Relationship between cardiac troponin-T and right ventricular Tei index in patients with hemodynamically stable pulmonary embolism: an observational study

Hemodinamik olarak stabil pulmoner embolili hastalarda sağ ventrikül Tei indeksi ve troponin-T arasındaki ilişki

Savaş Özsu, Abdülkadir Kırış, Yılmaz Bülbül, Funda Öztuna, Kayıhan Karaman[1], Merih Kutlu*, Tevfik Özlü*

From Departments of Chest Diseases and *Cardiology, Faculty of Medicine, Karadeniz Teknik University, Trabzon-*Turkey*
[1]Clinic of Cardiology, Kahramanmaraş State Hospital, Trabzon-*Turkey*

ABSTRACT

Objective: The role of increased troponin level in risk stratification of acute pulmonary embolism (PE) is well documented. However, relation between right ventricular (RV) myocardial performance (Tei) index and cardiac troponin-T (cTn-T) has not been well investigated. The purpose of this observational prospective study was to assess the relationship between the RV Tei index and cTn-T in patients with acute normotensive PE.

Methods: Thirty-eight patients with acute PE diagnosed by computed spiral tomography pulmonary angiography were enrolled to this prospective observational study. All study population underwent a comprehensive echocardiographic study including tissue Doppler imaging within first 12 hours of admission. cTn-T levels were measured on admission. Follow-up echocardiography was performed routinely at the 7th day of hospitalization. Echocardiographic evaluation was repeated at 90 days in patients with insufficient improvement of RV Tei index. The difference between the baseline and follow-up data was analyzed using the paired sample t-test or Wilcoxon test according to normality of distribution.

Results: The mean of the RV Tei index was 0.46±0.14 and the mean systolic pulmonary artery pressure (sPAP) was 40±20 mmHg. Increased cTn-T level was detected in 37% of the patients (normal value 0.01< ng/mL). Significant correlations were observed between RV Tei index and sPAP with cTn-T levels (r=0.467 and r=0.468, p<0.001, respectively). In logistic regression analysis, RV Tei index was associated with positive cTn-T values (OR-136, 95% CI: 1.3-14657, p=0.039). After the anticoagulant treatment, RV Tei index and sPAP were significantly improved.

Conclusion: RV Tei index is frequently impaired in patients with acute PE and a significant recovery is seen after the treatment. Therefore, RV Tei index may be used both the diagnosis of RV dysfunction and the assessment of treatment effectiveness. RV Tei index is may predict myocardial injury in PE. *(Anadolu Kardiyol Derg 2012; 12: 659-65)*

Key words: Pulmonary embolism, right ventricular Tei index, Doppler tissue imaging, troponin, regression analysis

ÖZET

Amaç: Akut pulmoner embolide (PE) risk tayinde kardiyak troponin-T (cTrop-T)'nin rolü iyi dokümante edilmiştir. Bununla birlikte, sağ ventrikül (SV) miyokardiyal performans (Tei) indeksi ve cTn-T arasındaki ilişki çok iyi araştırılmamıştır. Bu çalışmanın amacı, normotansif akut PE hastalarında SV Tei indeksi ile cTn-T arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Prospektif gözlemsel bu çalışmaya, bilgisayarlı spiral tomografik pulmoner anjiyografi ile tanısı konulan 38 PE hastası dahil edildi. Tüm çalışma popülâsyonuna, hastaneye kabulün ilk 12 saati içinde, doku Doppler görüntülemeyi içeren kapsamlı bir ekokardiyografik inceleme yapıldı. cTn-T seviyesi hastaneye kabulde ölçüldü. Hastanedeki tedavinin yedinci gününde rutin olarak takip ekokardiyografisi yapıldı. SV Tei indeksinde düzelme olmayan hastaların ekokardiyografisi doksanıncı günde tekrarlandı. Başlangıç ve takip değerleri dağılıma uygun olarak bağımsız örneklem t-testi veya Wilcoxon test ile değerlendirildi.

