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Left ventricular dysfunction in patients with chronic obstructive pulmonary disease

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Abstract: Objective: studying the effects of chronic obstructive pulmonary disease on left ventricle (LV) systolic and diastolic functions. Patients and Methods: A total of 70 cases of diagnosed chronic obstructive pulmonary disease patients (Current smokers or quitters) with 70 age, sex matched healthy control subjects were included in this study. This study was conducted at the Cardiology and pulmonolgy departments in Tishreen University Hospital in Lattakia Syria. All patients with COPD underwent for 2D Echocardiography and the same was done for the controls. . Results: We note a decrease in the mean values of the left ventricular ejection fraction (LVEF) in patients (53.85±6.5) compared to the controls (63.12 ± 4.1%) with (P<0.05). And within the group of cases, it was decreasing with the increasing stage of COPD. Diastolic dysfunction was noticed in patients with COPD. In patients, there was a statistically significant increase in IVRT [93.87±12.4 ms] VS.[77.49±1.6 ms] in control group (P<0.05) and it is increasing with the increasing stage of COPD. We noticed a statistically significant increase in Myocardial Performance Index(MPI) in COPD patients [0.49±0.05] VS. [0.37±0.01] in control group (P<0.05) and also increases with the increasing stage of COPD. Conclusion: In patients with chronic obstructive pulmonary disease, LV systolic function decreases, LV diastolic dysfunction increases and MPI also increases which reflect both systolic and diastolic LV dysfunction and both of them increases with increasing stage of COPD.

Keywords: Chronic obstructive pulmonary disease (COPD); Left Ventricular function; Doppler Echocardiography.

سوء وظيفة البطين الأيسر عند مرضى الداء الرئوي الانسدادي المزمن

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المستخلص: الهدف: دراسة تأثير الداء الرئوي الانسدادي المزمن على وظيفة البطين الأيسر الانقباضية والانبساطية. المرضى وطرق البحث: شملت هذه الدراسة 70 مريض من مرضى الداء الرئوي الانسدادي المزمن المشخصين (مدخنون حاليون أو مقلعون عن التدخين) مع 70 شخص من الشواهد الأصحاء المطابقين بالعمر والجنس مع المرضى. أجريت هذه الدراسة في قسم الأمراض القلبية وقسم الأمراض الصدرية في مشفى تشرين الجامعي في مدينة اللاذقية في سورية. أجري لكل مرضى الCOPD إيكو قلب ثنائي الأبعاد وكذلك الأمر بالنسبة للشواهد. النتائج: نلاحظ انخفاضًا في القيم المتوسطة للجزء المقذوف من البطين الأيسر (LVEF) عند المرضى (53.85 ± 6.5%) مقارنة بالشواهد (63.12 ± 4.1 %) مع (P <0.05). وضمن مجموعة الحالات، كانت القيم بتناقص مع زيادة درجة الإصابة بالCOPD. لوحظ وجود سوء وظيفة انبساطية عند مرضى الCOPD. عند مجموعة المرضى، كانت هناك زيادة ذات دلالة

إحصائية في IVRT [ميللي ثانية12.4±93.87] مقابل [ميللي ثانية1.6±77.49] في مجموعة الشاهد (P <0.05) كانت هذه القيمة في ازدياد مع زيادة درجة الCOPD. لاحظنا زيادة ذات دلالة إحصائية في مشعر أداء عضلة القلب (MPI) عند مرضى الCOPD [0.05±0.49] مقابل [0.01±0.37] في مجموعة الشاهد (P <0.05) وكانت هذه القيمة في ازدياد أيضا مع زيادة درجة الCOPD. الخلاصة: عند المرضى المصابين بالداء الرئوي الانسدادي المزمن COPD، تنخفض الوظيفة الانقباضية للبطين الأيسر، وتزداد سوء الوظيفة الانبساطية له ويزداد مشعر الMPI أيضًا مما يعكس وجود سوء بالوظيفة الانقباضية والانبساطية للبطين الأيسر وكل منهما يزداد مع زيادة درجة الإصابة بال COPD.

الكلمات المفتاحية: الداء الرئوي الانسدادي المزمن. وظيفة البطين الأيسر. إيكو قلب دوبلر.

Introduction.

Keeping a stable internal environment requires precise regulation of whole body homeostasis in which organ-organ communication plays critical roles. Hence the importance of the interaction between the Chronic obstructive pulmonary disease and the heart, as the hypoxia and systemic inflammation is responsible for a variety of physiological processes. [1]

COPD is a common global problem that has a significant impact on quality of life, mortality, hospitalization rates, and economic burden. According to the World Health Organization, the global prevalence of COPD in 2016 amounted to 251 million cases, 65 million of which were of moderate and severe degrees and it was responsible for 3.23 million deaths globally in 2019 [2] . In Syria, a statistical study was conducted in 2011 indicated that the prevalence of COPD was approximately 4% of the patients who were admitted in the pulmonolgy departments in Syrian hospitals[3].

