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The Relationship between Serum Pro-Brain Natriuretic Peptide (Pro-BNP) Levels and Pulmonary Arterial Hypertension (PAH) in Patients with Limited Scleroderma

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is a late progressive scleroderma-related complication, which can lead to right heart failure and cor pulmonale. Given that cardiac catheterization is a diagnostic method of choice for PAH, and considering the high risks of this method, the purpose of this study was to evaluate the relationship between serum Pro-Brain natriuretic peptide (Pro-BNP) Levels and PAH in patients with limited scleroderma.

Materials and Methods: In this cross sectional study , during June 2011- Dec 2013, referring patients to two major educational hospitals, Mashhad- Iran, with scleroderma, who were afflicted with the disease for at least two years (or more), were enrolled in the study if they met the inclusion and exclusion criteria. All the patients underwent echocardiography to determine the pulmonary artery pressure (PAP). Afterwards, the subjects were referred to a lung center for performing body plethysmography, carbon monoxide diffusing capacity (DLCO), and 6-minute walk test (6MWT). Pro-BNP Serum level was determined using flourescent immune assay method.

Results: The present study included 20 patients (18 female subjects) with the mean age of 43.28±9.56 yrs, and the mean pro-BNP level of 138 pg/ml. The logarithmic correlation between PAP values, Forced Vital Capacity /DLCO ratio, and pro-BNP level, which was measured using Pearson's correlation coefficient, showed a significant association among these variables(respectively, r=0.76, P<0.001; r=0.677, P=0.011). Moreover, the DLCO decrease was associated with increasing pro-BNP level, though this relationship was not significant.

Conclusion: This study showed that there was a significant relationship between the serum levels of pro-BNP marker and increased PAP in the echocardiography, DLCO reduction, and FVC/DLCO increase. In fact, this serum marker can be used in patients with systemic scleroderma (SSc) to evaluate the status of PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is one of the major causes of mortality in patients with systemic scleroderma (SSc), accounting for approximately 30% of these cases (1, 2).

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Significant advances have been made in revealing the pathogenesis of PAH in the last two decades, leading to the development of suitable treatments in idiopathic cases. However, due to the presence of SSc, the response to treatment in patients with PAH is less than desirable, and therefore, the survival rate is quite low (3-5).

In the early stages of the disease, systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is often asymptomatic or is manifested with very few symptoms. Therefore, this type of disease often reveals itself in the late stages of scleroderma, and more than 2/3rd of the patients are in the functional class (FC) III-IV, according to the World Health Organization (WHO) FC criteria (6-9). Considering this evidence, the early diagnosis of this scleroderma-related complication can lead to an improvement in the patients' survival rate. According to one study, the 3-year survival rate of treated patients with FC I-II was 70%, and the 3-year survival rate of patients with FC III-IV was reported as 20-50% (6).

Moreover, it has been shown that an early treatment delays the progression of SSC-PAH, and improves the FC (10, 11).

At present, right heart catheterization (RHC) is the only definitive test for PAH diagnosis; however, due to the invasive nature of this test, RHC is not an appropriate tool for screening SSC patients.

Therefore, performing RHC follows a diagnostic purpose in SSC-PAH patients who are clinically suggestive of PAH. The use of non-invasive screening tools for patient selection and referral for further evaluation/confirmation by RHC is the ultimate goal.

Transthoracic echocardiography, pulmonary function tests (PFT), and various biomarkers have been used for the early diagnosis of PAH in different studies; though each study has its own limitations. For instance, systolic pulmonary artery pressure (PAP) is not properly assessed in 20-39% of patients, due to lack of tricuspid regurgitation or high quality images (12-14).

Also, the study of Aruntheari et al. (15) did not indicate a significant relationship between PFT and hemodynamic factors in RHC. Various studies have been performed regarding blood biomarkers for PAH, either alone or in combination with other non-invasive screening evaluations, for the classification of PAH risk factors in patients with SSc. In this regard, pro-BNP has been one of the evaluated biomarkers for patients with SSc-PAH. The elevated serum level of this marker can be an early indicator of pulmonary artery hypertention with high specificity and sensitivity (16-18).

Considering the mentioned points, we aimed to evaluate the relationship between the serum levels of pro-BNP and PAH in patients with limited SSc.

Materials and Methods

In this cross-sectional study, from June 2011 to Dec 2013, referring patients to two major educational hospitals, Mashhad-Iran, with the diagnosis of limited SSc, who were afflicted with the disease for at least two years (or more), and were diagnosed by a rheumatologist according to the criteria of the American College of Rheumatology (ACR), were included in the study.