Bulgular: Ortalama SV Tei indeksi 0.46±0.14 ve ortalama sistolik pulmoner arter basıncı (sPAP) 40±20 mmHg idi. Hastaların %37'sinde artmış cTn-T düzeyi saptandı (normal değer 0.01< ng/mL). SV Tei indeksi, sPAP ve cTn-T düzeyi arasında anlamlı korelasyon gözlendi (r=0.467 ve r=0.468, p<0.001,

Address for Correspondence/Yazışma Adresi: Dr. Abdülkadir Kırış, Karadeniz Teknik Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Trabzon-*Turkey*
Phone: +90 462 377 55 57 Fax: +90 462 377 53 05 E-mail: akiris79@yahoo.com

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sırasıyla). Tek değişkenli analizde pozitif troponin için RV Tei index OR: 136 (%95 GA: 1.3-14657, p=0.039) idi. Antikoagülan tedavi sonrası SV Tei indeksi ve sPAP anlamlı olarak düzeldi.
Sonuç: SV Tei indeksi, akut PE hastalarında sıklıkla artmakta ve tedavi sonrası anlamlı düzelme görülmektedir. Bu nedenle, hem SV disfonksiyonu tanısında hem de tedavi etkinliğinin izlenmesinde SV Tei indeksi kullanılabilir ve sonuçta SV Tei indeksli, pulmoner embolide miyokart hasarını ön görebilir. *(Anadolu Kardiyol Derg 2012; 12: 659-65)*
Anahtar kelimeler: Pulmoner emboli, sağ ventrikül Tei indeksi, doku Doppler görüntüleme, troponin, regresyon analizi

Introduction

Pulmonary embolism (PE) is a potentially lethal disease with a variable clinical picture. The short-term mortality of the PE depends on hemodynamic status. In-hospital mortality ranges from 21 to 58% in patients who have PE and hypotensive (1-3). In addition, the presence of right ventricular dysfunction (RVD) is related to poor prognosis in normotensive patients with PE. Although in-hospital mortality rate is less than 3% in pulmonary embolism without RVD, this rate exceeds 15% in the presence of RVD (3-6). Therefore, determination of RVD in these patients is a very critical.

The presence of right ventricular (RV) dilatation or hypokinesis and increased RV/LV diameter ratio are the main echocardiographic findings of RV pressure overload caused by PE (7). However, the evaluation of RV function by echocardiography has some limitation because of its geometry and complex contraction mechanism. Recently, tissue Doppler imaging (TDI) echocardiography has been used to evaluate of the right ventricular function as a more quantitative method (8, 9). The myocardial performance (Tei) index is a reliable parameter suggesting global left ventricular function. Tei index has particularly been used for the evaluation of left ventricular function (10). It has also been used to evaluate the right ventricular function in various pulmonary disease such as pulmonary hypertension (PHT), chronic pulmonary disease (CPD) and cardiac amyloidosis (9, 11, 12). In addition, it was reported that effective treatment of PE corrected RV function evaluated by echocardiography (9, 13).

Cardiac troponin is a highly sensitive and specific marker of myocardial damage. The role of increased cardiac troponin-T (cTn-T) level in risk stratification of acute PE is well documented (14, 15). However, the relationship between cTn-T and RV Tei index in PE has not been well evaluated.

Therefore, in this study, we aimed to evaluate the relationship between the RV Tei index and cTn-T.

Methods

Study design and settings

This observational study prospectively enrolled patients with acute PE, who were diagnosed 2008 and 2009 years. The study was conducted at a university hospital, a tertiary care hospital that serves as a primary referral centre for patients with suspected PE. Because all PE patients in our hospital are treated and followed up by the pulmonology department, the study was approved by the local ethics committee and written informed consent was obtained from all patients.

Participants

Forty-six consecutive acute PE patients were prospectively enrolled in the study. Patients with massive acute PE, heart valve disease, acute coronary syndrome, cardiac arrhythmia, heart failure (left ventricular ejection fraction <40%) and poor echocardiographic imaging were excluded from the study. Massive PE was defined by the presence a systolic blood pressure <90 mm Hg or a pressure drop of ≥40 mm Hg for 15 min if not caused by new onset arrhythmia (6). All events were recorded up to 90 days after the diagnosis of acute PE in all studied patients.

