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Morphological overview of cardiovascular comorbidities in chronic obstructive pulmonary disease: Frank's sign

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ABSTRACT

Objective: Cardiovascular diseases are the most common and important comorbidities in patients with chronic obstructive pulmonary disease (COPD). Literature indicates that there may be a relationship between diagonal earlobe crease (DELC) and coronary artery disease (CAD). Accordingly, the present study aimed to assess the relationship with DELC and cardiac comorbidities in patients with COPD during routine physical examination.
Materials and Methods: In this prospective cohort study, we evaluated the demographic data, pulmonary function test (PFT) results, lipid profile, oxygen saturation, and the presence of DELC in patients with COPD and control subjects.
Results: DELC was diagnosed in 155 (62%) of COPD patients and these patients had a higher prevalence of CAD (p = 0.044). Moreover, DELC was diagnosed in 135 men (68.5%) and 20 (37.7%) women in the COPD group (p<0.001) and in 39 (48.8%) men and 14 (56.0%) women in the control group (p = 0.527). On the other hand, CAD was diagnosed in 18% of patients with early-stage COPD (n = 104) and in 30.8% of patients with late-stage COPD (n = 146) (p = 0.041). The sensitivity and specificity of DELC positivity in predicting CAD were 80.65% and 44.15% in COPD patients, respectively.
Conclusion: The presence of cardiac comorbidities in COPD patients may play a vital role in the severity of the disease, exacerbations, and may also reduce the treatment response. Accordingly, an earlobe examination of patients with COPD may be useful in predicting the presence of cardiac comorbidities with high sensitivity.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease threatening global health security. Although COPD is associated with lungs, it can be accompanied by numerous comorbidities that may affect its prognosis.[1] Of these, extrapulmonary comorbidities are responsible for up to 50% of mortality in patients with COPD,[2] which mostly include cardiovascular diseases (CVD) that constitute more than half of the causes of mortality in patients with severe airway obstruction.[3–5]

Diagonal earlobe crease (DELC), also known as Frank's sign, is defined as a wrinkle or fold line extending diagonally from the tragus and across the lobule to the rear edge of the auricle of the ear.[6] Although this sign has been positively correlated with coronary artery disease (CAD) and peripheral vascular disease (PVD),[7–10] the pathophysiological mechanism underlying this correlation remains unclear. In this study, we aimed to evaluate the association between Frank's sign and COPD to investigate the utility of this sign for identifying COPD patients with increased risk of ischemic heart disease.

Materials and methods

The study protocol was approved by XXX University Medical School Ethics Committee (Approval No.: 20,181,207/2) and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

This multicenter, prospective cohort study was performed at two hospitals located in two different provinces in Turkey between September and December 2018. The study included a patient group of 250

Abbreviations: COPD, chronic obstructive pulmonary disease; Delc, diagonal earlobe crease; Pft, pulmonary function tests; Cvd, cardiovascular diseases; Cad, coronary artery disease; Gold, global initiative for chronic obstructive lung disease; Fev1, forced expiratory volume at 1st second; FVC, Forced Vital Capacity; SaO2, Arterial oxygen saturation; CRP, C-Reactive Protein; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; hs-CRP, high-sensitivity C-reactive protein; PTX3, Pentraxin3; MDA-LDL, Malondialdehyde Low Density Lipoprotein

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COPD patients and a control group of 105 age- and sex-matched controls. All the patients had a diagnosis of COPD based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. Exclusion criteria included pierced ear, age younger than 40 years, a diagnosis of COPD not confirmed by pulmonary function test (PFT), and failure to provide a written consent. An informed consent was obtained from each participant. The patient group was divided into four subgroups (Groups A and B, early-stage COPD; Groups C and D, late-stage COPD) according to disease severity, using the GOLD guideline. PFT was performed for stable COPD patients using Vmax™ Encore PFT System (Germany). PFT parameters including post-bronchodilator forced expiratory volume at 1 sec (FEV1), forced vital capacity (FVC), and FEV1/FVC were measured based on the GOLD guideline.

