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ORIGINAL STUDY

Peripheral and central olfactory measurements in Chronic Obstructive Pulmonary Disease patients

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ABSTRACT

OBJECTIVES. We investigated peripheric and central olfactory pathways on MRI in Chronic Obstructive Pulmonary Disease (COPD) patients and the relationship between olfactory measurements of COPD patients and thorax CT images of emphysema classification in them.

MATERIAL AND METHODS. In this retrospective study, cranial MRI of 42 adult patients with COPD and 42 healthy adults without COPD were included. In both groups, peripheral (olfactory bulb (OB) volume and olfactory sulcus (OS) depth) and central olfactory areas (insular gyrus and corpus amygdala areas) were evaluated. We classified thorax CT findings according to emphysema by size as 1 to 4.

RESULTS. In the present study, left OB volume of the COPD group was significantly lower than that in the control group ($p<0.05$). On the right side, there were no significant differences between OB volumes of the COPD and control groups. Although right OB volume values were found to decrease proportionally, they were not found to be statistically significant. Also, insular gyrus and corpus amygdala areas of the COPD group were significantly lower than those in the control group, bilaterally ($p<0.05$). OS depths of the COPD group were significantly higher than those in the control group, bilaterally ($p<0.05$). In males, the right OB volume values were higher than those in females ($p<0.05$).

CONCLUSION. In COPD patients, left OB volumes decrease and OS depths increase bilaterally, and central areas decrease bilaterally, regardless of the thoracic emphysema classification. It may be related to hypoxemia that causes airway inflammation; inflammatory mediators may be harmful to the olfactory neuroepithelium.

KEYWORDS: Chronic Obstructive Pulmonary Disease (COPD), olfactory, cranial MRI, thorax CT, emphysema classification.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable disease associated with an increasing chronic inflammatory response in airways and lung, usually characterized by progressive permanent airflow limitation[1]. It occurs due to etiological factors, such as unhealthy diet, physical inactivity, smoking, air pollution, allergens, genetics, toxic particle exposure[2].

Inhaled noxious gases and particles cause an exaggerated inflammatory response in the lungs of COPD patients. The resulting chronic inflammatory response causes parenchymal tissue destruction (emphysema) and normal tissue repair and may lead to impaired defense mechanisms (fibrosis in the small airways). These pathological changes are also causing air confinement and progressive airflow limitation[1]. It leads to hypoxia and hypercapnia[3].

Although COPD is associated with many systemic diseases during hypoxia and hypercapnia, we could not find a study about olfactory pathways of COPD patients in the literature.

The purpose of our investigation was to investigate potential disparities by evaluating the peripheral and central olfactory pathways, utilizing MRI in individuals diagnosed with COPD and examining the correlation between olfactory assessments of COPD patients and emphysema classification, as seen on thorax scans of these patients.

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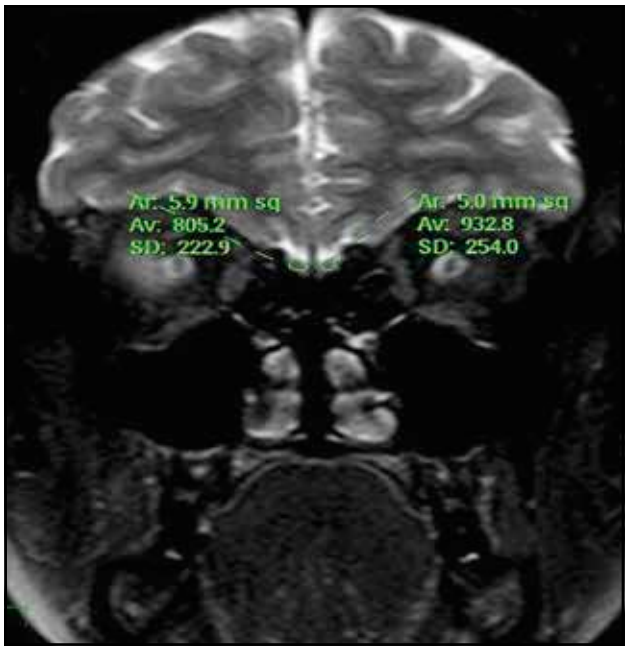

Figure 1. On coronal T2W FSE MRI image, OB volume measurements are shown.