Variables

The baseline characteristics of all patients including age, sex, vital findings, comorbidity, clinical symptoms, risk factors for PE and the presence of other diseases were recorded carefully. Biochemical blood tests (arterial blood gases, D-Dimer) and electrocardiography (ECG) were obtained from the entire study population on admission.

Diagnosis and treatment of PE

Spiral chest computed tomography pulmonary angiography (CTPA) was used for the diagnosis of the pulmonary embolism. In only one patient, however, lung perfusion scans was used for diagnosis due to renal disease. CTPA was performed using a 4- and 16-channel multislice scanner (Somatom Volume Zoom and Sensation 16, Siemens, Erlangen, Germany). Acute PE was diagnosed by the presence of at least one filling defect in the pulmonary arterial tree including the subsegmental level.

Standard anticoagulant treatment with unfractionated heparin (UFH) or low-molecular- weight heparin (LMWH) was initiated for patients who have acute PE. A bolus of 80 U/kg unfractionated heparin (UFH) was administered as initial treatment and followed by continuous infusion of 18U/kg per hour. The target activated partial thromboplastin time was 1.5-2.5 of the baseline level. LMWH was used as 100 IU/kg twice daily. Vitamin K antagonist (warfarin) was given for a period of at least 3 months with a goal to reach international normalized ratio of 2.0 -3.0 during follow-up.

Echocardiographic study

All study population underwent transthoracic echocardiographic evaluation including 2-dimensional (2D), M-mode, pulse-wave Doppler imaging and TDI according to the recommendations of the American Society of Echocardiography using a commercially available system (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). First echocardiographic assessment was

performed within the first 12 hours. Subjects were examined in the left lateral recumbent position using standard parasternal (short-and long-axis) and apical views (two chamber, four chamber, and long axis). Left ventricle (LV) dimensions were measured by M mode echocardiography in parasternal long axis view. RV diameters were detected by two-dimensional echocardiography in apical four -chamber view. Global LV function was assessed by LV ejection fraction using the modified biplane Simpson's rule (16). TDI was performed from the lateral mitral and tricuspid annulus. The peak systolic pulmonary arterial pressure (sPAP) was calculated by adding the right atrial pressure estimate to the systolic transtricuspid pressure gradient determined by maximal velocity of tricuspid regurgitation (TR Vmax) as previously described (17). Tei index was calculated from recordings of five consecutive cardiac cycles with simultaneous electrocardiography as previously described (9). Firstly, the time intervals; (a) from the end to the onset of tricuspid annular velocity pattern and the duration of the myocardial systolic wave (Sm), (b) from the onset to the end of the Sm was measured from the TDI recordings. Then, RV Tei index was computed by using the following equation: [isovolumetric contraction time (ICT)+isovolumic relaxation time(IRT)]/ejection time= a-b/b (Fig. 1). Follow up echocardiographic evaluations were routinely performed on the seventh day of hospitalization. At the end of the follow up period of three months, echocardiographic evaluation was repeated in patients who's the RV.

In our study, RV Tei index <0.55 was accepted as a proof of improvement of RV function duration of follow-up (18). RV/LV ratio was calculated by dividing RV diameter to LV diameter. A value ≥0.6 was considered as an indicator of significant RVD (19). In addition, RV Tei index was evaluated after 90 days of the anticoagulant treatment. All echocardiographic assessment was performed by the same echocardiographer who was blinded to the results of the patient's data

Biochemical analysis

Venous blood samples were collected on admission. Troponin T was determined with the use of a quantitative electrochemiluminescence method assay (Elecsys 2010; Roche, Mannheim, Germany, normal value <0.010 ng/mL). Arterial blood gases were analyzed on admission. Elevation of troponin T was defined ≥0.010 ng/mL.

Statistical analysis

Data were analyzed using SPSS statistical software (version 13.01, serial number 9069728, SPSS Inc, Chicago, Ill).

