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Local sympathetic stimulation not only have local effects in patients with Raynaud's phenomenon

K. KARABACAK[1], D. DOGAN[2], M. CELIK[3], E. KAYA[1], M. KADAN[1], H. ISIK[4], N. OCAL[5], S. DOGANCI[1], V. YILDIRIM[6], U. DEMIRKILIC[1]

[1]Department of Cardiovascular Surgery, Gulhane Military Academy of Medicine, Ankara, Turkey
[2]Department of Pulmonary Medicine, Gulhane Military Academy of Medicine, Ankara, Turkey
[3]Department of Cardiology, Gulhane Military Academy of Medicine, Ankara, Turkey
[4]Department of Thoracic Surgery, Hakkari Military Hospital, Hakkari, Turkey
[5]Department of Anesthesiology, Department of Pulmonary Medicine, Hakkari Military Hospital, Hakkari, Turkey
[6]Department of Anesthesiology, Gulhane Military Academy of Medicine, Ankara, Turke

Abstract. – OBJECTIVE: Many other organs and system can be affected in the course of Primary Raynaud's Phenomenon (RP). Simultaneously increased vasospasm in the pulmonary vascular bed may likely affect the pulmonary function. Therefore, we investigated the effect of Raynaud's phenomenon on the respiratory functions in this study.

PATIENTS AND METHODS: Between March 2014 and December 2014, 30 patients with the diagnosis of PRP more than two years and 32 age-sex matched healthy controls were enrolled into this study. Cold stimulation test (CST) was performed. Pulmonary function test were performed following 30 minutes after CST and spirometric measurements were calculated.

RESULTS: There were no statistically significant differences between two groups regarding their demographic and clinical data. Mean duration of symptoms from onset to present was 3.01 ± 1.05 years. Patients with Primary RP had significantly lower FVC and higher FEV_1/FVC values compared to the control groups (p = 0.015 and p=0.045, respectively).

CONCLUSIONS: We found that statistically significant decrease of FVC values in patients with Primary RP compared to the healthy controls could be a impaired innervation of pulmonary system and a predictor of pulmonary vasospasm and/or pulmonary Raynaud's phenomenon, which may develop in future periods.

Key Words:
Raynaud's phenomenon, Pulmonary function test, Pulmonary vasospasm.

Introduction

Primary RP is a relatively common disorder in worldwide population with the prevalence of 3.3% to 22%[1]. Episodic cyanosis, swelling and pallor on the distal part of the extremities with cold exposure are the main characteristic features of this disorder. This disorder has female dominancy and especially seen in 2nd and 3rd decades of life[2]. They can be classified into two groups according to underlying etiologic factors. If the pathogenesis depends on underlying disorder, it is called secondary (obstructive) form. The remaining forms without any underlying disorders are called primary form[1,3]. While primary RP has been considered to be a result of dysregulation of autonomic sympathetic system, many other organs and systems can also be affected simultaneously. Cardiovascular system and cardiac involvement have been mostly investigated in these patients. Although it is well known that sympathetic innervation of pulmonary system is provided by plexus pulmonalis T2-T5[4], which is believed as the same segment affected in primary RP, pulmonary function change in these patients has not been clarified yet. We hypothesized that pulmonary functions might be affected in patients with primary RP. The present study was, therefore, undertaken to investigate the pulmonary functions by the mean of spirometry as a non-invasive test in patients with primary RP.

Patients and Methods

Patient's Selection

This is a prospective study and approved by the local ethical committee. In a period of 9 months, 30 patients, who were diagnosed with

Corresponding Author: Kubilay Karabacak, MD; e-mail: kubilaykarabacak@yahoo.com

primary RP at least 2 years ago, were enrolled into this study. The diagnostic criteria of Wigley et al[5] were used. Taking into account the occurrence of frequent co-morbidities in elderly, only under 25 year-old males with primary RP were included also for ensuring standardization in study group, Several etiologic disorders such as systemic sclerosis and systemic lupus erythematosus, which can cause secondary primary RP, were excluded with detailed physical examination and several laboratory findings. Subjects with cardiovascular diseases such as valvular heart disease, congenital heart and lung diseases, pulmonary hypertension, coronary artery disease, atrial fibrillation, left ventricular systolic dysfunction, uncontrolled hypertension (systolic blood pressure > 190 mmHg), and presence of permanent pacemaker were regarded as exclusion criteria. The control group consisted of 32 age-sex matched healthy controls. Smoker patients and control subjects were not enrolled into this study.

Cold Stimulation Test (CST)

CST is performed as detailed in our previous study[6].