Demographic data, smoking status, comorbidities (such as hypertension, diabetes mellitus [DM], hyperlipidemia), history of CAD, arterial oxygen saturation (SaO2), C-reactive protein (CRP), and lipid profiles (cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) were recorded for each participant in both groups. In each participant, bilateral ear lobules were examined for DELC under sufficient lighting and in Fowler's position. DELC was defined as a diagonal wrinkle or deep furrow extending from the external part of the external acoustic meatus to the earlobe without a discontinuity. Unilateral or bilateral DELC were both considered as DELC-positive (Fig. 1).

Statistical analysis

Data were analyzed using SPSS for Windows Version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Normal distribution of continuous variables was determined using Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies (n) and percentages (%). Group means were compared using Chi-square test. Continuous variables were expressed as mean ± standard deviation (SD) for data with normal distribution and as median (minimum-maximum) for data with nonnormal distribution. Two groups were compared using Student's *t*-test for data with normal distribution and using Mann-Whitney U for data with nonnormal distribution. A p value of < 0.05 was considered significant.

Results

The COPD group comprised 197 (78.8%) men and 53 (21.2%) women with a mean age of 68.17 ± 9.15 years and the control group included 80 (76.2%) men and 25 (23.8%) women with a mean age of 67 ± 6.7 years. Of these, 90 (36.4%) patients with COPD and 30 (29.1%) control subjects were active smokers ($p < 0.001$). Table 1 presents the demographic characteristics, smoking habits, dyspnea scores, and CAD status in both groups. No significant difference was found between the two groups except for smoking status. Table 2 presents spirometric measurements, oxygen saturation, and serum CRP and lipid profiles in both groups. Although no significant difference was found between the two groups with regard to serum CRP and lipid profile, the spirometric measurements and SaO2 values were significantly higher in the patient group compared to the control group ($p < 0.001$).

Pulmonary function test (PFT) results were evaluated for the presence of DELC (Frank's sign). DELC was diagnosed in 155 (62%) of COPD patients and in 53 (50.5%) of control subjects ($p = 0.046$). Fig. 2 shows the prevalence of DELC in both genders. Collectively, DELC was diagnosed in 174 (62.8%) of all 277 men in both groups and in 34 (43.6%) of all 78 women ($p = 0.002$). Moreover, DELC was diagnosed in 135 men (68.5%) and 20 (37.7%) women in the COPD group ($p < 0.001$) and in 39 (48.8%) men and 14 (56.0%) women in the control group ($p = 0.527$). A history of CAD was present in 55 (27.9%) men and 7 (21.2%) women in the COPD group ($p = 0.028$) and in 20

Table 1
Demographic characteristics of COPD and control subjects*.

	COPD Group N = 250	Control group N = 105	p
Sex, Female, N(%)	53 (21.2)	25 (23.8)	0.588
Age (year)	68.17 ± 9.15	66.28 ± 6.96	0.085
Smoking status N(%)			
Non-smoker	25 (10.1))	29 (28.2)	<0.001
Ex-smoker	132 (53.4)	44 (42.7)	
Active	90 (36.4)	30 (29.1)	
Cigarette consumption, pack/year, Median (min-max)	40 (5–140)	30 (1–135)	0,006
BMI, kg/m^2	26.92 ± 5.23	27.96 ± 3.63	0.247
COPD Group, N(%)			
A	45 (18.0)		
B	59 (23.6)		
C	52 (20.8)		
D	93 (37.6)		
mMRC	1.87 ± 0.83	1.61 ± 0.89	0.008
Exacerbation per year, Median (min-max)	1 (0–6)		
Coronary Disease Status N(%)			
History of (CAD)	62 (24.8)	27 (26.0)	0.819
Coronary angiography	99 (39.6	40 (38.5)	0.842
Stent application	33 (13.2)	9 (28.8)	0.262

* Data are expressed as Mean ± SD unless otherwise indicated.
BMI; Body mass index, mMRC; Modified Medical Research Council, CAD; Coronary artery disease.