The normal distribution for continuous variables was assessed by Kolmogorov-Smirnov test. Continuous variables were described as mean±SD and were analyzed using by Student-t test or Mann-Whitney U test when appropriate. The difference between the baseline and follow-up data was analyzed using the paired sample t-test or Wilcoxon test according to normal distribution. Pearson's correlation coefficients were used for analysis. Multivariate logistic regression analysis was used a stepwise descending method from prognostic factors with significance p<0.1 in the univariate analysis. Results are given as OR (95% CI), and p value <0.05 was considered statistically significant. Chi-square test was used for comparison of categorical variables.

Results

Patient characteristics

Overall 46 consecutive patients with acute PE were included in this study. Eight patients were excluded from the study; two with severe arrhythmia, two with massive PE, one with heart valve disease and three who did not have follow-up echocardiography. After the onset of symptoms, 31 (82%) patients presented to the emergency department and 7 (18%) patients were diagnosed during hospitalization. Standard heparin treatment was used in 31 (82%) patients, whereas LMWH was used in other 7 (18%) patients. Complications of bleeding were observed in 3 patients and vena cava filter was used in two of these patients with complications. The mean hospital stay was 10 (range 4-22) days. Adverse clinical event was observed in 12 patients: 5 deaths, 3 respiratory failures, 2 catecholamine infusion and 2 persistent pulmonary hypertension.

The baseline patient characteristics are summarized in Table 1. The mean age was 61.2±17 years; and 21 patients (55%) were females. Distribution of comorbidities was as following: chronic obstructive lung disease (COPD, 3 patients), cerebrovascular disease (2 patients), diabetes mellitus (2 patients), and Behçet disease (one patient).

Troponin, echocardiographic findings and outcomes

Fourteen patients (37%) had elevated serum cTn-T (Table 2). The median cTn-T concentration was 0.018 ng/mL in patients with an adverse clinical outcome as opposed to 0.01 ng/mL in those with an uncomplicated course (p=0.017). The mean RV Tei index and the mean sPAP were significantly higher in patients with positive cTn-T values as compared with patients with normal cTn-T values (p=0.011 and p=0.003, respectively).

RV dysfunction was determined in 22 (58%) of 38 patients. The mean Tei index of RV was 0.53 in patients with an adverse clinical events as opposed to 0.43 in those with an uncomplicated course (p=0.026).

Positive correlations were found between cTn-T levels and both RV Tei index and sPAP (r=0467, p<0.003 and r=0.468, p<0.003, respectively) (Fig. 2). However, there was no significant correlation between cTn-T levels, end-diastolic diameter of RV and RV/left ventricular ratio.

Logistic regression analysis

In univariate logistic regression analysis, RV Tei index and sPAP were associated with positive troponin values- OR-136, 95% CI: 1.3-14657, p=0.039 and OR: 1.0, 95% CI: 1.0-1.1, p=0.011, respectively (Table 3), however this relationship was not significant in multivariate analysis.

Table 1. Characteristics of the patients with PE (n=38)

Age, years	62.2±17
Sex, female/male	21/17
Symptoms, n (%)	
Dyspnea	29 (79)
Chest/pleuritic pain	22 (58)
Hemoptysis	9 (24)
Syncope	5 (13)
Time to diagnosis, days	7.9±10
Presentation to diagnosis, days	3.4±6
Risk factors for PE, n (%)	
Cancer	9 (24)
Immobility	8 (21)
Surgery	6 (15)
Other	8 (21)
Unknown	7 (18)
Findings	
Heart pulse ≥ 100/min	9 (24)
DVT	18 (47)
pO_2,mm-Hg	79±25
pCO_2, mm-Hg	32±7
Troponin T mg/dL	0.03±0.05
Normal, n (%)	24(63)
Abnormal, n (%)	14(37)
D-Dimer	9±10
Abnormal, n (%)	38(100)
Treatment, n (%)	
Intravenous heparin	31 (82)
LMWH	7 (18)
Warfarin	19 (50)
VCF	2 (10)
Outcome	
Bleeding complications	3 (8)
Length of stay, days	10±4
All deaths	5 (13)
Echocardiographic parameters	
RV Tei	0.46±0.14
LV Tei	0.50±0.13
PA systolic pressure , mm-Hg	40±20
RV end-diastolic diameter, mm	30±8
LV end-diastolic diameter, mm	45±4
RV/LV ratio	0.63 (0.44-1.47)
Ejection fractions (%)	62 (40-70)
RV/LV ratio ≥0.6	22 (58)