The prevalence of COPD among patients with heart failure is 37.3%, and the rate of heart failure among patients with COPD is 17% and it was observed that the left ventricular dysfunction in patients with COPD increases the mortality significantly[4].

Chronic obstructive pulmonary diseases may affects significant cardiovascular changes such as left ventricular systolic and diastolic dysfunction in the absence of other cardiac disease. It affects left ventricular indirectly through its effect on the right heart whereas the septum between the ventricles and the cardiac circular muscle fibers are common to them and also it affects directly on left ventricular through hypoxia, systemic inflammation and recurrent infections[5].

This article highlights the Chronic obstructive pulmonary disease as a cause of left heart disease.

Patients and methods.

This case-control study was conducted at the Cardiology and pulmonolgy departments in Tishreen University Hospital, between April 2020 and September 2021, and included 70 patients (60 males and 10 females) with diagnosed chronic obstructive pulmonary disease categorized into patients with four stages of the disease (20,34,11,5 patients respectively), who were compared with 70 healthy participants (60 males and 10 females) as a control group. The two groups were matched in terms of age, gender, and cardiovascular risk factors. We excluded patients with ischemic heart diseases, rheumatic

heart diseases, valvular heart diseases, endocarditis, diabetes mellitus, hypertension and chronic kidney disease. The two groups were scrutinized for Transthoracic echocardiography where systolic and diastolic functions of left ventricle and MPI measurements were performed. Bi-dimensional, pulsed Doppler, M-mode, and color flow Doppler echocardiographic examinations were performed. Using MIR SpirolabIII spirometry machine, spirometry examinations were performed. Using Siemens Acuson x300 premium ultrasound machine, the LV diastolic function was evaluated according to the recommendations of the American Society of Echocardiography 2016, the LV systolic function was evaluated using modified Simpson method, and Myocardial Performance index (MPI) which is a Compound index of LV systolic and diastolic functions was also evaluated.

Definitions:

Mitral E/A ratio: Mitral valve E velocity divided by A-wave velocity, it is used to identify the filling patterns: normal, impaired relaxation (grade I), pseudonormal (grade II), and restrictive filling (grade III).

IVRT: Isovolumic relaxation time is the Time between aortic valve closure and MV opening. IVRT is=<70 ms in normal subjects and is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT shortens and its duration is inversely related to LV filling pressures in patients with cardiac disease.

Mitral E/é: MV E velocity divided by mitral annular é velocity. é velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/é ratio can be used to predict LV filling pressures. [6]

MPI: Myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter defined as the sum of the Isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for global left ventricular function. [7]

Statistical Analysis

Statistical assessment of our study was performed by using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 20, manufactured by IBM Corp., located in Armonk, N.Y., USA and summarized as frequencies and proportions. $P<0.05$ value was accepted to be statistically significant. The results were indicated in average ±SD and in percentage (%). One-way ANOVA was used for comparing groups. The independent-samples t test was used for comparing the 2 groups, and the t test was used for variables.

Results

A total of 70 chronic obstructive pulmonary disease patients and 70 healthy controls were included into the study. Patients were divided into four groups to be studied according to the stage of the disese (20 patients stage I, 34 patients stage II, 11 patients stage III and 5 patients stage IV).

The mean age of all patients was 60.4±4.5 years and the mean age of controls was 61.7±3.5, Sex ratio (M:F) was 6:1 .

The mean age and sex ratio of the controls groups were similar to those in patients groups.

Table (1) Distribution of the sample of patients according to the stage of COPD

Stage of COPD	Number	Percentage
I	20	28.57%
II	34	48.57%
III	11	15.71%
IV	5	7.14%

When we studied Myocardia Performance Index (MPI) in patients groups compared to controls, we noticed a statistically significant increase in MPI in COPD patients compared to controls (P-value=0.001)(Table 2). We also noticed a statistically significant difference between four patients groups (P-value= 0.0001) compared to the control group except stage I which was not statistically significant compared to controls (P-value= 0.1).

Table (2) Myocardial Performance Index (MPI) differences between COPD patients and controls in our study

MPI	Search Group		P- value
	Patients	Controls	**0.001**
	0.49±0.05	0.37±0.01	

Table (3) Myocardial Performance Index (MPI) differences between four stages COPD patients and controls in our study

MPI	COPD Patients				Controls
	I	II	III	IV	
	0.39±0.06	0.45±0.07	0.53±0.08	0.60±0.04	0.37±0.01
P-value	0.1	0.0001	0.0001	0.0001	1

When we studied left ventricle systolic function, we noticed a decrease in ejection fraction (EF) in patients with COPD compared to control group which was statistically significant (P-Value=0.001). The difference in the patients four groups was statistically significant compared to controls and was increasing with the increases in the stage of COPD (P-value= 0.03, 0.02,0.0001 and 0.0001 respectively).