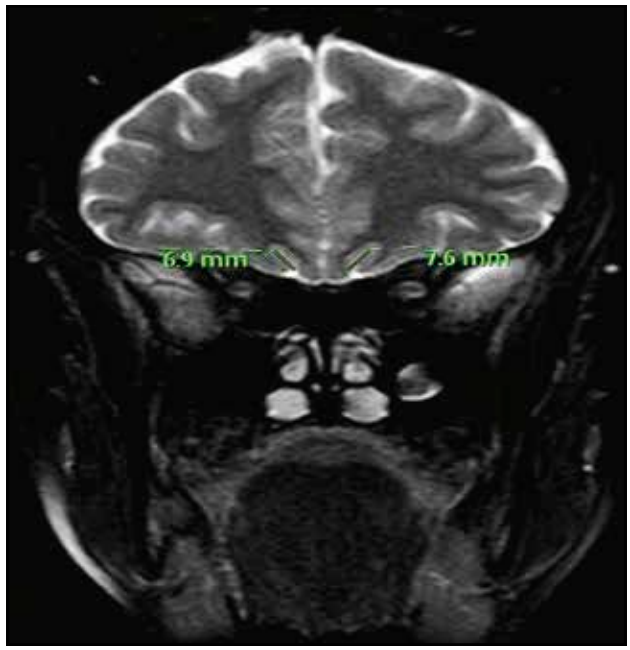

Figure 2. On coronal T2W FSE MRI scan, OS depth measurements are shown.

MATERIAL AND METHODS

This retrospective study was carried out in the Radiology Unit at the Faculty of Medicine of Kırıkkale University, adhering to the principles outlined in the Declaration of Helsinki. Imaging records, including cranial MRI and thorax CT scans, were retrieved from the database at the Radiology Department. Ethical approval for the study was obtained from the Non-invasive Research Ethics Committee at Kırıkkale University, with the approval date of April 27, 2022, and reference number 2022.04.30.

Subjects

Chronic Obstructive Pulmonary Disease Group

In this retrospective study, we examined medical images from the PACS (Picture archiving and communication systems) of our hospital, specifically focusing on brain MRI and chest CT scans of individuals under 75 who had been diagnosed with Chronic Obstructive Pulmonary Disease (COPD). The data for this investigation was collected from March 2013 until the present time. The chest CT scans were reviewed in relation to their proximity to the brain MRI, specifically those that were taken within a year of the brain MRI. Artefact-free images were utilized in the analysis; this resulted in a sample of 42 patients (32 males, 10 females) with COPD, with an average age of 64.23±6.30 (ranging between 49-72) years.

Control Group

A group of 42 healthy adults (32 males and 10 females) were selected as the control group. These individuals had undergone an MRI for the purpose of evaluating headaches and were found to have normal results. The control group participants were selected from the PACS system, and hospital records were reviewed to confirm that they did not have a diagnosis of COPD or any other lung diseases. The mean age of the individuals in the control group was 61.45 ±7.90 (ranging from 48 to 74) years.

Exclusion Criterias

We did not include individuals above the age of 75 in this research because of the potential for cerebral atrophy. Additionally, patients who had a history of stroke, cerebral atrophy, tumors, injuries, sinonasal issues, infections, surgery, Parkinson's disease, epilepsy and demyelinating diseases were also excluded from the study to prevent any potential impact on the outcome measurements.

Cranial MRI measurements

MRI exams were performed using a 1.5 Tesla MRI system (Philips MRI systems, Achieva Release; Philips Medical Systems Nederland B.V., Eindhoven, Noord-Brabant, Netherlands) with a cranial coil. T1-weighted images were taken in the axial plane (TR msn/TE ms: 596/15; FOV: 230x183 mm; matrix: 256x205 mm) and T2-weighted images in both axial and coronal planes (TR ms/TE ms: 6557/100; FOV: 220x175 mm; matrix: 224x165 mm) were acquired with 5-mm slice thickness and 1-mm intersection gap, 25-30 coronal sections were obtained.

The study evaluated the size of the olfactory bulb (OB) and the depth of the olfactory sulcus (OS) by analyzing coronal T2-weighted images (seen in Figures 1 and 2). Additionally, the area of the insular gyrus was measured using axial T2 FLAIR images, and the size of the corpus amygdala was evaluated through axial T1-weighted images (as illustrated in Figures 3 and 4).