*Values are given as the mean±SD, median (min-max) values and number (percentage)
DVT - deep venous thrombosis, LMWH - low molecular weight heparin, LV - left ventricle, PA - pulmonary artery, PE - pulmonary embolism, pCO_2 - partial carbon dioxide pressure, pO2- partial oxygen pressure, RV-right ventricle, VCF - vena cava filter

Table 2. Comparison of echocardiographic parameters according to cTn-T positivity in 38 patients

Variables	Troponin T (+) (n=14)	Troponin T (-) (n=24)	*p
RV Tei	0.53±0.15	0.42±0.10	0.011
LV Tei	0.53±0.10	0.49±0.14	NS
RV, EDD, mm	30±7	29±8	NS
LV, EDD, mm	43±4	45±4	NS
RV/LV ratio	0.62 (0.48-1.08)	0.63 (0.44-1.47)	NS
sPAP, mm-Hg	51±21	32±14	0.003
Ejection fraction	65 (40-65)	60 (50-70)	NS

Values are given as the mean ± SD and median(min-max) values
*Student t-test or Mann-Whitney U test
EDD - end - diastolic diameter, LV - left ventricle, NS - no significant, sPAP - systolic pulmonary artery pressure, RV - right ventricle

Table 3. Predictors of positive cardiac troponin T values (Univariate analysis)

Variables	OR	95% CI	*p
RV Tei index	136	1.3-14657	0.039
RV diameter	1.0	0.9-1.0	NS
sPAP	1.0	1.0-1.1	0.011
RV/LV	1.7	0.1-38	NS
LV diameter	0.9	0.8-1.1	NS
LV Tei index	3.5	0.1-248	NS
EF	0.9	0.9-1.0	NS

*Logistic regression analysis
EF - ejection fraction, LV - left ventricle, NS - not significant, sPAP - systolic pulmonary artery pressure, RV - right ventricle

Table 4. Comparison of baseline and follow up echocardiographic data in 30 patients

Variables	Baseline	Follow-up	*p
RV Tei	0.49±0.13	0.40±0.10	0.002
sPAP, mm-Hg	39±20	31±20	0.005
RV/LV ratio	0.64 (0.44-1.1)	0.68 (0.38-1.2)	NS
LV Tei	0.50±0.13	0.48±0.14	NS
Ejection fraction	64 (40-70)	63 (30-72)	NS

Values are given as the mean±SD and median (min-max) values
*Paired sample t-test or Wilcoxon test
RV - right ventricle, LV - left ventricle, sPAP - systolic pulmonary artery pressure, NS - not significant

Long-term outcomes

At the end of third month, echocardiographic evaluation was performed in 16 (42%) patients who had no improvement during the one-week control period. Five patients died during the study period (2 in-hospital-one patient PE-related death, one patient lymphoma and 3 follow-up due to cancer and 3 follow-up). The echocardiographic follow-up was not available for three patients. At the end of 90 days, RV Tei index and systolic PA pressure significantly improved in 30 patients (respectively, $p<0.002$ and $p<0.005$) (Fig. 3). LV Tei index did not change at follow-up. RV Tei

