Research Article

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The predictive value of serum SCUBE-1 level for left ventricular thrombus in patients with post myocardial infarction heart failure

Miyokard enfarktüsü sonrası kalp yetmezliği olan hastalarda sol ventrikül trombüsü için serum SCUBE-1 seviyesinin prediktif değeri

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Abstract

Objectives: Left ventricular thrombus is regarded as one of the main myocardial infarction complications. Knowing the left ventricular thrombus symptoms prevents serious complications that may occur. This study aims to reveal any association between SCUBE-1 and left ventricular thrombus, thought to be involved in platelet aggregation and adhesion.

Methods: The study included 80 patients diagnosed with heart failure following acute myocardial infarction, applying for the cardiology outpatient clinic for third-month follow-up. The patients were included in two groups to see if the left ventricular thrombus was present. Thus, 22 patients were found to have left ventricular thrombus. The

two groups were compared based on clinical laboratory and echocardiographic parameters.

Results: It was found that the patients with left ventricular thrombus had significantly higher Serum SCUBE-1 levels ($p < 0.001$). The optimal cutoff point of SCUBE-1 levels for predicting the LVT was >35.1 ms, with the specificity of 86% and sensitivity of 68.4% (AUC=0.815; 95% CI, 0.699–0.931; $p < 0.0001$). SCUBE-1 level (OR=1.090, 95% CI: 1.034–1.150, $p < 0.001$) in the multiple logistic regression model continue to significantly predict LVT after adjusting for the confounding variables, as statistically significant in the univariate analysis of the variables which correlated with the SCUBE-1 levels.

Conclusions: SCUBE-1 level was determined to independently predict the left ventricular thrombus after a previous anterior myocardial infarction.

Keywords: acute myocardial infarction; left ventricular thrombus; LVT; SCUBE-1.

Öz

Amaç: Sol ventrikül trombüsü, miyokard enfarktüsün ana komplikasyonlarından biri olarak kabul edilir. Sol ventrikül trombüsü semptomlarının bilinmesi oluşabilecek ciddi komplikasyonları önler. Bu çalışma, trombosit agregasyonu ve adezyonunda rol oynadığı düşünülen SCUBE-1 ile sol ventrikül trombüsü arasındaki herhangi bir ilişkiyi ortaya çıkarmayı amaçlamaktadır.

Gereç ve Yöntem: Akut miyokard enfarktüsü sonrası kalp yetmezliği tanısı alan ve üçüncü ay takibi için kardiyoloji polikliniğine başvuran 80 hasta çalışmaya alındı. Hastalar, sol ventrikül trombüsü olup olmadığını görmek için iki

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gruba ayrıldı. 22 Hastada sol ventrikül trombüsü tespit edildi. İki grup klinik laboratuvar ve ekokardiyografik parametrelere göre karşılaştırıldı.

Bulgular: Sol ventrikül trombüsü olan hastalarda serum SCUBE-1 düzeylerinin anlamlı düzeyde yüksek olduğu saptandı ($p<0.001$). SCUBE-1 seviyelerinin sol ventrikül trombüsünü tahmin etmek için optimal eşik değeri, %86 özgüllük ve %68,4'lük duyarlılıkla >35.1 ms idi, (AUC=0.815; %95 GA, 0.699–0.931; $p<0.0001$). Tek değişkenli analizde istatistiksel olarak anlamlı SCUBE-1 ile ilişkili gösterilen değişkenler, çoklu lojistik regresyon modelinde karıştırıcı değişkenler için düzeltme yapıldıktan sonra, SCUBE -1 seviyesi (OR=1.090, %95 CI: 1.034–1.150, $p<0.001$), LVT'yi önemli ölçüde tahmin etmeye devam etti.

Sonuç: SCUBE-1 seviyesinin, ön duvar miyokard enfarktüsünden sonra sol ventrikül trombüs gelişiminde bağımsız prediktör olduğu saptandı.

Anahtar kelimeler: Sol ventrikül trombüsü; SCUBE-1; Akut miyokard infarktüsü.

Introduction

Left ventricular thrombus (LVT) is one of the myocardial infarction (MI) main complications [1]. LVT has been reported relatively frequently, although recent progress has been made in the reperfusion strategy of increased ST-segment elevation myocardial infarction (STEMI) [2]. Recent studies pointed out that LVT incidence ranged between 2.5–15%, but after acute anterior MI, this rate was found to be 23.5% [3–7]. LVT usually occurs when there is a left ventricular aneurysm (LVA) and LV apical akinesis, which develop after widespread anterior MI. Stasis and inflammatory processes in the aneurysm segment facilitate thrombus formation [8].

