Original Article

Tenascin-C May Be a Predictor of Acute Pulmonary Thromboembolism

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***Aim*: Numerous studies have shown an increase in NT-pro BNP, troponin I and D-dimer levels with right ventricular dysfunction on echocardiography in patients with acute pulmonary thromboembolism (PTE). We found no data about the relation between tenascin-C and acute PTE in the literature. The aim of this study was to evaluate tenascin-C levels in acute PTE and correlate them with NT-pro BNP, troponin I and D-dimer.**

***Method*: Thirty-four patients who have massive or submassive PTE on spiral thorax CT (PTE group) and twenty healthy volunteers (non-PTE group) were evaluated. In all patients, right ventricular functions were obtained on transthoracic echocardiography and plasma tenascin-C, NT-pro BNP, troponin I, and D-dimer levels were measured.**

***Results*: The left ventricular systolic diameter, left ventricular diastolic diameter and left ventricular ejection fraction were similar in the two groups. The right heart chamber sizes and main pulmonary artery diameter were significantly larger in the PTE group and systolic pulmonary artery pressures were also significantly higher in this group. Tenascin-C, NT-pro BNP, and D-dimer levels were also significantly higher in the PTE group than in the non-PTE group ($p<0.001$). The troponin I levels did not differ between the two groups ($p=0.4$). Tenascin-C was found to be highly correlated with sPAP and NT-pro BNP and correlated with D-dimer; however, troponin I was not correlated with tenascin-C.**

***Conclusion*: This study demonstrates that tenascin-C may be an indicator of acute PTE.**

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Key words; Tenascin- C, NT- pro BNP, acute pulmonary thromboembolism

Introduction

Several cardiac biomarkers especially brain natriuretic peptide (BNP) have been used as indicators of right ventricular dysfunction in patients with acute pulmonary thromboembolism (PTE). Various studies examined the role of either BNP or NT-pro BNP in the risk stratification of patients with PTE[1-6]. The relationship between BNP increase in acute pulmonary embolism and the increase in mortality and morbidity is very well known; however, the role of tenascin-C in patients with acute PTE is not known. Tenascin-C is a large oligomeric glycoprotein in the extracellular matrix that has multiple functions, such as cell proliferation[7], migration[8], differentiation[9] and apoptosis[10]. Tenascin-C is also expressed in various pathological conditions, including human coronary atherosclerotic plaque[11], abdominal aortic aneurysm[12], myocardial infarction[13, 14], myocarditis, hibernating myocardium and malignant tumors[15-18]. It has also been demonstrated that increased expression of tenascin-C is associated with the progression of pulmonary hyperten-

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sion[19-21]. Increased elastase activity and deposition of tenascin-C, codistributed with proliferating smooth muscle cells, are features of pulmonary vascular disease[22]. Pulmonary vascular remodeling is an important pathological part of pulmonary hypertension, leading to increased pulmonary vascular resistance and reduced vascular compliance. The increase in tenascin-C stimulates pulmonary vasculary remodeling[23].

Cowan *et al*. showed in rats that pulmonary artery pressure and muscularization were reduced by myocyte apoptosis and loss of extracellular matrix, specifically elastin and tenascin-C[24].

The purpose of this study was to evaluate the importance of tenascin-C in acute PTE and the relation between the levels of tenascin-C and other biomarkers in acute PTE.

Methods

The study was approved by the ethics review board of Erciyes University. All patients were informed about the study, and their written consent was obtained.

Study population

In this study, we screened 34 consecutive PTE patients diagnosed by spiral computed chest tomography and echocardiography and 20 healthy volunteers (non-PTE group). Exclusion criteria consisted acute myocardial infarction, history of previous pulmonary thromboembolism, coronary artery disease, heart failure and cardiomyopathy.

Biochemical analysis

Blood samples were obtained within 24 hours of presentation. Blood samples for NT-pro BNP (ELISA Kit for Human N-Terminal Pro Brain Natriuretic Peptide-Uscn Life Science Inc.) and tenascin-C (ELISA Kit for Human Tenascin-Uscn Life Science Inc.) were obtained and centrifuged then stored at −70℃. Tenascin-C and NT-pro BNP levels were analyzed after blood samples were obtained from all study patients. D-dimer (Sysmex CA-7000 System) and troponin I (Access® 2 Immunoassay System; Beckman Coulter, Inc.) levels were also measured in all patients.