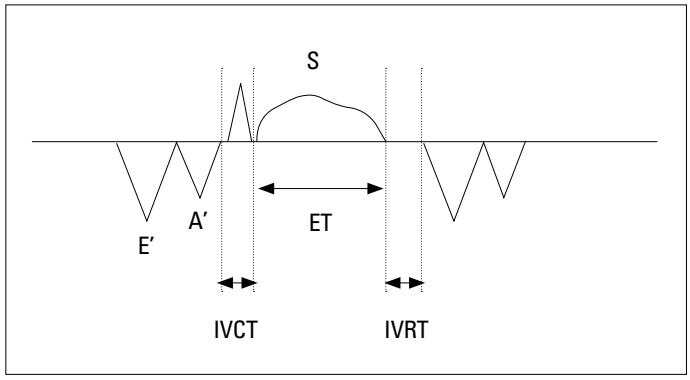

Figure 1. RV Tei index was calculated as: [isovolumetric contraction time (ICT)+isovulemic relaxation time(IRT)]/RV ejection time (ET)=a-b/b) (9)
RV - right ventricular

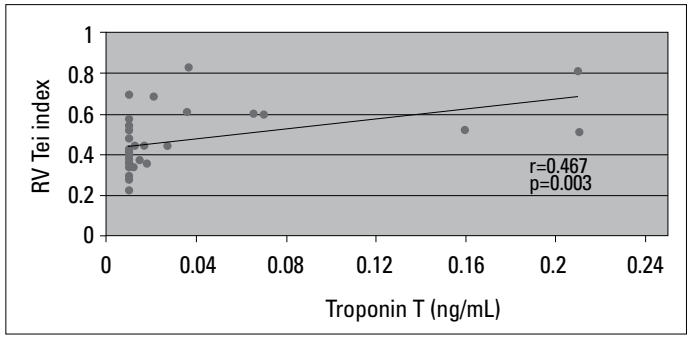

Figure 2. The correlation between RV Tei index and troponin-T levels
RV - right ventricular

index over 0.55 were detected in one patient (severe COPD) at the end of three months. Follow-up echocardiography parameters are summarized in Table 4. Baseline and follow-up RV Tei index values are shown Figure 3. At follow-up period, re-embolism and/or bleeding complication were not seen in any of patients.

Discussion

In this study, we found a relationship between cTn-T levels and RV Tei index and sPAP on admission. Moreover, we observed that impaired RV function assessed by Tei index in patients with acute normotensive PE improved with successful anticoagulant treatment.

The Tei index, combining systolic and diastolic function, is a non-geometric measure of ventricular function (12). In previous studies, RV Tei index was assessed in patients with PHT, cardiac amyloidosis and CPD (9, 11, 12). However, there is a limited data in the literature about evaluation of the RV function by Tei index in patients with acute PE. Impaired RV Tei index has been improved with effective treatment in two previous studies (9, 13). RV Tei index is an important factor to predict outcomes in patients with acute PE. On the other hand, in our study the mean RV Tei index was lower compared to previous two studies. Ten of 20 patients in Park et al. (13) study and only 4 of 50 patients in the study of Hsiao et al. (9) had received thrombolysis therapy. In

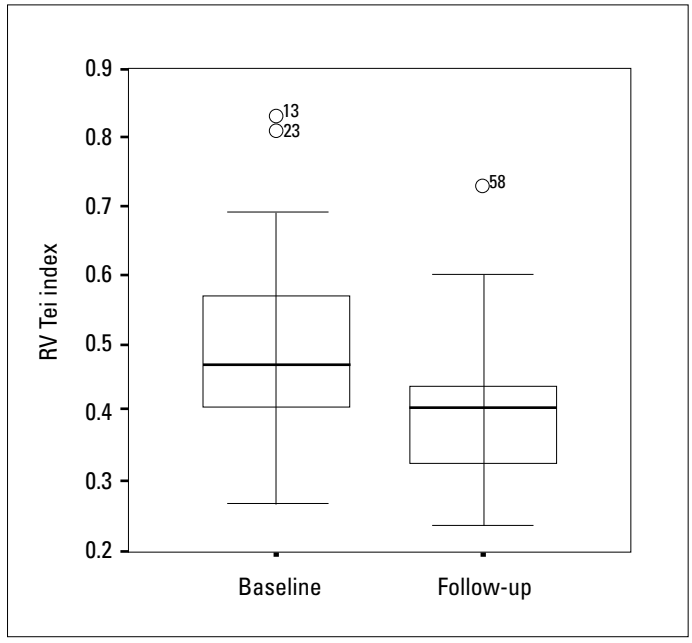

Figure 3. Baseline and after anticoagulant treatment RV Tei index values in patients with pulmonary embolism
RV - right ventricular

addition, patients with massive PE were included in these two studies and RVD improved effectively with thrombolytic therapy. In our study, right ventricular function was normal in 16 (42%) patients and our study did not include patients with massive PE.