All measurements were done by the same radiologist, P.Z.B.S, who has 12 years of experience in radi-

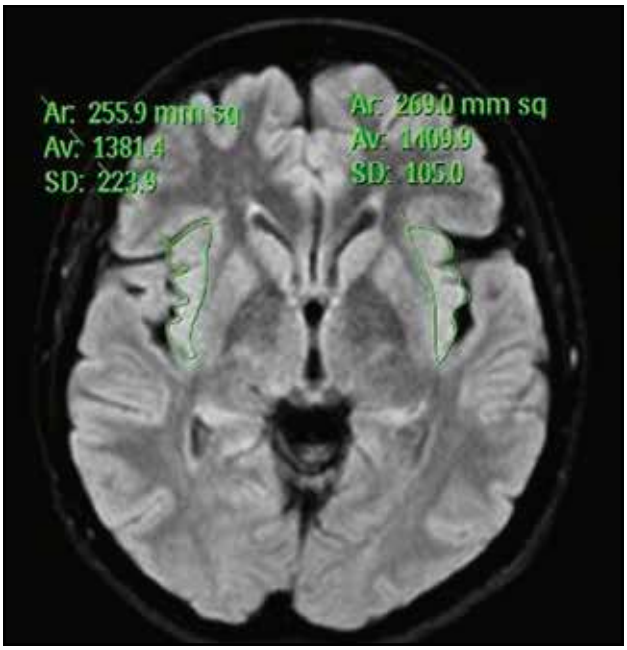

Figure 3. On axial FLAIR MRI scan, the insular gyrus area is measured at maximum section as mm^2.

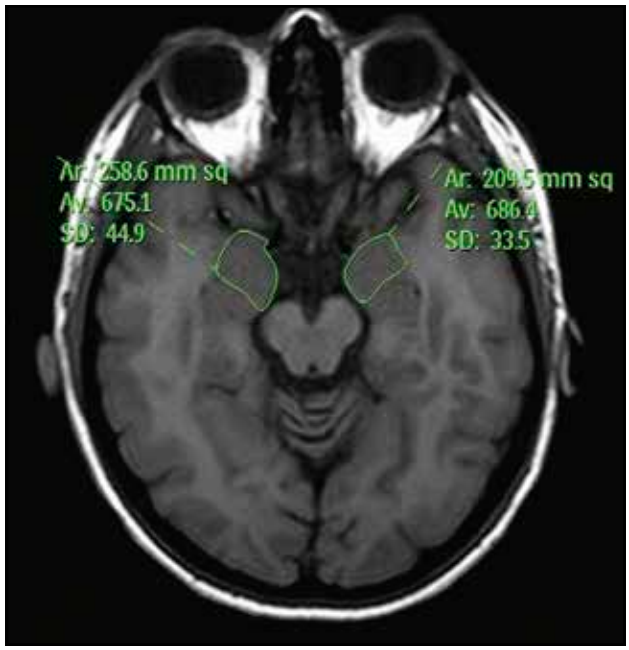

Figure 4. On axial FLAIR MRI scan, the corpus amygdala area is measured at maximum section as mm^2.

ology and performed these evaluations on a high-resolution display monitor.

Peripheral Olfactory Areas

In our research, we used measurements of OB volume and OS depth as indicators of peripheral olfactory areas. To find OB volume, we analyzed coronal T2-weighted SPIR sequence sections, and manually determined the OB area in mm^3 using an electronic cursor on the most distinct section. We calculated the volume by multiplying the area by the slice thickness, and recorded the results in cubic millimeters.

To measure OS depth, we examined coronal T2-weighted SPIR sequence sections, and drew a virtual line connecting the "inferior orbital gyrus and gyrus recti in the posterior plane of the orbit." Then, we drew a perpendicular line from this point to the deepest point of the OS and measured the length of this line; this value represents OS depth and was recorded in millimeters[4,5].

Central Olfactory Areas

We assessed the area of the insular gyrus by analyzing axial T2-weighted images, focusing on the section where it appeared to be the largest. The insular gyrus area was determined on images in which both the head of the caudate nucleus and the putamen were visible at the same time. The area of the corpus amygdala was evaluated using axial T1-weighted images by measuring the maximum visible area (mm^2)[6,7].