The superfamily of EGF is a set of growth factors, extracellular matrix proteins, and cytokine-like mediators. In 2002, a novel gene for an EGF-related protein was isolated in growing mice. A protein with a signal peptide at the amino-terminus is encoded by this new mammalian gene before one CUB (complementC1r/C1s) domain at the carboxyl terminus and several EGF (epidermal growth factor)-like repeats. Such a family of genes was called SCUBE-1 for proteins containing signal-peptide-CUB-EGF-like domain [9–11]. SCUBE-1 (protein 1 containing signal peptide-cub-EGF-like domain) has been identified in platelet-rich thrombus and atherosclerotic lesions. The recombinant fragments of SCUBE-1 were found to increase aggregation and adhesion of platelets [12, 13].

Platelets are activated by adhering to the sub-endothelial matrix, thus secreting SCUBE-1. Therefore, SCUBE-1, which acts as an endothelial adhesion molecule, plays a role in thrombus formation [14]. Due to myocyte necrosis after transmural MI and the inflammatory response, the sub-endocardial area becomes flat and weak. Platelets that adhere to the sub-endocardial matrix during the inflammatory process cause thrombus formation [8].

This study aimed to investigate the relationship between LVT and serum SCUBE-1 levels in patients suffering from heart failure after MI.

Materials and methods

Study population

This prospective observational study included 110 patients who had acute ST elevation MI and in the third-month follow-up in Research Hospital of Medical Faculty, University, between June 2020 and September 2020. The patients who were excluded from the study were those with ejection fraction (EF) above 45%, essential thrombocytosis, chronic kidney disease, atrial fibrillation, mechanical prosthetic valve, severe valve pathologies, also those receiving warfarin and oral anticoagulant therapy, patients suffering from the acute coronary syndrome or patients who have a cerebrovascular event during the application process, and those with thromboembolic disease, protein C/S deficiency, patients with antiphospholipid antibody syndrome and paroxysmal nocturnal hemoglobinuria, and patients with the myeloproliferative disease. All patients included in the study were already receiving dual antiplatelet therapy at the initiation of the study. 95 of the patients were on ticagrelor + acetylsalicylic acid (ASA), 10 patients were on clopidogrel + ASA and 5 patients were on prasugrel + ASA combination therapy. Clopidogrel + oral anticoagulant treatment was started in these patients with intracardiac thrombus. Those who refused treatment were excluded from the study. Patients with no loss or no regression of intracardiac thrombus during the first 45 days of treatment were excluded. The follow-up of the intracardiac mass under treatment was used to confirm the diagnosis of thrombus. It was observed that the initial treatments of all patients included in the study were ticagrelor + ASA combination. According to these criteria, 80 patients suffering from heart failure after acute ST elevations and MI were included in the study. The patient's demographic and laboratory data were recorded. Echocardiographic examination was performed on all patients. Patients were included in two groups in terms of LVT.

Plasma SCUBE-1 assays: we performed a complete blood count and investigated routine biochemistry and cardiac enzymes from blood specimens collected from the patients and the controls. 2 mL of blood was also collected in citrate tubes from the patients and the controls once they were admitted to our hospital (before antiplatelet therapy and primary PCI procedure) for investigation. There was centrifugation of the specimens for 15 min in a 4000-cycle centrifuge device at $+4^{\circ}\text{C}$. We placed serum (1 cL3) in an Eppendorf tube and kept them at -80°C to perform the assay. We removed and put the Eppendorf tubes in a $+4^{\circ}\text{C}$ environment 24 h before the SCUBE-1 evaluation. We gradually thawed Sera for more than 24 h and

measured SCUBE-1 levels for the samples reaching room temperature. We used an enzyme-linked immunosorbent assay kit for the determination of SCUBE-1 levels as instructed by the manufacturer. We determined specimen absorbance on a VERSA max tunable microplate reader (Molecular Devices, Sunnyvale, CA, USA) at a wavelength of 450 nm. We expressed the results as ng/mL.