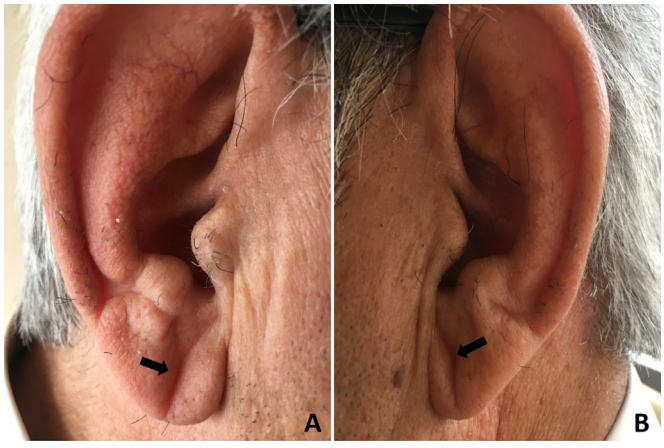

Fig. 1. Frank's sign (diagonal earlobe crease, DELC) detected on bilateral ear lobes of a patient (black arrows).

Table 2
Spirometric measurements, oxygen saturation and serum CRP and lipid profiles of study groups*.

	COPD	Control Group	p
Spirometric values			
FVC,%	63.56 ± 19.58	86.85 ± 19.31	<0.001
FEV1,%	50.46 ± 17.36	83.26 ± 19.12	<0.001
FEV1/FVC	56.66 ± 10.17	77.12 ± 9.37	<0.001
SaO2,%	91.26 ± 8.14	95.12 ± 2.39	<0.001
CRP, Median (min-max)	2.5 (0.01–145.4)	1.17 (0,01–58.40)	0.029
Serum Lipid Profile			
Total Cholesterol, mg/dl	178.18 ± 45.82	189.78 ± 42.81	0.028
LDL, mg/dl	112.04 ± 40.39	111.86 ± 27.69	0.897
HDL, mg/dl	47.32 ± 12.03	50.02 ± 12.58	0.079
TG, mg/dl	137.48 ± 68.93	123.07 ± 56.25	0.092

* Data are expressed as Mean ± SD unless otherwise indicated.
FVC; Forced vital capacity, FEV1; Forced expiratory volume in 1 sec, SaO2; Arterial oxygen saturation, CRP; C-reactive protein, LDL; Low-density lipoprotein, HDL; High-density lipoprotein, TG; Triglycerides.

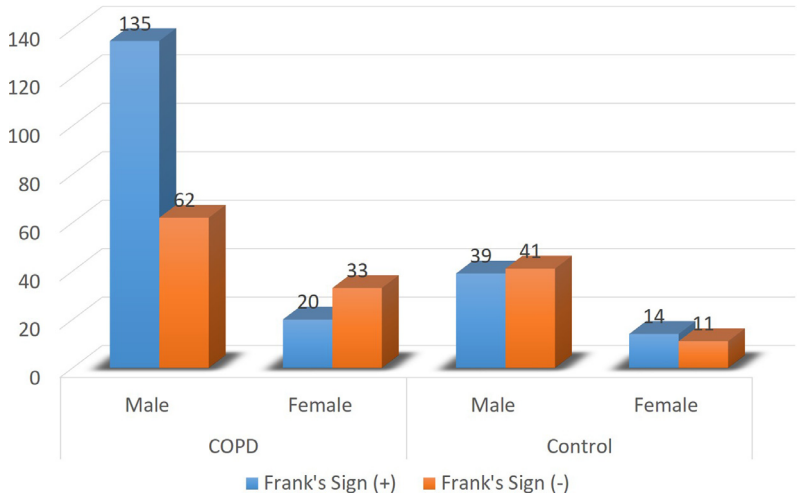

Fig. 2. Gender-based prevalence of DELC (Frank's sign) in COPD and control groups.