Thorax CT Imaging and Analysis

All CT scans were performed using routine thorax computed tomography imaging, with or without contrast, in the supine position. The scans were conducted using a 64-slice CT (MSCT; Brilliance 64, Philips Medical System, Best, the Netherlands) with the following parameters: 120 kV tube voltage, 300 effective mAs, 3 mm slice thickness, 375 mm field of view (FOV), and 512×512 image matrix. The images were transferred to a commercially available workstation, where the raw data was reconstructed using pulmonary parenchyma algorithms. After scanning, the images were reconstructed with a slice thickness of 1.00 mm and presented in coronal, axial, and sagittal planes, with a preference for coronal and axial views.

COPD includes two components which are chronic bronchitis-small airways disease and emphysema. CT findings in chronic bronchitis are not quite specific. So, emphysema was the most obvious candidate for the COPD subclassification[8].

We classified thorax CT findings according to emphysema by size. We separated the emphysema pattern into 4 groups according to CT images: Group 1 – paraseptal or single lobe centrilobular emphysema, Group 2 – centrilobular emphysema at upper lobes, Group 3 – diffuse centrilobular or panlobular emphysema at upper lobes, Group 4 – diffuse panlobular emphysema (Figure 5, Figure 6).

Statistical Analysis

The data collected in this study was analyzed using the SPSS for Windows 16.0 software (SPSS, INC, an IBM Company, Chicago, Illinois). Several statistical tests such as Chi-square test, independent samples t-test, paired samples t-test, Pearson correlation test and Spearman's correlation rho efficient test were applied.

A p-value of <0.05 was considered statistically significant.

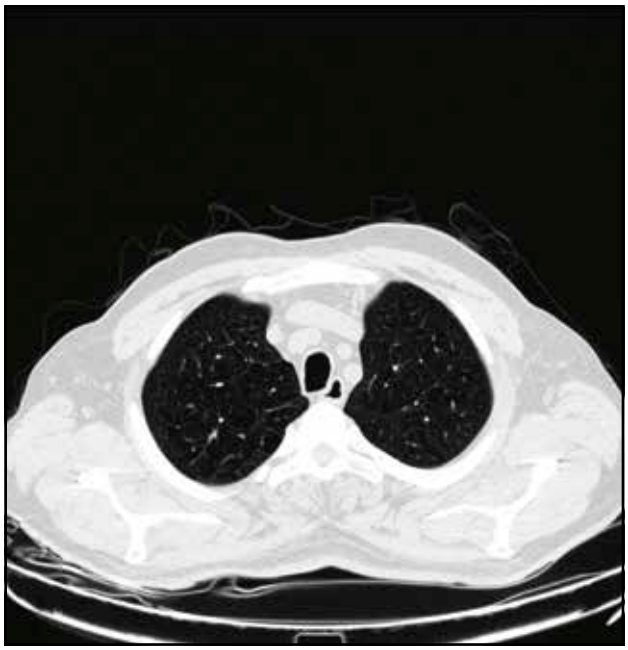

Figure 5. On axial thorax CT scan, group 2 centrilobular emphysema at upper lobes is shown.

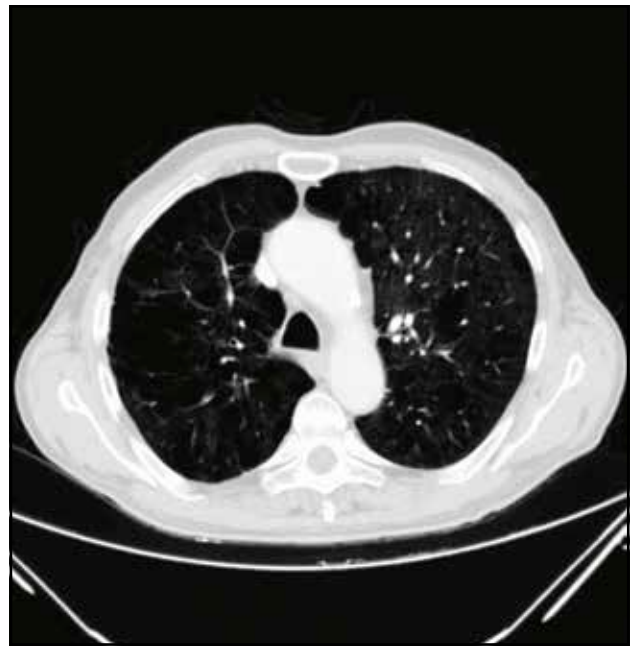

Figure 6. On axial thorax CT scan, group 4 diffuse panlobular emphysema is shown.