Pulmonary Function Test (PFT)

In order to observe the effect of evoked sympathetic system on pulmonary functions, spirometry (COSMED QUARK TST.1, Chicago, IL, USA) was performed 30 minutes after CST. Volume that has been exhaled at the end of the first second of forced expiration (% FEV_1), forced vital capacity (% FVC), FEV_1/FVC, forced expiratory flow (FEF) 25%, FEF 50% and FEF 75% were measured in all subjects enrolled to this study. Spirometric measurements were calculated as a percentage of the predicted value according to the subjects' age, sex and body surface areas. All evaluations were done according to the 2005 European Respiratory Society Standardization of Spirometry Guideline[7].

Statistical Analysis

SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL, USA) was used for statistical evaluation. Kolmogorov-Smirnov test was used for analyzing the distribution pattern of data and normally distributed continuous variables were expressed as mean ± standard deviation. Comparisons of the parametric values were performed with student-t test for normally distributed groups. A p value of < 0.05 was considered as statistically significant with a 95% confidence interval.

Results

Our study and control group were consisting of young (under 25 year-old) males with a mean age of 21.80 ± 1.76 and 22.06 ± 1.10, respectively. None of the patients was smoker and had any diagnosed pulmonary disease or co-morbid disorders such as hypertension and diabetes mellitus, etc. There were no statistically significant differences between two groups regarding their demographic and clinical data (Table I). The most common complaints were cyanosis (22 patients, 73.3%), numbness (20 patients, 66.6%), and hyperhidrosis (19 patients, 63.3%). Mean duration of symptoms from onset to present was 3.01 ± 1.05 years. Mean BMI, heart rate, systolic and diastolic blood pressure values of both groups did not significantly differ from each other.

While the mean %FVC of the control group was 109.03 ± 5.95, mean % FVC of the study group was 102.12 ± 14.15. The difference between groups was statistically significant (p =

Table I. Basal demographical data.

	Patients (n = 30)	Control (n = 32)	*p* value
Age, years	21.80 ± 1.76	22.06 ± 1.10	0.483
BMI (kg/m^2)	22.98 ± 2.03	23.02 ± 2.53	0.948
Heart rate (bpm)	76.80 ± 12.99	75.87 ± 11.72	0.769
Systolic Blood Pressure (mmHg)	116.76 ± 10.45	119.31 ± 9.99	0.331
Diastolic Blood Pressure (mmHg)	74.43 ± 7.81	75.56 ± 9.15	0.605
Duration of symptoms (years)	3.01 ± 1.05		N/A

BMI: Body mass index.

0.015) (Figure 1). FEV_1/FVC results of control and study groups were 85.01 ± 4.51 and 87.93 ± 6.56, respectively. In this regard, the difference between groups also was statistically significant ($p = 0.045$). On the other hand, mean % FEV_1, FEF 25%, FEF 50% and FEF 75% values of groups did not represent significant differences ($p > 0.05$) (Table II).

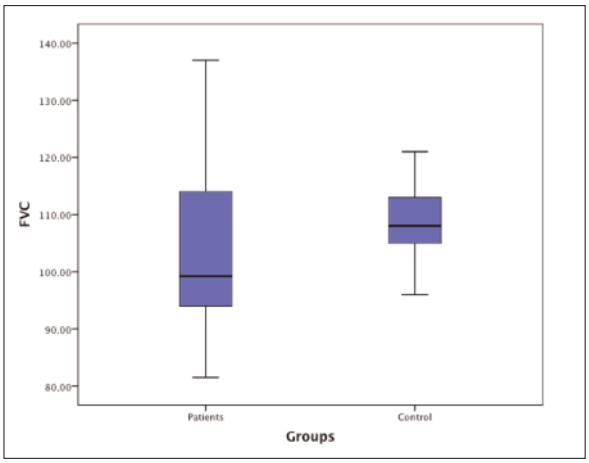

Figure 1. Comparison of FVC values between two groups.

Discussion

Raynaud's phenomenon is a condition, whose symptoms are results of the vasospasm of arterioles in smooth muscle. Although the pathogenesis of Raynaud's phenomenon is not fully elucidated, neural and intravascular mechanisms are involved in this process. Plexus pulmonalis provides innervation of the respiratory system is created by sympathetic nerves originating from the T2-5 level and parasympathetic fibers originating from the vagus nerve[4]. Considering the fact that increased sympathetic activity is blamed to be the cause of this phenomenon, nerve and muscle atrophy may accompany with this pathological condition as a result of vasospasm, and also other organ systems such as respiratory muscles are likely to be affected. Chronic vasospasm in nutritional arteries of respiratory muscles and pulmonary tissue may cause atrophy and mild infarctions, which results with increase in dead space respiration and residual volume.