Patients with the following diseases were excluded from the study: PAH such as primary PAH and secondary PAH due to chronic cardiac and pulmonary diseases including chronic obstructive pulmonary disease and pulmonary parenchymal fibrosis disease, chronic liver disease, pulmonary thromboembolic disease, sickle cell, thalassemia, hemolytic anemia, and systemic-to-pulmonary shunts in the heart.

Firstly, a questionnaire regarding the demographic characteristics, clinical symptoms, and physical examinations was completed. All the subjects underwent transthoracic echocardiography to determine the PAP; the procedure was performed by one single cardiologist. Afterwards, the patients were referred to a lung center for performing body plethysmography, DLCO (Diffusing Capacity for Carbon Monoxide), and 6-minute walk test (6MWT); the results were reported by two pulmonologists.

Table 1. Quantitative data regarding the assessment of patients using echocardiography, PFT, and DLCO

Variables	Minimum	Maximum	Mean	SD
EF(%)	35.00	70.00	57.10	8.71
6MWT(m)	158.00	480.00	383.63	93.26
TLC	60.00	140.00	92.33	21.12
FEV1	45.00	112.00	82.63	18.05
FVC (predicted%)	61.00	116.00	83.76	15.93
FEV1/FVC(%)	77.00	86.00	81.00	2.64
PAP (mmHg)	20.00	60.00	26.05	10.21
DLCO	48.00	125.00	86.26	21.19
FVC/DLCO	0.86	1.58	1.06	0.203

EF: Ejection Fraction
6 MWT (m): 6-minute walk test
TLC: Total Lung Capacity
FEV1: Forced expiratory volume in one secend
FVC: Forced vital capacity
DLCO: Diffusing capacity for carbon monoxide
PAP: Pulmonary Artery Pressure

Table 2. The relationship between pro-BNP values and PAP, DLCO, and FVC/DLCO ratio, using Mann-Whitney test

Variables		Pro-BNP (pg/ml)		P-value
		Mean	SD	
PAP	35 mmHg<	64.11	60.02	0.046
	≤35mmHg	835.00	1042.27	
DLCO	50%<	48.76	26.40	0.009
	≤50%	648.66	804.56	
FVC/DLCO	1.4<	48.76	26.40	0.004
	≤1.4	648.66	804.56	

FVC: Forced vital capacity
DLCO: Diffusing capacity for carbon monoxide
POP: Pulmonary Artery Pressure

A non-fasting venous blood sample (5 cc) was obtained from the participants to determine serum pro-BNP levels. The serum of all the samples was separated and kept in a -70°C refrigerator, after being frozen. Pro-BNP serum level was determined using flourescent immune assay method.

For data analysis, SPSS version 14 was used. The quantitative and qualitative data were described by the measures of central tendency and distribution, and the mean and standard deviation (SD) were used to express these values.

Distribution of quantitative variables in the subgroups of qualitative variables was analyzed using student's t-test. Also, to investigate the relationship between the quantitative variables, Scatter/dot graph and Spearman correlation coefficient were applied.

Prior to performing statistical analysis, the normal distribution of quantitative variables was measured using Kolmogrov-Smirnov test. In case the variable was not normally distributed, non-parametric tests were applied. P-value less than 0.05 was considered statistically significant.

Results

A total of 20 patients, who were examined by a rheumatologist according to ACR criteria, (and were afflicted with the disease for at least two years or more) were studied. Ten percent and 90% (18 cases) of the patients were males and females, respectively. The mean age of the patients was 43.28 ± 9.56 years (within the range of 25-57 years).

The clinical assessment of the patients included the following tests: 6MWT, the rate of oxygen saturation before and after this test, breathing test measures including total lung capacity (TLC), DLCO, forced expired volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, residual volume (RV), RV/TLC ratio, and the echocardiography evaluation including PAP and ejection fraction (EF). The values of these variables and pro-BNP are presented in Table 1.

Due to the non normal distribution of values of pro-BNP, we used Mann-Whitney test to evaluate the relationship between this factor and PAP, DLCO, and FVC/DLCO ratio; the results can be seen in Table 2.

All these variables showed a significant association with pro–BNP values; the P-values can be seen in Table 2.

As presented in Figure 1, PAP values increase as the Pro-BNP level elevates; the correlation coefficient between these two factors is 0.760, and the P-value is less than 0.001.