Table 1. Measurement results for olfactory bulb volume, olfactory sulcus depth, insular gyrus area and corpus amygdala area in COPD and control groups.

		Group 1 (COPD) (n=42)			Group 2 (Control group) (n=42)			P*
		Mean	Median	Std.Dev.	Mean	Median	Std.Dev.	
Age		52.63	56.00	16.46	48.31	50.00	13.67	0.097
Measurement results								
Olfactory bulb (OB) volume (mm^3)	R	27.15	28.00	9.03	30.25	30.50	7.17	0.086
	L	25.20	23.75	8.04	31.55	31.50	7.86	0.000
	P**		0.097			0.224		
Olfactory sulcus (OS) depth (mm)	R	7.78	7.70	1.07	6.89	6.60	1.12	0.000
	L	7.55	7.45	1.16	6.87	6.80	1.02	0.006
	P**		0.248			0.883		
Insular gyrus area (mm^2)	R	235.69	243.00	36.17	272.57	276.00	28.08	0.000
	L	229.11	222.50	41.24	263.57	265.00	28.88	0.000
	P**		0.212			0.133		
Corpus amygdala area (mm^2)	R	218.21	215.50	41.50	255.57	254.00	34.52	0.000
	L	216.54	212.50	33.58	250.52	249.00	31.36	0.000
	P**		0.804			0.293		

*p-value shows the results of independent samples t-test
**p-value shows the results of paired samples t-test

Table 2. Measurement results according to the COPD subclassification (1 to 4) in COPD group.

Measurement results		COPD 1 (n=16)			COPD 2 (n=13)			COPD 3 (n=9)			COPD 4 (n=4)			P*
		Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	
Olfactory bulb (OB) volume (mm^3)	R	25.84	28.25	9.85	25.19	22.50	8.55	28.11	28.00	6.17	36.62	39.50	9.41	0.218
	L	24.25	22.25	10.12	23.42	23.00	5.40	26.11	25.50	7.13	32.75	33.50	4.59	0.116
	P**		0.378			0.479			0.260			0.144		
Olfactory sulcus (OS) depth (mm)	R	7.33	7.30	1.03	8.23	8.10	1.36	7.76	7.70	0.43	8.12	8.10	0.55	0.233
	L	7.40	7.65	1.02	7.98	8.10	1.35	7.35	6.90	1.34	7.25	7.15	0.38	0.481
	P**		0.979			0.875			0.374			0.144		
Insular gyrus area (mm^2)	R	234.12	237.00	40.05	241.00	255.00	37.21	224.77	238.00	31.77	249.25	249.50	29.84	0.540
	L	224.56	218.00	47.53	242.15	236.00	36.78	217.33	222.00	41.60	231.50	236.00	25.37	0.450
	P**		0.352			0.650			0.441			0.715		
Corpus amygdala area (mm^2)	R	221.62	216.00	40.84	206.00	195.00	52.64	224.00	218.00	29.42	231.25	238.00	27.77	0.683
	L	220.50	220.00	37.89	209.15	212.00	28.91	225.88	227.00	34.649	203.75	203.50	29.73	0.604
	P**		0.642			0.834			0.594			0.068		

*p-value shows the results of Kruskal Wallis Variance analysis
**p-value shows the results of Wilcoxon signed ranks test

RESULTS

In the COPD group, there were 32 males, accounting for 76.2% of the group, and 10 females, making up the remaining 23.8%. Similarly, in the control group, there were 32 males (76.2%) and 10 females (23.8%) (p=1.000, $\chi 2$: 0.000). The study found no significant differences in the ages of the individuals between the two groups (p>0.05) (Table 1).

Table 1 illustrates the measurements of the olfactory bulb volume, olfactory sulcus depth, insular gyrus area and corpus amygdala area for both COPD and control groups.

OB volume

The left OB volume of the COPD group was significantly smaller when compared to the control group (p<0.05). However, there were no significant differences in the right OB volume between the COPD and control groups (p>0.05) (Table 1). Additionally, within each group (COPD and control), there were no significant differences in OB volume between the left and right sides (p>0.05) (Table 1).

