

# Cardio-ankle vascular index may be an important marker of silent neuronal injury after percutaneous coronary angiography and intervention: a prospective observational study on diagnostic accuracy

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## ABSTRACT

**Objective:** The relationship between silent neuronal injury (SNI) and arterial stiffness assessed by cardio-ankle vascular index (CAVI) has not been evaluated in patients treated with coronary angiography and intervention due to acute coronary syndrome (ACS). The aim of this study is to evaluate the value of CAVI in prediction of SNI after percutaneous coronary angiography and intervention in patients presented with ACS.

**Methods:** Eighty-three consecutive patients presented with ACS, who underwent percutaneous coronary angiography and intervention, were included in this prospective observational study on diagnostic accuracy. Neuron specific enolase (NSE) was studied before and 18 hour after the coronary angiography and intervention. CAVI was measured by VaSera-1000 instrument. Clinical and echocardiographic characteristics were analyzed and independent predictors of SNI were evaluated. Chi-square, Student t-test, Mann-Whitney U test, correlation analysis and logistic regression analysis was used for statistical analysis.

**Results:** NSE levels significantly increased after cardiac catheterization ( $9.82 \pm 3.22$  mg/dL vs.  $13.15 \pm 8.55$  mg/dL,  $p < 0.001$ ). CAVI (OR=2.992, 95% CI: 1.494-5.713,  $p=0.002$ ), left ventricular ejection fraction (LVEF) (OR=0.911, 95% CI: 0.843-0.983,  $p=0.017$ ) and undergoing percutaneous coronary intervention (OR=4.430, 95% CI: 1.034-18.97,  $p=0.045$ ) were the independent predictors of SNI in logistic regression analysis. The cut-off value to show SNI for CAVI was 10.45 (sensitivity=71.8%, specificity=91.5%) in receiver operator characteristic (ROC) curve analysis. The area under curve was 0.832 (95% CI=0.746-0.918,  $p < 0.001$ ).

**Conclusion:** Besides undergoing PCI and having LVEF, measurement of CAVI may be a useful tool for predicting the development of SNI after percutaneous coronary angiography and intervention in patients with ACS. (*Anadolu Kardiyol Derg 2014; 14: 606-11*)

**Key words:** angiography, cardio-ankle vascular index, silent neuronal injury, myocardial infarction, stroke, cerebral, regression analysis, diagnostic accuracy, sensitivity, specificity

## Introduction

Silent neuronal injury (SNI) is defined as embolic neuronal lesion that is incidentally diagnosed in healthy patients. The SNI is 7-9 times common than clinically significant cerebral ischemia and is associated with dementia (1). Even in asymptomatic patients without history of stroke, cranial infarcts may be observed incidentally in cranial imaging modalities. The prevalence of SNI is 11-28% and increases with increasing age (1, 2). Although the patients are usually asymptomatic, mild perception and behavioral disturbances may be present.

Coronary angiography (CAG) is the gold standard diagnostic modality for the assessment of coronary artery disease (CAD) (3).

Percutaneous coronary intervention (PCI) is a safe and effective alternative of coronary artery bypass graft surgery (CABG) and medical therapy (4). However PCI related complications including heart chamber perforation, myocardial infarction (MI), arrhythmia, vascular complications, dye allergy, hemodynamic derangements and stroke may ensue (5, 6). Retrospective data analysis revealed that 0.11-0.38% of patients undergoing CAG experienced clinically evident cerebral infarction, while the incidence of SNI was 13-22% (7-10). SNI is described in 18.5-23% of patients after cerebral angiography (11, 12). Atherosclerotic thromboembolism due to catheter manipulation, thrombus formation on the catheter, air embolism and contrast agent may cause cerebral injury (12-15). Moreover, increase in incidence of stroke in patients with history of PCI was reported in a previous study (10).

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Neuron specific enolase (NSE) is a neuronal cytoplasmic enzyme with a half life of 48 hours (16). Increased level of NSE is a sensitive and specific marker of neuronal injury. NSE level is correlated with the size of cerebral infarct and Glasgow coma scale (16-19).