Table (4) Ejection fraction (EF) differences between COPD patients and controls in our study

EF	Search Group		P- value
	Patients	Controls	0.001
	53.85±6.5	63.12±4.1	

Table (5) Ejection fraction (EF) differences between four stages COPD patients and controls in our study

EF	COPD Patients				Controls
	I	II	III	IV	
	59.85±6.4	59.97±7.1	49.18±6.9	46.60±8.9	63.12±4.1
P-value	0.03	0.02	0.0001	0.0001	1

When we studied left ventricle diastolic function in COPD patients, we noticed statistically significant changes in LV diastolic function in cases compared to controls (P-value= 0.0001) (Table 6). And we noticed that most COPD patients in progressed stages were having gradeII and gradeIII LV diastolic dysfunction according to early stages which were almost normal or grade I LV diastolic dysfunction.(Table 7)

Table (6) Left ventricle diastolic dysfunction differences between COPD patients and controls in our study

LV Diastolic Disfunction	Search Group		P- value
	Patients	Controls	0.0001
	71.4%	17.5%	

Table (7) Left ventricle diastolic function changes in COPD patients and controls in our study

LV Diastolic function	COPD Patients				Controls
	I	II	III	IV	
Normal	16(80%)	4(9.8%)	0(0%)	0(0%)	52(82.5%)
Grade I	4(20%)	29(70.7%)	2(18.2%)	0(0%)	11(17.5%)
Grade II	0(0%)	8(19.5%)	6(54.5%)	2(40%)	0(0%)
Grade III	0(0%)	0(0%)	3(27.3%)	3(60%)	0(0%)

We also noticed a statistically significant increase in Isovolumic relaxation time IVRT in patients with COPD (93.87±12.4 ms) as compared to controls (77.49±1.6ms) (p-value=0.0001) and we also noticed a statistically significant increase in E/é parameter in patients with COPD (9.08±2.6) as compared to controls (7.07±0.3) with (p-value=0.0001) ,but we did not notice any statistically significance in E/A and parameters between patients and controls (P-Value=0.4) (Table7).

Table (8) Left Ventricle diastolic function differences between COPD patients and controls in our study

LV Diastolic function	COPD Patients	Controls	p-value
E/A	1.11±0.4	1.07±0.2	0.4
IVRTS	93.87±12.4	77.49±1.6	0.0001
E/e´	9.08±2.6	7.07±0.3	0.0001

Discussion.

The heart and lung are two closely interrelated organs, as the lung is a mirror of the heart. Just as the left heart dysfunction manifests in the form of pulmonary edema, chronic pulmonary diseases (COPD consider the most common one) are reflected in the right heart and manifest as Cor Pulmonale , but COPD has more important corolation with left heart as the LV dysfuction and COPD share the same pathophsioloy and epidemiology and COPD increases mortality by its systimmic effects on left heart [(1)(4)], all of this prompted us to study the potential effects of COPD on the left heart. What we observed in this study is that COPD is associated with important cardiovascular changes. Current study is a case-control study with male predominance of 80% in patients group, that can be due to the distribution of COPD between the genders as it is more common in males.

Firstly we studied Myocardial Performance Index (MPI) values which reflect both systolic and diastolic function of left ventricle and showed a statistically significant increase in COPD patients compared to controls (p-value=0.001). This increase in MPI prompted us to study left ventricle systolic and diastolic function separately. When we studied left ventricle systolic function, we noticed a decrease in ejection fraction (EF) in patients with COPD compared to control group which was statistically significant (P-Value=0.001). When we studied left ventricle diastolic function in COPD patients, we noticed statistically significant changes in the grade of LV diastolic function in patients compared to controls (P-value= 0.0001) and in patients group we noticed that most COPD patients in progressed stages were having gradeII and gradeIII LV diastolic dysfunction according to early stages which were almost normal or grade I LV diastolic dysfunction. We also noticed a statistically significant increase in Isovolumic relaxation time IVRT and E/é parameter in patients with COPD as compared to controls (p-value=0.0001) ,but we did not notice any statistically significance in E/A and parameters between patients and controls , that may be because most of our patients had grade I diastolic dysfunction.