OS depth

The OS depths of the COPD group were significantly larger in comparison to the control group on both sides (p<0.05). Separately, within the COPD and control groups, there were no significant variations in OS depths between the left and right sides (p>0.05) (Table 1).

Insular gyrus area

The insular gyrus areas of the COPD group were significantly smaller in comparison to the control group, bilaterally (p<0.05). Additionally, within the COPD and control groups separately, there were no significant differences in the insular gyrus areas between the right and left sides (p>0.05) (Table 1).

Corpus amygdala area

The corpus amygdala area of the COPD group was found to be significantly smaller than that of the control group, on both sides (p<0.05). Furthermore, within the COPD and control groups separately, there were no significant differences in the corpus amygdala areas between the right and left sides (p>0.05) (Table 1).

Measurement results according to the COPD subclassification (1 to 4) in COPD group are shown in Table 2.

Table 3. Correlation test results in group 1 (COPD).

			OB Volume (mm^3)		OS Depth (mm)		Insular gyrus area (mm^2)		Corpus amygdala area (mm^2)	
			R	L	R	L	R	L	R	L
OB volume (mm^3)	R	r		0.626	-0.158	-0.104	-0.239	-0.185	-0.043	-0.067
		P*		0.000	0.316	0.512	0.128	0.242	0.789	0.673
	L	r	0.626		-0.115	-0.014	-0.267	-0.077	0.132	0.025
		P*	0.000		0.469	0.928	0.088	0.627	0.404	0.873
OS Depth (mm)	R	r	-0.101	-0.098	.	0.486	0.175	0.108	-0.064	-0.015
		P**	0.525	0.538		0.001	0.268	0.495	0.686	0.926
	L	r	-0.075	0.043	0.486	.	0.198	0.156	0.022	-0.017
		P*	0.635	0.786	0.001		0.209	0.324	0.890	0.913
Insular gyrus area (mm^2)	R	r	-0.239	-0.267	0.229	0.186		0.631	-0.016	-0.018
		P*	0.128	0.088	0.144	0.238		0.000	0.922	0.910
	L	r	-0.185	-0.077	0.146	0.147	0.631		-0.120	0.104
		P*	0.242	0.627	0.356	0.354	0.000		0.450	0.512
Corpus amygdala area (mm^2)	R	r	-0.043	0.132	-0.113	-0.029	-0.016	-0.120		0.352
		P*	0.789	0.404	0.475	0.853	0.922	0.450		0.022
	L	r	-0.067	0.025	-0.017	-0.008	-0.018	0.104	0.352	
		P*	0.673	0.873	0.913	0.957	0.910	0.512	0.022	
Age		r	-0.226	-0.181	0.175	-0.018	0.113	0.162	0.226	0.026
		P*	0.151	0.251	0.268	0.909	0.476	0.306	0.150	0.870
Gender (Code 1: Male, Code 2: Female)		r	-0.397	-0.016	-0.143	-0.009	0.039	0.106	0.106	0.067
		P**	0.009	0.919	0.366	0.954	0.805	0.503	0.504	0.674
COPD subclassification (1 to 4)		r	0.203	0.269	0.259	-0.017	-0.023	0.031	0.047	-0.046
		P**	0.197	0.084	0.097	0.915	0.883	0.847	0.767	0.772

*p-value shows the results of Pearson correlation test
**p-value shows the results of Spearman's correlation rho efficient test

In COPD group, subclassifications were 16 (38.1%) patients in COPD 1, 13 (31.0%) patients in COPD 2, 9 (21.4%) patients in COPD 3 and 4 (9.5%) patients in COPD 4. There were no significant differences between peripheral and central olfactory areas (OB volume, OS depth, insular gyrus area and corpus amygdala area) values of the COPD 1 to COPD 4 groups ($p>0.05$) (Table 2). In each of the COPD subclassification groups separately, there were no significant differences between measurement results of the right and left sides ($p>0.05$) (Table 2).

Correlation test results in Group 1 (COPD patients) are shown in Table 3.

There were positive correlations between OB volumes, OS depths, insular gyrus areas and corpus amygdala areas ($p<0.05$) (Table 3). In males, right OB volume values were higher than those in the females ($p<0.05$) (Table 3). There were no significant correlations between age and COPD subclassifications and peripheral and central olfactory areas ($p>0.05$) (Table 3).