Although Figure 2 indicates a decrease in DLCO with increasing pro-BNP, this correlation is not significant considering the correlation coefficient of -0.375 and P-value=0.113. Figure 3

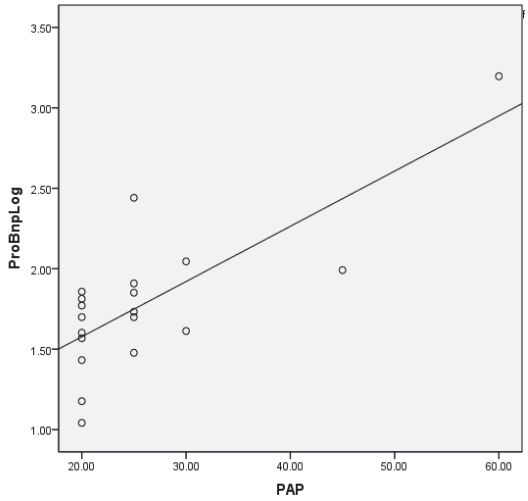

Figure 1. The logarithmic correlation between pro-BNP levels and PAP values

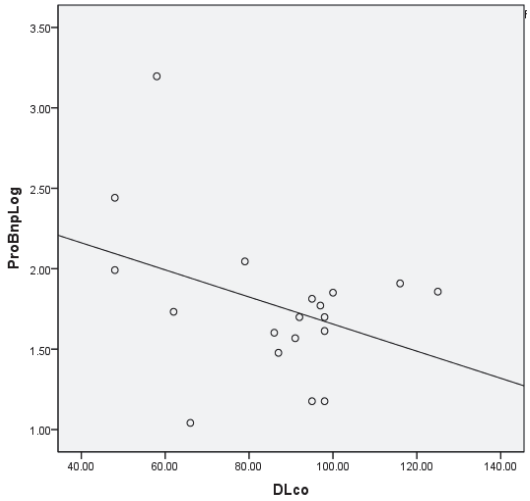

Figure 2. The logarithmic correlation between Pro-BNP levels and DLCO values

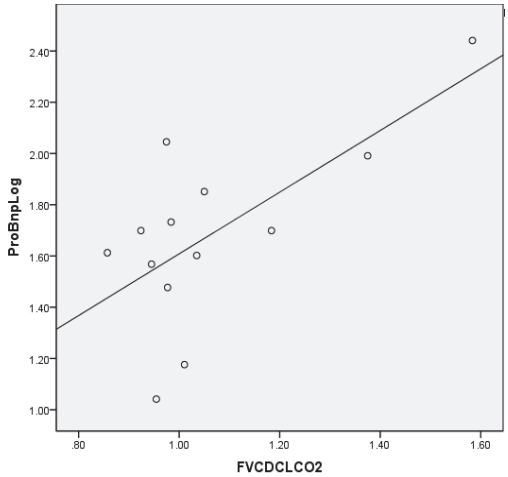

Figure 3. The logarithmic correlation between pro-BNP levels and FVC/DLCO values

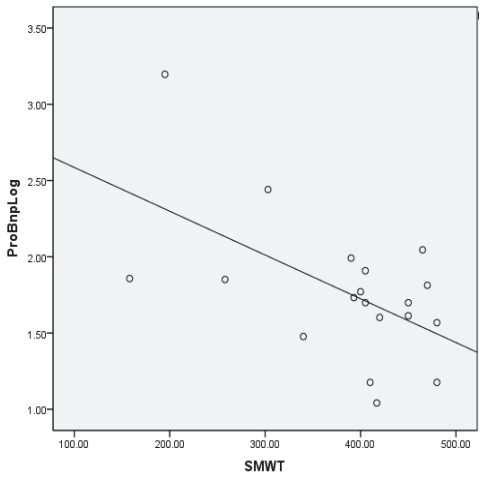

Figure 4. The correlation between 6 MWT results and Pro-BNP levels

also shows an increase in FVC/DLCO ratio as the pro-BNP level increases; this correlation is significant, considering the correlation coefficient of 0.677 and P-value=0.011.

The results related to 6WMT and pro-BNP level were analyzed using scatter/dot graph and Pearson correlation coefficient; as it can be seen in Figure 4, with increasing pro–BNP level, the distance traveled in this test significantly decreased (P=0.012, r=0.563).

Discussion

As shown in the present study, pro-BNP level was significantly differed between determined normal and abnormal values of PAP, DLCO, and DLCO/FVC ratio. Additionally, the linear correlation between this factor and PAP, FVC/DLCO ratio, and 6MWP was significant, in a way that this factor had a direct relationship with PAP and FVC/DLCO values. It also had an inverse relationship with 6MWT values. Although the linear relationship between pro-BNP levels and DLCO values was not significant, the slope of the relationship between these two factors indicated a possible relationship.

Most of the performed studies in this field confirm the prognostic role of pro–BNP level for PAH in patients with SSc. Thahkcar et al. (19) presented an algorithm for screening patients with SSc-PAH, and suggested that patients with pro-BNP level >209.8 pg/ml or DLCO <70.3% and FVC/DLCO ratio >1.82 should be referred for further analysis by HRCT, 6MWT, and RHC.