We can explain these changes in left ventricular function from a pathophysiological point of view by contribution of several direct and indirect factors: 1) Indirect through its effect on the right heart, as the septum between the ventricles and the cardiac circular muscle fibers are common to them, so the increase in pressures within the right ventricle, which is seen in COPD, will negatively affect the left ventricle through the shift of the septum towards the left [(8)], and thus decreased in the volume of its fullness and

decreased in stroke volume leads to activate the nervous system and activate the renin-angiotensin-aldosterone system, which increases the secretion of angiotensin II which increases the reabsorption of water and sodium and increases the burden on the left ventricle [9]. In addition, activating the sympathetic nervous system and increasing levels of catecholamines (adrenaline, noradrenaline) will increase LV dysfunction by increasing the need of cardiac muscle for oxygen and increasing arrhythmias [10].

2)Direct through several mechanisms:

I. **Hopxia**: In response to hypoxia, the cells of the body secrete Hypoxia inducible factor (HIF), which activates several genes [11] that lead to : **a)** Erythropoisis (In patients not treated with oxygen) followed by the occurrence of secondary polycythemia [12] which increases encidece of myocardial infarction and ischemic heart failure. **b)** Anaerobic cellular metabolism: which leads to a defect in the structure of mitochondria and increases production of free radicals, produce less energy and thus exacerbate heart failure and leads to acidosis, which negatively affects the contractility of the cardiac muscle[13] . **c)** Induce Inflammation which produces more free radicals and cytokines[14] .

II. **inflammation:** It is considered the most important mechanism due to the various effects that inflammatory mediators and cytokines play on the body as a whole and on the heart in particular, which include: **a)** Normocytic Normochromic anemia [15] (In patients treated with oxygen) which causes tachycardia and increasing the need of cardiac muscle for oxygen, and over time it develops into high-output heart failure [16] . **b**) Striated muscules atrophy (including cardiac muscle) caused by increased protein catabolism by tumor necrosis factor (TNFa) as it disrupts the differentiation process and increases the rate of catabolism in mature muscle cells [17] . Studies have shown that this process is carried out by free radicals ROS and activation of NF-kb, which is a transcription factor that regulates the action of proteases, which accelerates the process of protein catabolism and thus exacerbates muscular weakness, including heart muscle, and all of this exacerbates left ventricular dysfunction [18] . **c)** Endothelial damage caused by inflammatory free radicals which are considered one of the most important factors in the occurrence of endothelial damage to coronary arteries and development of ischemic heart disease, that is through increasing oxidation of low-density lipoprotein (LDL) particles, which increases its tendency to deposit in the walls of blood vessels and the occurrence of atherosclerosis, disruption of nitric oxide NO that is secreted from endothelial cells and through the direct cytotoxicity to endothelial cells[19].

III. **Infections**: Recurrent infections that are common in patients with COPD and the accompanying inflammatory condition, elevated temperature, and the use of nebulization are among factors that exacerbate subclinical heart failure and cause arrhythmias[20] and high-output heart

failure[21], as secondary infection will increase the oxidative stress and thus increase production of free radicals.

This depth of pathophysiology confirms the importance of hypoxia, systemic inflammation and infection (which increases with the stage of COPD) in development of left ventricular dysfunction and the results of our study confirm that there is significant deterioration in LV systolic and diastolic function with increasing stage of COPD through the influence of these combined factors directly on its function.

Comparing with other studies:

1- In a case-control study was conducted in Egypt in 2017 entitled as " Left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease: Impact of methods of assessment " [22], it included 35 patients with chronic obstructive pulmonary disease and 18 age-matched controls. Echocardiography was performed to diagnose and classify left ventricular diastolic dysfunction according to the recommendations of the American Society. The results showed that there were 20 patients with LV diastolic dysfunction by assessing the flow through the mitral valve using echocardiography (P=0.001) and this is consistent with the present study, but our study is more comprehensive because we also studied the systolic function and MPI.

2- Another study entitled as "Evaluation of left ventricular function in patients with chronic obstructive pulmonary disease with or without pulmonary hypertension" [23], and was conducted in Menoufiya University Hospitals in the period from May 2010 to August 2011 included 36 patients with stable COPD confirmed by medical history and pulmonary function tests who were admitted to Chest Department and twelve healthy age and sex matched persons with normal spirometry were used as a control group for comparison. Echocardiographic assessment of left ventricular diastolic function revealed a statistically significant difference between patient and control groups ($P \leqslant 0.001$) and this is consistent with our study, but the difference between the four stages of COPD was statistically non significant (P>0.05) which is different from our study. And also the difference between both groups was statistically nonsignificant regarding to left ventricular systolic function (P>0.05) which is also different from our study.

Conclusion.

In patients with COPD, left ventricular systolic and diastolic function was abnormal, in addition Myocardial Performance Index (MPI) which reflects both systolic and diastolic left ventricular function was abnormally increased compared to healthy subjects matched of in age, gender, and cardiovascular risk factors which means that COPD is considered as an important risk factor to promot LV dysfunction and we need to manage it in early stages before it getting worst.

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