DISCUSSIONS

COPD is a chronic disease that causes damage at lungs with chronic bronchitis and emphysema. Chronic symptoms and detection of established airflow obstruction on spirometric examination (post-bronchodilator FEV1/FVC< 70%) in middle-aged adults with a history of expo-

sure to risk factors confirm the diagnosis[9]. According to the WHO, by the year 2030, COPD will be the 3rd death leading cause in worldwide[10]. It causes multiple metabolic diseases. It is known that the metabolic syndrome is detected as comorbidity in up to 50% of COPD patients. Currently, it is not known whether the metabolic syndrome is "an independent co-existing condition or a direct consequence of the progressive lung pathology" in COPD patients[11]. This may be according to hypoxia and hypercarbia. "Ventilation/perfusion mismatch resulting from progressive airflow limitation" and emphysema are the main reasons of hypoxia. Hypoxia can be exacerbated by sleep and exercise in COPD patients[12]. This can lead to nocturnal hypoxemia in patients with COPD[13]. Especially nocturnal hypoxia may also affect olfactory functions[14].

Olfactory bulb volume measurement on MRI allows us to learn about olfactory functions[15]. Therefore, we investigated olfactory functions of patients with COPD by measuring OB volume, OS depth, insular gyrus area and corpus amygdala area on MRI.

In the present study, left OB volume of the COPD group was significantly lower than that in the control group. On the right side, there were no significant differences between OB volumes of the COPD and control groups. Although right OB volume values were found to decrease proportionally, they were not found to be statistically significant. This may be due to the small number of patients. Different results may be obtained with a larger patient group. Also in our study, insular gyrus and corpus amygdala areas of the COPD group were significantly lower than those in the control group, bilaterally. OS depth of the COPD group was significantly higher than that in the control group bilaterally.

According to literature survey, there are some studies about olfactor bulbus and olfactor sulcus depth in some neurophysiatric patient groups, such as posttrauma, epilepsy, depression, schizophrenia, Parkinson's disease[16-20]. Also, in another study by Güney et al. olfactory changes in the postcovid chronic period were revealed by MRI measurements. They found that OB volume, OS depth values were significantly lower in the group of post-COVID-19 compared to the control group[21].

Our literature survey showed that the relationship between COPD and central and peripheric olfactory areas volumes have not been previously reported. Thorstensen et al. demonstrated with clinical tests that there was a decrease in olfactory functions in patients with COPD. They found that hyposmia and anosmia were present in up to 79% of patients with COPD[22].

To our best of knowledge, our study is the first study to show that the OB volume, OS depth, central areas are possibly influenced by COPD. Our results point out a relationship between COPD patient and olfactory areas; the exact mechanism still remains unclear. Possibly, chronic hypoxia resulting in olfactory neuroepithelium atrophy may be considered the pathophysiological mechanism of this finding.

According to the literature studies, OS depth generally decreases with OB volume. In our study, we found that OS depths of the COPD group were significantly higher than those in the control group, bilaterally. It can be due to brain atrophy in COPD patients[23]. Grey matter atrophy may affect the OS depth.

We could not find a connection between the changing olfactory field values and our thorax classification. This may be due to the fact that hypoxia and hypercarbia cause dose and duration independent olfactory damage.

The limitation of our study was the limited number of patients. More useful studies can be obtained with large number of patient series. Also, the number of patients in the thoracic groups was not evenly distributed. A study with equal numbers of empysema classification may be statistically more meaningful.

CONCLUSIONS

In patients with COPD, left OB volumes decrease and OS increases bilaterally, and central areas decrease bilaterally, regardless of thoracic emphysema classification. It may be related to hypoxemia that causes airway inflammation, and inflammatory mediators may be harmful to the olfactory neuroepithelium.

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Ethics committee approval: This study is retrospective. Ethics committee approval was obtained from Kırıkkale University Non-invasive Research Ethics Committee (Date: 27.04.2022 Number: 2022.04.30).

There is no need to take informed consent, because the data was evaluated retrospectively.

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Contribution of authors: Pelin Zeynep Bekin Sarikaya: Planning, designing, data collection, literature survey, active intellectual support, writing. Nuray Bayar Muluk: Planning, designing, literature survey, statistical analysis, active intellectual support, writing, submission. Alper Göncüoğlu: Planning, designing, literature survey. Adnan Özdemir: Planning, designing, literature survey. Aydanur Ekici: Planning, designing, data collection, literature survey.

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