Increased arterial stiffness is associated with adverse major cardiovascular events (20). Arterial stiffness can be detected by various methods including pulse wave velocity, augmentation index, aortic distensibility and beta stiffness index. These methods however substantially affected by blood pressure levels. Cardio-ankle vascular index (CAVI) is a novel method of arterial stiffness measurement that reflects the stiffness of all arterial tree including aorta, femoral artery and tibial artery. Unlike other methods of arterial stiffness measurement, CAVI is not influenced by blood pressure levels and is associated with coronary atherosclerosis, cardiac functions, carotid atherosclerosis, stroke, cognitive functions and hypertension (21-23).

To date limited data were available regarding the occurrence and predictors of SNI after PCI. Arterial stiffness using CAVI has not been evaluated in association with SNI in patients treated with PCI due to acute coronary syndrome (ACS). The aim of this study is to evaluate the value of CAVI in prediction of SNI after percutaneous coronary angiography and intervention by serial measurement of serum NSE levels in patients presented with ACS.

## Methods

### Study design

This study was designed as a prospective observational study on diagnostic accuracy.

### Study population

From June 2012 to August 2012, 83 consecutive patients (65 men) presented with ACS that underwent percutaneous coronary angiography and interventions were enrolled in this prospective study. Patients with recent or previous cerebrovascular accident, intracranial hemorrhage, head trauma, central nervous system tumor, degenerative central nervous system disorders, schizophrenia, septic shock, pneumonia, neuroendocrine tumor, malignancy, Creutzfeldt-Jakob disease, Gullian-Barre syndrome and hemodynamic decompensation were excluded from the study. Patients with intracardiac thrombus and hemolyzed blood samples were also excluded from the study.

### Study protocol

Neuron specific enolase levels were measured before and 18 hours after the PCI. Detailed neurological examination along with general physical examination was performed to each patient before, 24 and 48 after the PCI and before the discharge. All patients were neurologically intact before the enrollment. The left ventricular ejection fraction (LVEF) was measured according to the biplane Simpson method. All patients gave

informed consent before enrollment and the study protocol was approved by Ethic Committee.

### Neuron specific enolase

Neuron specific enolase was studied before and 18 hours after the PCI. Blood samples were analyzed by Cobas 601 immunologic analyzer (Roche Diagnostic, Mannheim, Germany) and Elecsys NSE kits with ECLIA [electroemilumineson immunologic test (eCobas 601 module, Mannheim, Germany)] method. An NSE level above 17.0 mg/dL was accepted positive according to manufacturer's instructions and a measurement above this cut-off value was accepted as SNI.

### Cardio-ankle vascular index

CAVI was measured using a VaSera VS-1000 CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) by the methods described previously (21). CAVI was measured in the morning after 15 minutes of rest. Briefly, cuff was applied to the bilateral upper arms and ankles, with the subject supine and the head held in the midline position. Electrocardiography, phonocardiography, and pressures and waveforms of brachial and ankle arteries were measured and pulse wave velocity and subsequently CAVI were calculated automatically. CAVI measurements were performed by experienced cardiologist. CAVI is determined by the following equation:  $CAVI: a[(2r/\Delta P) \times \ln(Ps/Pd)PWV^2] + b$ .

Where Ps and Pd are systolic blood pressure and diastolic blood pressure, respectively, PWV is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery,  $\Delta P$  is Ps-Pd (systolic blood pressure- diastolic blood pressure), r is blood density and a and b are constants. The equation is derived from Bramwell-Hill's equation and the stiffness parameter  $\beta$ , and CAVI was adjusted for blood pressure based on the stiffness parameter  $\beta$ . Therefore, CAVI reflects the stiffness of the aorta, femoral artery and tibial artery as a whole; theoretically, it is not affected by blood pressure. After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Denshi, Tokyo, Japan), and the values of right and left CAVI were calculated. The average of the right and left CAVIs was used for analysis.

### Coronary angiography data

All cases underwent CAG. Acetyl salicylic acid 300 mg, 600 mg loading dose of clopidogrel and intravenous heparin 70 units/kg was administered before the CAG. Acetyl salicylic acid, clopidogrel, heparin, statin, angiotensin converting enzyme inhibitor, beta-blocker maintenance therapy was administered after the PCI according to current guidelines (24).