Echocardiography

Echocardiography was carried out by a cardiology specialist in the echocardiography laboratory in our cardiology department using Vivid 7 apposatus (GE Medical Systems, Milwaukee, WI, USA), with a 2.5-MHz transducer and harmonic imaging. All echocardiography results were obtained during the first day of hospitalization. Tricuspid regurgitation jet flow was assessed from the apical view. Systolic pulmonary artery pressure (PAP) was measured with a continuous-wave Doppler. The maximum peak TR velocity was used to determine right ventricular systolic pressure with the simplified Bernoulli equation [PAP = 4V2 + right atrial pressure (RAP)]. RAP was estimated using the caval respiratory index as described by Kircher *et al.*[25]. The main pulmonary artery diameter was measured from the parasternal short axis. Using the apical four- chamber view, the right atrial diameter and area were measured. The right ventricular end diastolic diameters were also measured on the apical four-chamber view. RV wall thicknesses were measured on the parasternal long axis.

Statistical analysis

Continuous variables are given as the mean ± SD; categorical variables were defined as a percentage. A value of $p < 0.05$ was considered significant. Comparisons between groups were carried out using an independent-samples *t*-test. Correlation analyses were performed using the Pearson coefficient of correlation. SPSS 15.0 software was used for basic statistical analysis (Version 15; SPSS Inc., Chicago, IL, USA).

Results

The mean age was 62 ± 14 years in the PTE group and 56 ± 7 years in the non-PTE Group ($p = 0.07$). The rates of gender, smoking, hypertension and malignancy were similar in the two groups. There was no difference in systolic blood pressure between the two groups. The transcutaneous O_2 saturation was significantly lower in the PTE group (91.6 ± 2.0 in PTE group and 97.9 ± 1.1 in the non-PTE group; $p < 0.001$). The history of deep vein thrombosis (DVT), surgery in one month and diabetes mellitus (DM) were seen to be significantly more frequent in the PTE group than in the non-PTE group. The demographic characteristics of patients in the two groups are shown in **Table 1**. Three patients had massive embolisms and 31 patients had submassive pulmonary embolisms.

In the echocardiographic evaluation, left ventricular systolic diameter, left ventricular diastolic diameter and left ventricular ejection fraction were similar between the two groups. Left atrial diameter, left atrial area, right atrial diameter, right atrial area, right ventricular diameter, RV acceleration time, tricuspid regurgitation peak flow velosity, MPAD and systolic pulmonary artery pressure (sPAP) were significantly higher in the PTE group than in the non-PTE group (**Table 2**). The right ventricular wall thickness was

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Table 1. Demographic characteristics of patients

	PTE Group ($n=34$)	Non-PTE Group ($n=20$)	p value
Age (mean ± SD)	62 ± 14	56 ± 7	0.07
Female (%)	52	55	0.8
Transcutaneous O_2 saturation (%)	91.6 ± 2.0	97.9 ± 1.1	< 0.001
Systolic Blood Pressure (mmHg)	122 ± 22	125 ± 18	0.6
History of (%)			
DM	20%	0%	0.03
HT	35%	30%	0.6
Smoking	35%	30%	0.6
DVT	26%	0%	0.01
Surgery	17%	0%	0.04
Malignancy	2%	0%	0.4

Data expressed as the mean ± SD, or percentage. $p < 0.05$ was accepted as statistically significant.
(DM = diabetes mellitus, HT = hypertension, DVT = deep vein thrombosis)