(25.3%) men and 7 (28.0%) women in the control group (p = 0.790) (Fig. 3). Both FVC and FEV1 values were significantly lower in COPD patients with DELC compared to those without DELC (p = 0.030 and p = 0.029, respectively). Similarly, both FVC and FEV1 values were significantly lower in control subjects with DELC compared to those without DELC (p = 0.026 and p = 0.046, respectively) (Table 3).

Coronary artery disease (CAD) was diagnosed in 18% of patients with early-stage COPD (n = 104) and in 30.8% of patients with late-stage COPD (n = 146) (p = 0.041) (Fig. 4).

The sensitivity and specificity of DELC positivity in predicting CAD were 80.65% and 44.15% in COPD patients and were 74.07% and 57.14% in control subjects, respectively.

Discussion

To the best of our knowledge, this is the first study in the literature evaluating the relationship between DELC (Frank's sign) and CAD in COPD patients. The results indicated that there is a significant association between DELC positivity and lower FEV1 and FVC values and also showed that the sensitivity and specificity of DELC positivity in predicting CAD in COPD patients were found to be 80.65% and 44.15%, respectively. Moreover, the prevalence of DELC was higher in male patients with COPD compared to females and was higher in patients with late-stage COPD (GOLD C and D groups) compared patients with early-stage COPD (GOLD A and B groups).

Several previous studies have suggested that DELC is independently and significantly associated with an increased prevalence of CAD.[11–15] Montazeri et al. reported that the prevalence of DELC in their patients was 62% and the prevalence of smoking and hyperlipidemia was significantly higher in patients with DELC compared to controls.[8] Similarly, Shmilovic et al. demonstrated that Frank's sign was significantly associated with increased prevalence, extent, and severity of CAD in 430 patients imaged with computed tomography (CT) coronary angiography. The authors also noted that although the sensitivity of DELC in detecting CAD was high (78%), it provided a low specificity (43%).[15]

Another study showed that DELC positivity provided a sensitivity and specificity of 60% and 48% in diagnosing CAD, respectively.[16] In our study, the sensitivity and specificity of DELC positivity in predicting CAD were 80.65% and 44.15% in COPD patients and were 74.07% and 57.14% in control subjects, respectively. Accordingly, the sensitivity and specificity values detected in our COPD and control groups were higher than those reported in the literature, which could be due to increased inflammation in patients with COPD.

The association between DELC and cardiovascular diseases has been well documented in the literature. In a previous prospective

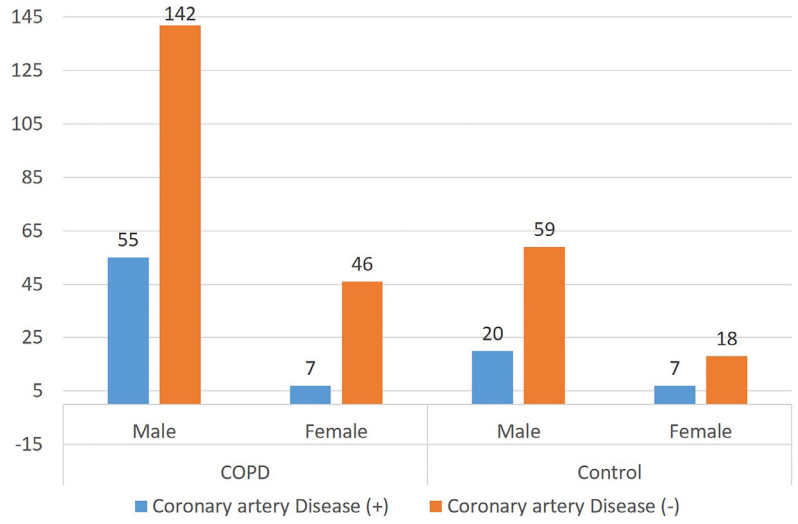

Fig. 3. Gender distribution of the coexistence of CAD in COPD and control groups.

Table 3
Spirometric measurements, oxygen saturation and serum CRP and lipid profiles of study groups according to Frank's sign*.