### Clinical, laboratory and echocardiographic data

For each patient, vascular risk factor, including hypertension, diabetes mellitus, hypercholesterolemia, smoking status and history of ischemic stroke, were obtained. Patients with blood pressure  $\geq 140/90$  mm Hg at two occasions or on antihyperten-

sive medication were accepted hypertensive. Diabetes mellitus was defined as fasting blood glucose >126 mg/dL or patients on oral antidiabetic or insulin therapy. Hyperlipidemia is accepted as fasting LDL level >160mg/dL or patients at antihyperlipidemia therapy. The laboratory data which were measured before CAG (on the day of admission) were recorded. The laboratory data included hemoglobin, fasting glucose, total cholesterol, low density lipoprotein, urea and creatinine. Height and weight of patients were recorded and body mass index was calculated. The estimated creatinine clearance rate was calculated according to Cockcroft and Gault formula. Transthoracic echocardiographic assessment (Vivid S5 General Electric, Norway) was performed in all patients according to the standards of the American Society of Echocardiography and LV EF was calculated according to bi-plane Simpsons method.

### Statistical analysis

SPSS for Windows 17.0 (SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Continuous variables with normal distribution are expressed as mean±standard deviation (SD), with non-normal distribution as median (inter quartile range, IQR) and categorical variables are expressed as percentage. Analysis of normality was performed with the Kolmogorov-Smirnov test. Comparisons of continuous variables between the two groups were performed using the independent samples t-test or Mann-Whitney U test as appropriate. Pearson and Spearman correlation analysis were used to analyze correlates of CAVI. Categorical variables were compared with the chi-square test. Repeated measure test was used for dependent variable analyses. Logistic regression analysis was used to find independent associates of SNI. The sensitivity and specificity of CAVI to predict SNI was evaluated with receiver operative characteristic (ROC) analysis. Results were evaluated between the 95% confidence interval and  $p<0.05$  was accepted significant.

### Results

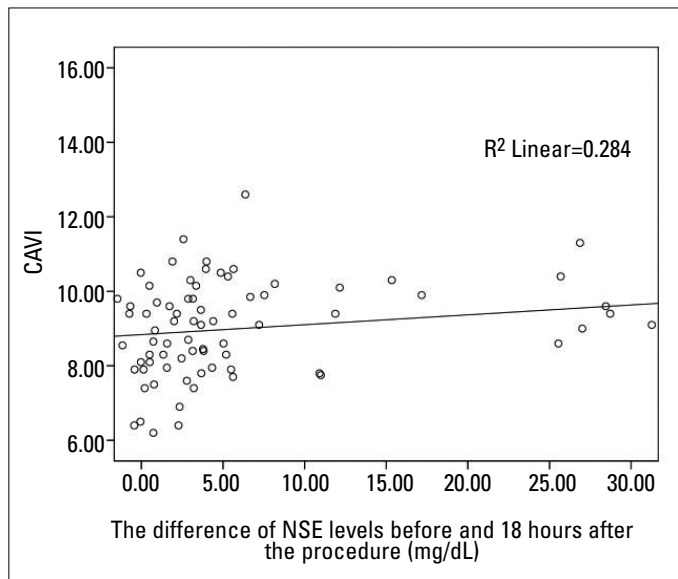
CAG was performed to all patients. Baseline patient characteristics are shown in Table 1. Of the 83 patients, 15 (18.1%) patients presented with unstable angina pectoris, 43 patients (51.8%) with non-ST elevation myocardial infarction and 25 patients (30.1%) patients with ST elevation myocardial infarction (15 patients with anterior MI and 10 patients with inferior MI). PCI was performed to 42 (50.6%) patients. SNI was detected in 24 (28.9%) patients. NSE levels significantly increased 18 hours after CAG compared to pre CAG levels ( $22.31\pm 29.64$  mg/dL and  $9.82\pm 3.22$  mg/dL consecutively  $p<0.001$ ). Basal NSE level of SNI+(SNI positive) group was  $12.41\pm 3.13$  mg/dL and SNI-(SNI negative group) was  $8.76\pm 2.64$  mg/dL. Post procedural NSE levels of patients with SNI and those without were 29.28 (53.69) and 10.89 (4.74) mg/dL successively. Age, gender, presence of atrial fibrillation and frequency of coronary risk factors including smoking, diabetes, hypertension, and hyperlipidemia were similar between groups. There is no significant difference in labora-