Standard echocardiography

The experienced echocardiographers not knowing the clinical details of each subject used the Vivid 7[®] cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway) with probes of 2.5 to 5 MHz for transthoracic echocardiographic examinations. Each patient underwent 2D, pulsed, M-mode, and color flow doppler echocardiography examination based on the left supine and lateral positions. M-mode measurements and conventional Doppler echocardiographic examinations were based on criteria of the guideline issued by the European Society of Echocardiography [15]. 2D images and Doppler tracings of apical and subcostal views and parasternal long and short axes were used. The posterior and septal wall thicknesses, end-systolic and end-diastolic dimensions and left and right atrial dimension of the LV, and diastolic LV were measured. The left atrial volumes were measured using the disc method, and LV EF was used to estimate Simpson's rule. Diagnosis of LVT was due to visualization of an echo dense mass clearly separated from LV wall border at least in the 2 different orthogonal echocardiographic planes, near the area anterior wall of myocardium affected. Two experienced cardiologists were blinded to the angiographic data and evaluated the images.

Statistical analysis

Data were managed and analyzed with the SPSS software version 14 (SPSS Inc., Chicago, IL, USA) and it was found that a two-sided p -value ≤ 0.05 was regarded as statistically significant. Where applicable, the number of cases and percentage and continuous variables as interquartile ranges (IQR), median, and mean $\pm$ standard deviation (SD) were regarded as categorical variables. Univariate data were evaluated with the Kolmogorov–Smirnov test, while the homogeneity of variance was evaluated with the Levene test. In the comparison of the two groups, an independent two-sample t -test was used when the data showed normal distribution, and the Mann–Whitney U test was used when they did not show normal distribution. Effect sizes were calculated using the Cramer's V formula for the chi-square test, the Cohen scoring formula for the two-sample t -test, and the z -score formula for the results obtained in the Mann–Whitney test. If appropriate, categorical data were evaluated using the chi-square test. Correlation analysis was done using the Spearman correlation test used for non-normally distributed variables and the Pearson correlation test for normally distributed variables. In the study correlation analysis, the relationships between scube-1 level and proBNP and MPV were evaluated. Since monotonic relationships were observed between the variables, they were evaluated with Spearman's analysis. The optimal cut-off point of serum SCUBE-1 level was identified to predict LVT through ROC curve analysis. MedCalc was used for ROC curve analysis (v12.7.8). LVT was predicted to estimate the AUC with a 95% confidence interval. The association between variables and LVT was quantified using the univariate analysis. It was found that the variables were statistically significant in the univariate analysis and

the independent prognostic factors of LVT were determined using other potential confounders in the multivariate logistic regression model with the backward stepwise method. The effect of scube levels on predicting intracardiac thrombus development was demonstrated by post hoc power analysis. A post hoc analysis was applied for a retrospective power analysis and it was determined that a cohort size of 80 patients (22 with LVT and 58 without LVT) had a power of %99.3 to detect a difference at the 0.05 significance level. To avoid the risk of type 1 errors, post hoc pairwise comparisons were made for the Chi-square test. A two-tailed p -value of <0.05 was accepted as statistically significant.

Results

Eighty patients with left ventricular failure after MI participated in the study. Of these patients, 70 were patients with acute anterior MI, and 10 were patients with acute MI history other than anterior MI. LVT was detected in 2 of 10 patients with acute MI other than anterior MI, 20 of the 70 patients with anterior MI, and 22 of all patients were included in the study. Also, LVAs were detected in 21 patients with anterior MI. LVT was seen in 11 patients with a LVA. Patients were included in two groups in terms of LVT. Table 1 shows clinical, echocardiographic, and laboratory data from the two groups. The group with LVT had a significantly higher rate of hypertension ($p=0.019$). However, no significant difference was found between the groups in age, smoking, gender, and diabetes mellitus rate. The standard echocardiographic measurements showed that the LVT group had a significantly higher left atrial diameter than the non-LVT group, while EF was significantly lower ($p=0.001$, $p=0.017$). The LVT group had significantly higher laboratory parameters of SCUBE-1, NT-proBNP and LDL cholesterol ($p=0.001$, $p=0.002$, $p=0.049$). Both groups had other similar laboratory parameters. Serum SCUBE-1 levels had a positive correlation with NT-proBNP and were found to be negatively correlated with MPV (Table 2).

The receiver operating characteristic (ROC) curve shows that the optimal cut-off point of SCUBE-1 levels used to predict LVT was >35.1 ms, with a sensitivity of 68.4% and specificity of 86% (AUC=0.815 95% CI, 0.699–0.931; $p<0.001$) (Figure 1).

SCUBE-1 level (OR=1.090, 95% CI: 1.034–1.150, $p<0.001$), NT-proBNP (OR=1.001, 95% CI: 1.000–1.002, $p=0.003$) and left atrial diameter (OR=1.406, 95% CI: 1.124–1.759, $p=0.003$) in the multiple logistic regression model, continued to significantly predict LVT after adjusting for the confounding variables, as statistically significant in the univariate analysis of the variables which had correlation with the SCUBE-1 levels (Table 3).