Table 2. Echocardiographic evaluation of patients in each group

	PTE Group ($n=34$)	Non-PTE Group ($n=20$)	p value
LVSD (cm)	2.8 ± 0.4	2.8 ± 0.4	0.7
LVDD (cm)	4.5 ± 0.4	4.5 ± 0.4	0.7
LVEF (%)	65 ± 7	66 ± 7	0.7
LAD (cm)	3.5 ± 0.4	3 ± 0.2	< 0.001
LAA (cm^2)	14 ± 4	10 ± 1	< 0.001
RAD (cm)	4.2 ± 0.4	3.2 ± 0.3	< 0.001
RAA (cm^2)	19 ± 5	11 ± 1	< 0.001
RVDD (cm)	4.2 ± 0.4	3.2 ± 0.3	< 0.001
RV/LV	0.94 ± 0.12	0.71 ± 0.07	< 0.001
RVWT (mm)	4.1 ± 0.7	3.8 ± 0.2	0.05
RVACT (msec)	19 ± 5	144 ± 8	< 0.001
TRPFV	3.1 ± 0.4	1.7 ± 0.3	< 0.001
VCID (cm)	2.9 ± 0.4	1.9 ± 0.08	< 0.001
MPAD (cm)	2.9 ± 0.5	1.9 ± 0.1	< 0.001
sPAP (mmHg)	49 ± 13	19 ± 4	< 0.001

Data are expressed as the mean ± SD, or percentage. $p < 0.05$ was accepted as statistically significant.
(LVSD = left ventricular systolic diameter, LVDD = left ventricular diastolic diameter, LVEF = left ventricular ejection fraction, LAD = left atrial diameter, LAA = left atrial area, RAD = right atrial diameter, RAA = right atrial area, RVDD = right ventricular diastolic diameter, RVDD/LVDD = ratio of right ventricular diastolic diameter to left ventricular diastolic diameter, RVWT = right ventricular wall thickness, RVACT = RV acceleration time, TRPFV = tricuspid regurgitation peak flow velosity, VCID = vena cava inferior diameter, MPAD = main pulmonary artery diameter, sPAP = systolic pulmonary artery pressure)

higher in the PTE group but it was not significant (**Table 2**).

Fig. 1 shows the comparison of tenascin-C and NT-pro BNP levels in the two groups. The tenascin-C levels and NT-pro BNP levels were significantly higher in the PTE group than in the non-PTE group (tenascin-C; 12.0 ± 3.8 ng/dL in PTE group and 1.6 ± 0.3 ng/dL in the Non-PTE group, $p < 0.001$. NT-pro BNP; 9273 ± 6136 pg/dL in PTE group and 109 ± 33 pg/dL in the non-PTE group, $p < 0.001$).

Fig. 2 shows the comparison of D-dimer and troponin I levels in the two groups. The D-dimer levels were significantly higher in the PTE group than in the non-PTE group (6558 ± 6825 mcg/L in the PTE group, 85 ± 35 mcg/L in the non-PTE group, $p < 0.001$). The troponin I levels were not significantly

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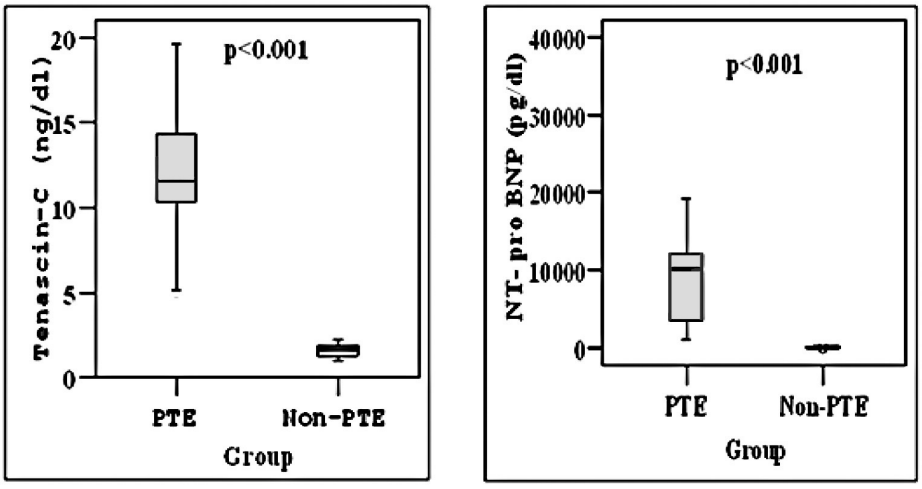

Fig. 1. Comparison of tenascin-C and NT-pro BNP levels in two groups.