	COPD		P	Control		p
	Frank's sign (+)	Frank's sign (-)		Frank's sign (+)	Frank's sign (-)	
Spirometric values						
FVC,%	62.88 ± 19.30	68.95 ± 14.15	0.030	85.69 ± 21.08	92.21 ± 15.24	0.026
FEV1,%	49.44 ± 17.26	54.84 ± 15.30	0.029	81.39 ± 19.64	87.21 ± 17.33	0.046
FEV1/FVC	60.06 ± 10.70	60.15 ± 8.56	0.888	74.91 ± 9.99	76.62 ± 9.22	0.498
SaO2,%	91.87 ± 5.82	93.83 ± 3.77	0.181	94.33 ± 2.07	95.94 ± 2.12	0.196
CRP, Median (min-max)	2.87(0.01–100.20)	1.22(0.01–66.00)	<0.001	1.60 (0.01–58.40)	1.70 (0.01–43.00)	0.799
Serum Lipid Profile						
Total Cholesterol, mg/dl	175.89 ± 37.08	193.05 ± 58.23	0.010	192.06 ± 41.86	179.76 ± 48.24	0.375
LDL, mg/dl	109.97 ± 31.83	121.58 ± 53.80	0.047	114.24 ± 30.89	107.26 ± 24.65	0.265
HDL, mg/dl	46.65 ± 12.66	49.43 ± 11.21	0.217	48.29 ± 11.34	47.94 ± 12.12	0.334
TG, mg/dl	146.08 ± 73.60	133.13 ± 64.06	0.101	126.24 ± 54.98	113.94 ± 53.52	0.033

* Data are (Mean ± SD) unless otherwise indicated
FVC; Forced vital capacity, FEV1; Forced expiratory volume in 1 sec, SaO2; Arterial oxygen saturation, CRP; C-reactive protein, LDL; Low-density lipoprotein, HDL; High-density lipoprotein, TG; Triglyceride.

study, DELC was found to be associated with a poor survival rate and higher risk of cardiac death.[17] However, some other studies suggested that the pathophysiologic mechanism underlying this association remains unclear and various mechanisms are still being discussed, such as unstable ratio of collagen/elastin, degeneration or loss of elastin, shortening of telomeres, injury, or anatomical changes.[12,13]

Koyama et al. found that serum inflammatory and oxidative stress biomarker levels were significantly higher in DELC-positive patients compared to DELC-negative patients. The authors also noted that systemic vascular inflammatory responses were associated with the appearance of DELC.[12] Endothelial dysfunction is a pathogenic mechanism in the early stages of systemic atherosclerosis and plays an important role in the development of the disease.[18] Moreover, Oda et al. demonstrated that the presence of bilateral earlobe creases (ELCs) was an independent predictor of endothelial dysfunction.[19]

Besides cerebrovascular diseases, atherosclerotic process has also been shown to be associated with Frank's sign. A recent review evaluated the association between Frank's sign and cerebrovascular diseases and suggested that DELC could be a risk factor for ischemic stroke independently from ischemic heart disease. The authors also noted that DELC can be easily noticed and may serve to identify high-risk patients.

Literature indicates that the pathophysiological changes above-mentioned have also been seen in COPD patients. Accordingly, since lungs are exposed to environmental factors such as smoke, air pollution, and infections, this exposure triggers proinflammatory processes.[20] On the other hand, pulmonary inflammation that develops in response to these factors evolves into systemic reaction, thereby resulting in chronic low-grade systemic inflammation.[21] Another pathophysiological explanation to the relationship between COPD and DELC is that several conditions including oxidant-antioxidant imbalances in both the lungs and the circulation, gene polymorphisms, activation of transcription factors, increased plasma pro-inflammatory cytokines, and hypoxia cause endothelial dysfunction.[22]