Table 1: Baseline characteristics of study patients.

Baseline characteristics	Left ventricular thrombus (n=22)	Without left ventricular thrombus (n=58)	p-Value	Effect size
Age, years ^a	62 ± 10	58 ± 13	0.226	0.344
Male/female, n*	18/4	44/14	0.766	0.064
Hypertension, n, %*	17(77.3)	26(44.8)	0.019	0.290
Smoker, n, %*	6(27.3)	28(48.3)	0.149	0.190
Diabetes mellitus, n, %*	12(54.5)	19(32.8)	0.074	0.200
Laboratory data				
BUN, mg/dL ^b	16.5(8.25)	15(9)	0.319	0.065
Creatinine, mg/dL ^a	0.9 ± 0.3	0.9 ± 0.2	0.725	0.254
Potassium, mmol/L ^a	4.3 ± 0.5	4.3 ± 0.6	0.834	0.552
Sodium, mmol/L ^a	137 ± 3	138 ± 3	0.395	0.333
Total cholesterol, mg/dL ^b	157(64)	150(55)	0.857	0.051
HDL, mg/dL ^a	39 ± 7	38 ± 7	0.590	0.142
LDL, mg/dL ^b	126.5(64)	108(54)	0.049	0.213
Triglycerides, mg/dL ^b	116.5(83)	108(83)	0.310	0.063
D-dimer, mg/L ^b	0.300(0.4)	0.360(0.35)	0.316	0.149
Platelets, 10 ⁹ /L ^a	259.4 ± 73	265.7 ± 78.6	0.743	0.083
WBC, 10 ⁹ /L ^a	8.48 ± 1.17	8.87 ± 1.45	0.274	0.300
RBC, 10 ⁶ U/L ^a	4.8 ± 0.5	4.8 ± 0.5	0.927	–
Hemoglobin, g/dL ^a	14 ± 1.7	13.8 ± 1.7	0.602	0.520
Hematocrit, % ^a	41.9 ± 4.7	41.2 ± 4.0	0.486	0.160
proBNP, ng/L ^b	2360(3836)	852(1497)	0.002	0.476
SCUBE-1, ng/mL ^a	47.5 ± 21.3	22.6 ± 15.2	<0.001	1.318
Echocardiography parameters				
LV EF, % ^a	32 ± 5	36 ± 6	0.017	0.724
Left atrial diameter, cm ^a	39.2 ± 4.4	35.5 ± 4.3	0.001	0.8500
Septum thickness, mm ^a	13.1 ± 1.0	9.8 ± 1.4	0.383	2.710
Posterior wall thickness, mm ^a	8.0 ± 1.2	8.47 ± 1.1	0.122	0.408

^aMean ± standard deviation, ^bmedian (interquartile range),*chi-square ($p \leq 0.05$ was considered statistically significant).

BUN, blood urea nitrogen; HDL, high-density lipoprotein; IQR, interquartile ranges; LDL, low-density lipoprotein; WBC, white blood cells; RBC, red blood cells; BNP, brain natriuretic peptide; LV, left ventricle.

Table 2: Correlation coefficients with SCUBE-1.

Variables correlating with SCUBE-1	R	p-Value
Pro-BNP	0.272	0.030
MPV	–0.259	0.030

BNP, brain natriuretic peptide; MPV, mean platelet volume.

Discussion

The current study showed that serum SCUBE-1 level predicts LVT after the previous anterior MI, which is an independent predictor. We also found that NT-proBNP levels and left atrial diameters were independent predictors for LVT in these patients.