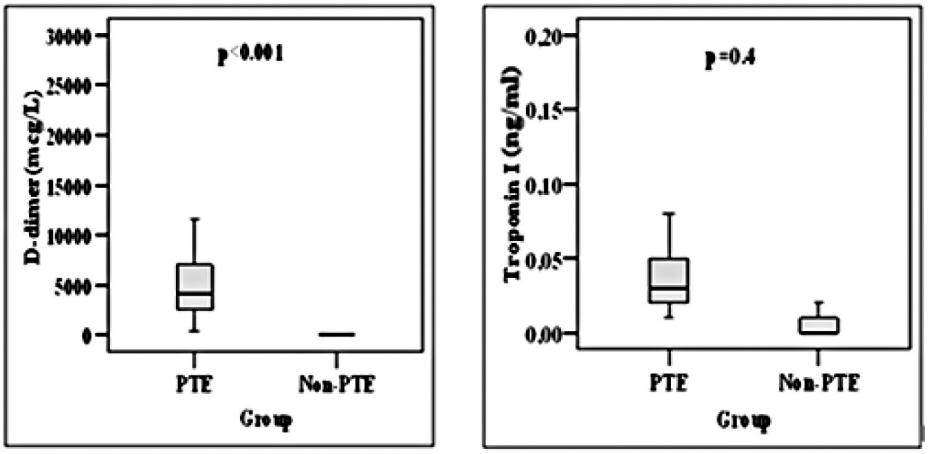

Fig. 2. Comparison of D-dimer and troponin I levels in two groups.

different between the two groups (the mean was 0.03 ± 0.02 ng/mL in the PTE group and 0.01 ± 0.04 ng/mL in the non-PTE group, $p = 0.4$.)

A high correlation was observed between tenascin-C levels and sPAB (**Fig. 3**). Tenascin-C and NT-pro BNP levels were also highly correlated in all patients (**Fig. 4**). There was a correlation between tenascin-C and D-dimer levels in all patients ($r = 0.589$, $p < 0.001$). There was no correlation between tenascin-C and troponin I levels in all patients ($r = 0.210$, $p = 0.1$).

Discussion

In the present study, tenascin-C levels significantly increased with NT-pro BNP and D-dimer in patients with acute PTE. This is the first study demonstrating high tenascin-C levels in acute PTE.

It was seen that the right chambers of the heart, including the pulmonary artery, were dilated in the PTE group. Right ventricular enlargement is a frequent result of PTE and determines its severity; therefore, it is necessary to demonstrate RV functions with various methods such as echocardiography, BNP and various scoring systems. NT-pro BNP or troponin testing with echocardiography are used to determine the risk stratification of acute pulmonary embolism. Increased D-dimer plasma levels were consequently identified as a diagnostic marker for PTE and hence, PTE diagnosis is excluded from differential diagnosis with lower plasma levels of D-dimer. Grau *et al.* showed that patients with D-dimer ≥ 5000 ng/mL showed a higher risk of death from fatal pulmonary embolism[26]. In our study, D-dimer levels were naturally significantly higher in the PTE group and were correlated with tenascin-C levels.

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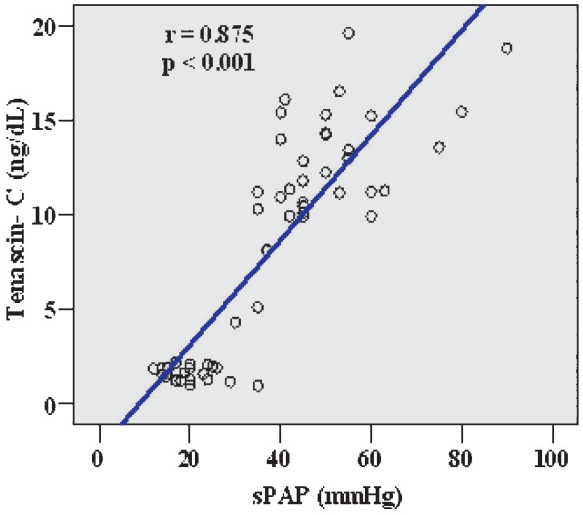