It is reported that right ventricular overload and hypoxia in acute pulmonary embolism may lead to right ventricular myocardial injury reflected by elevated cardiac troponin levels (14). The rate of elevated troponin in haemodynamically stable patients with acute PE varies between 21-50% (20-22). In our study, we found 37% increase in the level of cTn-T. However, elevated cTn-T may be associated with sepsis, and chronic renal disease which are common concomitant comorbid conditions in patients with acute PE (23-25). Therefore, it would be misleading to make a connection between elevated cTn-T and acute PE. However, we have found a significant correlation between increased cTn-T levels and both RV Tei index and sPAP, respectively. Interestingly, in our study there was no correlation between cTn-T levels and other echocardiographic parameters, such as RV/LV ratio and end-diastolic diameter of RV. Although Kostrubiec et al. (21) reported correlation between N-terminal pro-BNP (NT-proBNP) and RVD, there was no correlation between cTn-T and RVD in that study. Bova et al. (26) did not find any differences in RVD between patients with positive and negative cTn-T levels. Moreover, in patients with acute PE and normal cTn-T level, the prevalence of RVD was noted as 15 to 28% (27, 28). In the literature, different threshold levels were considered in the evaluation of RVD with echocardiography. Similarly different cut-off values were common in the measurement of biomarkers and various kits were used. Therefore, Tei index may be a more objective parameter in the assessment of RV function

in acute PE. Also, other investigators found the RV Tei index was easy to measure and to be reproducible (9,13).

In acute PE, cTn-T levels rise in the first 6-12 hours of admission and then return to normal levels within 2-3 days (29). However, delayed diagnosis of acute PE is seen frequently and this situation may affect the level of cTn-T. Therefore, rapid diagnosis and treatment of acute PE may be life saving for the patients, given that some of patients died within 1 hour of presentation (7). Therefore, in the emergency room quick evaluation of RV function with the help of the RV Tei index may improve both treatment outcome and prognosis.

Study limitations

The present study has some limitations. First, our study population had a small number of patients. Secondly, correlation between other biomarkers (eg. brain natriuretic peptide (BNP), NT-proBNP) and RV Tei index was not determined in this study. Moreover tricuspid annular plane systolic excursion (TAPSE) as a measure of global RV systolic function is related to presence and extent of PE (30, 31), and was not evaluated in this study. Because the number of patients was small, prognostic value for Tei index on mortality could not be determined. Combination of the RV Tei index and cardiac enzymes in larger studies may provide more valuable results about short-term prognosis PE. In the literature, the combination of RVD and cardiac enzymes have a predictive value for mortality in risk stratification of acute PE (15, 32). We also know that thrombolysis therapy in patients with acute submassive PE remains controversial in the literature (33).

Perhaps, serial values of the RV Tei index may be helpful for selection of thrombolysis therapy in patient with normotensive acute PE. However, this approach may be addressed by further studies.

Conclusion

This study showed that RV Tei index may be used as an easily repeated and a quick method in the quantitative evaluation of the RV function in patients with normotensive acute PE. RV Tei index is associated with myocardial damage in PE patients.

Conflict of Interest: None declared.

Authorship contributions. Concept-S.Ö., A.K.; Design- S.Ö., A.K.; Supervision -T.Ö., M.K.; Resource- K.K., M.K.; Data collection&/or Processing- Y.B., F.Ö., K.K.; Analysis &/or interpretation- T.Ö., M.K.; Literature search- S.Ö., A.K.; Writing - S.Ö., A.K.; Critical review- S.Ö., A.K., Y.B., F.Ö.

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