LVT is regarded as one of the prevalent complications in patients with acute anterior MI. Determining the presence of LVT can significantly prevent and treat embolic complications. Some clinical, echocardiographic, and angiographic parameters are markers of LVT in previous studies [4, 16]. But there are not enough studies on this subject at the molecular level. The prolonged ischemia in STEMI leads to sub-endocardial and endothelial damage while increasing procoagulant factors concentration. The akinetic areas of the resulting necrotic myocardium result in blood stasis, particularly at the apex of the left ventricle [17]. In addition, after MI, necrotic tissues replace with fibrotic scar tissue over time, causing myocardial tissue weakening. This thinning of the myocardial tissue may lead to aneurysms [16, 18]. Myocardial tissue with reduced wall thickness expands during systole, causing the contractile energy generated by the myocardium to be wasted. This causes mechanical damage to the entire ventricle [19, 20]. This may facilitate thrombus formation by causing intraventricular stasis and endocardial damage [21]. The inflammatory process associated with subendothelial and endothelial damage triggers the activation of platelets and contributes to thrombus formation [17]. SCUBE-1 is a new adhesion molecule found in human endothelial platelets and cells. There is a normal storage of SCUBE-1 protein in platelet alpha granules transported to the surface through thrombin activation [10–12]. SCUBE-1 protein is also integrated with the growing thrombus [13]. Platelet–platelet interaction is also promoted by the molecule, playing a role in platelet adhesion to the subendothelial matrix [22–25]. SCUBE-1 levels may be important in platelet adhesion and platelet aggregation to the subendothelial and endothelial damaged area of the left ventricle after MI. Serum SCUBE-1 levels were also high in acute coronary syndromes and thromboembolic cerebrovascular diseases [22, 26]. Similarly, the present study showed high serum SCUBE-1 levels in patients with LVT.

Stretched myocytes synthesized and secreted NT-proBNP mainly through volume expansion or overpressure charge of the ventricle [27–30]. NT-proBNP is considered as the most reliable and valuable biomarker of cardiac dysfunction in heart failure [31, 32]. It has been

Figure 1: Receiver operator characteristic (ROC) curve of SCUBE-1 level to predict LVT.

Table 3: Univariate and Multivariate analysis.

Variables	Univariate analysis						Multivariate analysis					
	B	SE	WALD	p-Value	OR	CI	B	SE	WALD	p-Value	OR	CI
Serum SCUBE-1 level	0.900	0.030	9.110	0.003	1.094	1.032–1.160	0.086	0.027	10.093	0.001	1.090	1.034–1.150
Pro-BNP	0.001	0.000	8.011	0.005	1.001	1.000–1.002	0.001	0.000	9.121	0.003	1.001	1.000–1.002
Left atrial diameter	0.566	0.219	6.690	0.010	1.761	1.147–2.703	0.341	0.114	8.896	0.003	1.406	1.124–1.759
LV EF	−0.41	0.092	0.200	0.655	0.960	0.802–1.149						
Hypertension	2.987	1.856	2.591	0.107	19.829	0.522–753.310						
Variables correlating with SCUBE-1												
MPV	−0.282	0.206	1.879	0.170	0.754	0.504–1.129						

Pro-BNP, pro b-type natriuretic peptide; LV, left ventricle; MPV, mean platelet volume.

demonstrated in many studies that left ventricular dysfunction is a predictor of LVT [6, 33]. We found that the LVT group had significantly higher NT-proBNP, a biomarker of heart failure, and independently predicted the LVT. However, although EF was significantly lower in LVT, it was found to be not an independent predictor. The reason for this can be explained by the involvement of patients of heart failure with EF that is below 45% in the research.

The left atrium is highly effective in cardiovascular homeostasis due to its important duty in regulating cardiac filling. Left atrial remodeling and the increase in left atrial volume often occur with hypertension, pulmonary

diseases, ischemia, and heart failure [34]. Cardiovascular events and thromboembolic events are also prognostic markers, especially in atrial fibrillation due to remodeling. However, cardiovascular risk and thromboembolic events are also associated with an increase in atrial dilation, which exists without atrial fibrillation, independent of other risk factors and comorbid events [35]. This situation is explained by atrial cardiomyopathy. Endothelial dysfunction and hypercoagulability in atrial cardiomyopathy contribute to LVT formation [36]. Similarly, left atrial dilation was found to independently predict the LVT in the present study.

Limitations of the study

This study has one main limitation, which is the determination of LVT presence. Echocardiography was used to determine if the LVT was present, and studies were showing that cardiac MRI was more sensitive in the LVT diagnosis. In this study, patients assumed to be suboptimal were evaluated with transesophageal echocardiography (TEE), and patients who did not consent to TEE were excluded. In patients who do not consent to TEE, the absence of contrast Echo is another limitation. In addition, echocardiographic control was done to determine if the LVT was present in the third month, which is another limitation. The fact that serum SCUBE-1 levels are also affected by various physiological variables can also be considered a limitation.

Conclusions

LVT is regarded as one of the prevalent complications of acute MI. Identifying LVT predictors is important for both prevention of complications and the determination of treatment strategy. Serum SCUBE-1 levels can be used as a simple, easily accessible biomarker to predict LVT.

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