Fig. 3. Correlation between tenascin-C and sPAP in study patients

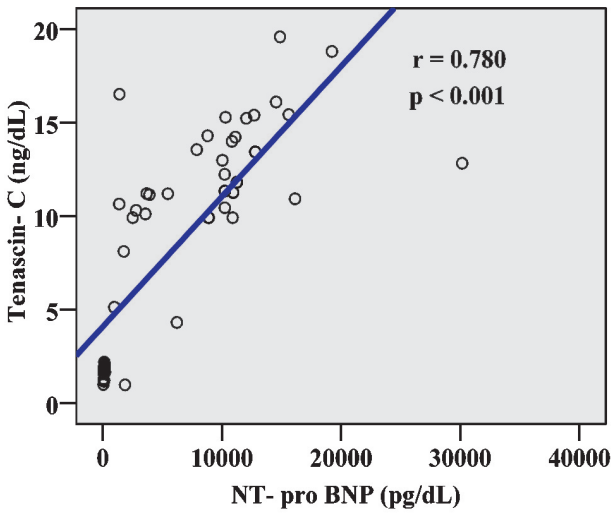

Fig. 4. Correlation between tenascin-C and NT-pro BNP in study patients

Several studies showed that serum troponin I levels have a role in risk stratification in patients with acute pulmonary embolism[27-29] and they are used as a marker of right ventricular dysfunction and severity of pulmonary embolism[30]. In the present study, we did not find a significant difference in troponin I levels between the two groups although serum troponin-I has been reported as a good marker of severity of PTE and RV dysfunction. The troponin I levels were higher in the PTE group but they did not differ statistically, so in our opinion, tenascin-C levels were more valuable for determining the severity of PTE than troponin I levels. We also found no correlation between troponin I levels and tenascin-C levels.

Low levels of tenascin-C are secreted in the normal adult heart. With cardiac injury and inflammation, its levels increase and tenascin-C is also used as a marker to show the severity of viral myocarditis[31]. Tenascin-C is also detected in the marginal zone between the infarcted area and the intact area after myocardial infarction[14, 32] and it is thought to be a useful marker to predict left ventricular remodeling and prognosis after acute myocardial infarction[33]. Although the increase of tenascin-C in left ventricular dysfunction was known, its relation with right ventricular dysfunction is undetermined; therefore, there are no data showing the relation between tenascin-C and PTE in the literature.

Schumann *et al*. compared plasma tenascin-C levels in patients with pulmonary hypertension and healthy volunteers to evaluate the circulating biomarkers of tissue remodeling in pulmonary hypertension[34]. Tenascin-C levels were significantly increased in patients with pulmonary hypertension compared with healthy age-matched volunteers. In the present study, similar results were seen. Significantly increased tenascin-C levels were seen in patients with pulmonary hypertension (PTE group).

Pulmonary hypertension is characterized by intense remodeling, resulting in a progressive increase in pulmonary vascular resistance and PAP. Other pathological mechanisms of pulmonary hypertension, including intimal, medial and adventitial proliferation, are regulated by mitogenic stimuli after endothelial injury. Tenascin-C was shown as a mitogenic factor of the extracellular matrix that stimulated proliferation, which is the major underlying pathomechanism of pulmonary hypertension[34-36]. This may be the reason for increased tenascin-C levels in PTE which can cause endothelial damage in the pulmonary artery. This study demonstrated that tenascin-C may be a useful marker for a suspected diagnosis of PTE and pulmonary hypertension because of PTE.

Limitations

The main limitation of the present study was the small number of patients with acute PTE. In addition there was no follow-up to show tenascin-C and its relation with the prognosis of PTE; therefore, large and long-term follow-up studies are needed.

Conclusion

This study demonstrated high tenascin-C levels in patients with acute PTE and that tenascin-C may

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be an indicator of acute PTE.

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