ECG.

This study sought to find new values for the P-wave axis and P-wave amplitude parameters for clinical use. It was found that the cut-off value for the P wave axis was 56.3 degrees (Tan 56.3° = 1.5 or the amplitude ratio of the aVF and I Lead = 3: 2) where the P wave axis value greater than 56.3 had a strong correlation with severe COPD ($r = 0.706$). This value is good for differentiating between mild-moderate COPD and severe COPD with a sensitivity reaching 85% and specificity of 80%. Previous study explained that it means if the P wave axis rotation is vertical (inferior), emphysema has occured in patients with severe COPD or vice versa.

The new value of the P wave amplitude parameter is also found in this study, which is equal to 1.5 mm (0.15 mV) in lead II. This new value can be easily applied in daily clinical practice where this value has a better discriminatory (80% NPP, 80% PPV) and has a higher event compared to classic pulmonary P markers. In this study the amplitude of P = 1.5 mm has a fairly good sensitivity (reaching 80%) when compared with the classic P pulmonary marker which only has a 50% sensitivity in theJatav study.[6]

Changes in the P wave axis turned out to be used to help differentiate the severity of COPD where the cut-off value found in this study was 56.3 degrees. In addition to increasing the sensitivity value of the P pulmonary marker assessment, this study tries to offer a new alternative for the assessment of P wave amplitude where the P wave amplitude value > 0.15 mV shows a fairly good sensitivity and specificity (80% sensitivity, 80% specificity) for distinguish patients with severe degrees of COPD in COPD population.

Lengthening of the QT interval was also found to be significantly different in mild-moderate and severe COPD patients. This is consistent with previous studies conducted by Nilsson et al. and Jegan who found that patients with severe COPD were found to experience prolonged QT interval more frequently.16,17 The mean value of the QT interval found in this study was 438ms where this value was still in the normal range of the QT interval. This study also found a fairly standard deviation value, which is probably due to weak exclusion criteria for patients with coronary heart disease or a history of previous coronary problems that are not diagnosedby

coronary angiography. Medium correlation values (moderate) may also be caused by similar reasons.

Conclusion

There is significant relationship between the severity of COPD and marker of structural and functional changesfrom the ECG assessment at H. Adam Malik General Hospital Medan. In this study, RBBB marker, P wave axis rotation towards inferior and increased P wave amplitude can be used as a marker in patients with more severe COPD. The P wave axis value is more than 56.3 degrees and the P wave amplitude is more than 0.15 mV can be used as an initial reference to assess more severe COPD from an ECG modality with a sensitivity value of 80-85% and specificity 80%.

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Disclosures and Ethics

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