Although it is well known that chronic vasospasm commonly occurrs in fingers, it also occurs in other systemic vascular structures such as pulmonary arteries. Vasospasms in the pulmonary vascular bed may lead to a disorder named as "Pulmonary Raynaud's Phenomenon". Pulmonary Raynaud's phenomenon is defined as the increase of pulmonary arterial pressure due to the pulmonary vasoconstriction as a result of the long-term sympathetic hyperstimulation in the pulmonary vascular bed[8]. Pulmonary arterial hypertension and reduction of the carbon monoxide diffusing capacity (DLCO) are common in Pulmonary Raynaud's Phenomenon. It is a well-known fact that pulmonary vasospasm and bronchodilatation occurred after the cold pressure test performed in patients with Raynaud's Phenomenon[9]. With resultant pulmonary vasospasm, alveolar's dead space increases and thereby, respiratory frequency increases to protect from the respiratory failure brought by increased alveolar dead space. In addition, increased vasospasm in areas well ventilated may cause redistribution of pulmonary perfusion and an increase in respiratory dead space and residual volume. When all these issues are taken into consideration, spirometry is likely to be affected in Raynaud's phenomenon[8,10].

Although there are studies reporting significant findings about Pulmonary Raynaud's phe-

Table II. Pulmonary function test results.

	Patients (n = 30)	Control (n = 32)	*p* value
FVC	102.12 ± 14.15	109.03 ± 5.95	0.015
FEV_1	104.71 ± 11.56	107.70 ± 7.23	0.225
FEV_1/FVC	87.93 ± 6.56	85.01 ± 4.51	0.045
FEF 25	105.03 ± 29.63	105.71 ± 18.49	0.913
FEF 50	109.01 ± 21.55	110.15 ± 21.64	0.836
FEF 75	108.74 ± 27.51	106.09 ± 19.25	0.660
FEF 25-75	102.90 ± 21.70	111.96 ± 19.94	0.092

FVC: Forced Vital Capacity, FEV: Forced Expiratory Volume; FEF: Forced Expiratory Flow.

nomenon, pulmonary hypertension and DLCO we have not meet any study about spirometric alterations on primary RP cases who are asymptomatic in pulmonary respect and do not have pulmonary hypertension. The findings of our study demonstrated that patients with primary Raynaud's phenomenon have lower %FVC and higher FEV_1/FVC compared with healthy controls. In this study, we suggest that FVC decline detected in these patients might be due to the pulmonary vasospasm and thereby, increase of alveolar dead space and respiratory frequency. Nonetheless; possible atrophy in respiratory muscles and pulmonary tissue should be kept in mind at the etiology of spirometric changes.

Raynaud's phenomenon also constitutes a part of the CREST syndrome and pulmonary hypertension, decline of DLCO and FVC in systemic sclerosis are well-known facts[11]. There were no other elements of systemic sclerosis or CREST syndrome in any of our patients. On the other hand it has been shown that systemic sclerosis can develop during long-term follow-up of these patients, but our patients have not been followed-up that long yet. These pathologies may be some forms of secondary pulmonary hypertension[12].

In their report, Mukerjee et al[13] found that pulmonary vasospasm in response to a cold stimulus that elicits digital vasospasm is unlikely to play a major role in the pathogenesis of pulmonary hypertension in systemic sclerosis. However, they measured mean pulmonary artery pressure, total pulmonary vascular resistance, and cardiac output via cardiac catheterization. It might be harmful to perform an invasive test such as cardiac catheterization in a patient free of pulmonary symptoms. Therefore, we aimed to evaluate the pulmonary functions in a non-invasive manner.

Conclusions

It would be more correct to emphasize that local sympathetic stimulation not only have local but also systemic effects in patients with primary RP. The findings of our study suggest that the lower, but still in the normal range, FVC and FEV1/FVC values, might be an indicator of affected pulmonary sympathetic innervation in patients with primary RP but no respiratory symptoms. We believe that the statistically significant decrease of FVC values in patients with primary Raynaud's phenomenon, compared to the control group, could be a predictor of pulmonary vasospasm and/or Pulmonary Raynaud's Phenomenon, which may develop in future periods. However, the underlying pathophysiological mechanisms are largely unresolved and further, long-termed studies are needed to clarify this confusion.

Annotation

This was an observational study based on a single center registry with a relatively small number of patients. Also, because our institutional patient population mostly comprised of men, all of the cases were male. For this reason, it may be difficult to make a generalized comment for both genders regarding with the results. Despite these limitations, our study can give inspiration for further larger sample-sized prospective studies.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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