Diagonal earlobe crease (DELC) is usually absent at birth and in young children and is more common in the elderly.[23] Evrengul et al. evaluated 415 patients for the presence of bilateral ELC and revealed that the prevalence of DELC positively correlated with age, hypertension, male gender, and smoking.[24] Similarly, a large-scale prospective study showed that people aged over 40 years with an ELC were at risk for vascular diseases due to atherosclerosis.[25] Moreover, Wang et al. reported that the prevalence of bilateral DELC was higher among male patients, older people, and those with more severe CAD in patients diagnosed by coronary angiography. In the same study, no difference was detected between the groups with or without DELC with regard to smoking status.[26]

Brutto et al. showed that the association between ELC and abnormal ankle-brachial index, which was used as a surrogate of peripheral

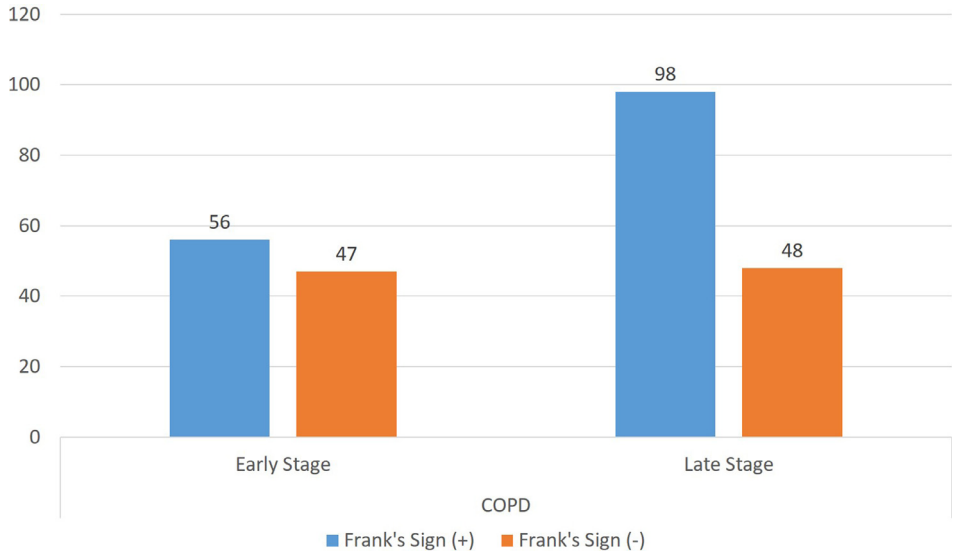

Fig. 4. Prevalence of DELC (Frank's sign) in early- and late-stage COPD patients.

artery disease, was attenuated by the high prevalence of both conditions in older people.[27] In our study, in a similar way to previous studies, there was a male gender predominance in both groups and the prevalence of elderly patients and smoking was higher in the COPD group compared to the control group. It is commonly known that smoking increases the production of free oxygen radicals and oxidative stress substantially. In a previous, Ambrose et al. found a positive correlation between increased oxidative stress and the presence and progression of CAD, which was associated with smoking.[28] Taken together, these findings implicate that smoking may be a possible underlying mechanism for the increased prevalence of DELC and the increased susceptibility to CAD in COPD patients.

Our study was limited in several ways. First, the study had a small patient population. Second, in patients with DELC, the depth of the crease was not graded (e.g. mild, moderate, and severe) and the length of the crease was not classified (e.g. complete or incomplete). Finally, the mean age of our study population was 67 years old.

In conclusion, cardiac diseases are the most common comorbidities of COPD that can be easily predicted with a simple and easily applicable physical examination finding. However, timely diagnosis and treatment of CVD in COPD patients is of paramount importance since cardiac comorbidities may affect the severity of the disease, trigger exacerbations, and reduce treatment response. Therefore, in patients with COPD, cardiac comorbidities can be predicted via physical examination of bilateral earlobes and may lead the physicians to investigate undiagnosed CAD. However, further studies with larger populations are needed to investigate the role of DELC findings (according to the depth, completeness of the crease and age status) in predicting CAD in COPD patients. Moreover, although previous studies showed that DELC was useful for detecting ischemic heart diseases in people aged older than 40 years, further studies with larger populations are needed to clarify which age is more useful to evoke attention for atherosclerosis in COPD patients.

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