Additionally, AalyiaYaghub (4) in literature review, introduced high levels of pro-BNP as a reflection of the severity of right ventricular dysfunction. Moreover, the elevated level of this factor is significantly related to poorer hemodynamic status of functional capacity and lower survival rate in SSC-PAH patients. Similarly, Dimitroulal et al. (20) in a review study (a review of studies from 1999 to December 2008) provided similar findings.

Oravec and colleagues (21) also reported that the predicted percentage of DLCO was significantly and inversely associated with the level of pro-BNP. The study of William et al. (11) also showed a significant positive association between pro-BNP and PAP, and an inverse relationship with 6MWT test results. Moreover, Allonore et al. (18) in their study, observed an increase in PAP and pro-BNP in patients who had progressed to PAH. All the results of the present study are in consistence with the findings of the mentioned studies.

In the present study, the lower levels of pro-BNP (with an average of 138.75±342.09), compared with other studies, indicate an association between this factor and PAH in SSc patients. This difference is due to some factors. Firstly, in other studies, patients with diffuse and limited SSc were evaluated. For instance, as Choi et al. (22) showed, the rate of this serum marker was significantly higher in the diffuse SSc group. In their study, the average level (98.6) of this factor in the limited SSc group was close to that of the present study.

The second reason for this discrepancy is the evaluation of confirmed PAH patients in other studies. For instance, in the study of Thahkar et al. (19), who studied four groups of patients, the mean pro-BNP was 1.818 pg/ml in the confirmed PAH group, and 278 pg/ml in the group at risk of PAH. In the group at risk of PAH, the mean PAP (43.8 mmhg) and the FVC/DLCO ratio (1.73) were higher than our study; however, the mean of DLCO (61 %) was lower in comparison with the present study.

In fact, these observations suggest that the findings of the present study are consistent with previous studies. Measurement of pro–BNP level, as a tool for screening patients with SSC-PAH,

confirmed by RHC, has been shown in different studies.

In the study by Williams et al. (17), sensitivity and specificity of 51% was achieved at a cut-off point of 91 pg/ml. Mukerjee et al. (23) indicated a cut-off point of 395.34 pg/ml with sensitivity of 69% and specificity of 100%; Allanore et al. (18) achieved the sensitivity and specificity of 80% with a cut-off point of 178.3 pg/ml, and Oravec et al. (21) indicated a cut-off point of 157.8 with 100% sensitivity and 72.3% specificity. Finally, Thahkar and colleagues (19) reached a cut-off point of 209.8, with sensitivity and specificity of 100% for identifying patients with SSC-PAH.

In the present study, due to the low number of patients with PAP> 35 mmHg, or DLCO < 50%, or FVC/DLCO ratio more than 25%, (the inclusion criteria) and also lack of a control group, data analysis was not reliable enough to obtain the cut-off point; therefore, only the significant positive and negative relationships were demonstrated.

The differences in the cut-off point between the mentioned studies can be attributed to several possible reasons: differences in the sample size of these studies, variations in the clinical characteristics of the patients, and differences in including PAH patients. For instance, in the studies of Mukerjee (23), Williams (17), and Thakhar (19), the RHC method was used as the gold standard for the diagnosis of patients. However, in the study of Allonore (18), PAP>40 mmHg, in the study of Oravec (21), gradient across the tricuspid valve>36 mmHg or >31 mmHg along with dyspnea were considered as indicators of PAH in SSc patients.

Regarding 6MWT, it should be mentioned that the test results depend on the hemodynamic status of patients. According to the literature (24-26), since hemodynamic changes in PAH-SSc patients are less prominent in early stages, compared with idiopathic PAH patients, therefore, the diagnostic value of this test for assessing PAH severity in SSC patients is suspected. However, few studies have evaluated this test with regard to SSc-PAH (27).

In this regard, Allonare et al. (18) evaluated the results of this test in the evaluation of Bosentan treatment results in patients with SSc-PAH. Although the average level of pro-BNP significantly reduced from 474 pg/ml to 238 pg/ml, no significant improvement was observed in the results of 6MWT. For this reason, Garin et al. (28) suggest that this test is not suitable for the evaluation of patients with SSc-PAH. In fact, this test actually evaluates the global assessment of the patient's daily function, and other associated morbidities such as pain and musculoskeletal dysfunction indicate that the reliability of this test is under question.

In the present study, 6MWT showed a significant inverse linear relationship with pro-BNP level; the study of William et al. (17) has indicated a similar result. This finding may suggest that the consideration of pro-BNP level along with 6MWT can produce more reliable results in the early stages of the disease.

This study showed that the pro-BNP level is related to increased PAP in echocardiography, decreased DLCO, and increased FVC/DLCO ratio. Additionally, this serum marker can be used in SSc patients to evaluate their PAH status.

Conflict of Interest

The authors declare no conflict of interest.

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