**Table 1. Patient characteristics**

Variable	SNI+ (n=24)	SNI- (n=59)	P
Age, years	64.21±9.37	63.37±11.10	0.746 <sup>a</sup>
Male, n (%)	19 (79.2%)	46 (78.0%)	0.904 <sup>b</sup>
BMI, kg/m <sup>2</sup>	28.43±4.16	28.59±4.96	0.887 <sup>a</sup>
Hypertension, n (%)	6 (25.0%)	24 (40.7%)	0.178 <sup>b</sup>
Diabetes, n (%)	6 (25.0%)	22 (37.3%)	0.283 <sup>b</sup>
Hyperlipidemia, n (%)	8 (33.3%)	17 (29.3%)	0.719 <sup>b</sup>
Smoking, n (%)	7 (29.2%)	23 (39.0%)	0.399 <sup>b</sup>
Atrial fibrillation, n (%)	2 (8.3%)	7 (11.9%)	0.639 <sup>b</sup>
MAP, mm Hg	99.63±13.62	98.19±11.77	0.632 <sup>a</sup>
PCI, n(%)	17 (70.8%)	25 (42.4%)	0.019 <sup>b</sup>
CAVI	10.36±1.31	8.69±1.18	<0.001 <sup>a</sup>
FT, min	6.04±4.30	4.65±4.31	0.186 <sup>a</sup>
eCrCl, mL/min	103.79±31.88	98.31±34.07	0.501 <sup>a</sup>
Glucose, mg/dL	103.5 (40)	110 (45)	0.581 <sup>c</sup>
LDL, mg/dL	141.67±43.61	135.54±42.46	0.556 <sup>a</sup>
TC, mg/dL	198.85±71.29	201.73±54.62	0.843 <sup>a</sup>
Hemoglobin, g/dL	14.20±1.48	14.04±1.68	0.685 <sup>a</sup>
CK-MB, ng/mL	64.27 (170.70)	13.20 (64)	0.008 <sup>c</sup>
Troponin-I, ng/mL	22.87 (50.84)	5.30 (36.41)	0.009 <sup>c</sup>
EF, %	40.83±12.39	51.20±9.37	<0.001 <sup>a</sup>
Diagnosis			0.730 <sup>b</sup>
USAP, n (%)	3 (12.5%)	12 (20.3%)	
NSTEMI, n (%)	11 (45.8%)	32 (54.2%)	
STEMI, n (%)	10 (41.7%)	15 (25.4%)	

BMI - body mass index; CAVI - cardio-ankle vascular index; CK-MB - creatinine kinase myocardial band; eCrCl - estimated creatinine clearance; EF - ejection fraction; FT - fluoroscopy time; MAP - mean arterial pressure; LDL - low density lipoprotein; NSTEMI - non-ST segment elevation myocardial infarction; PCI - percutaneous coronary intervention; SNI - silent neuronal injury; STEMI - ST segment elevation myocardial infarction; TC - total cholesterol; USAP - unstable angina pectoris  
Data are presented as number (percentage), mean±standard deviation, median (inter quartile range) <sup>a</sup>independent samples t-test; <sup>b</sup>Chi-square test; <sup>c</sup>Mann-Whitney U test

tory data including fasting blood glucose, LDL, HDL, total cholesterol and hemoglobin levels between patients with SNI and those without SNI. Left ventricular ejection fraction in the SNI+ group was significantly lower than that of the SNI- group ( $40.83\pm 12.39\%$  vs.  $51.20\pm 9.37\%$ ,  $p=0.001$ ). Although the mean fluoroscopy time of SNI+ group was higher ( $6.04\pm 4.30$  min vs.  $4.65\pm 4.31$  min,  $p=0.186$ ) it was not significant. Maximal CK-MB [ $64.27$  (170.70) vs.  $13.20$  (64),  $p=0.008$ ] and Troponin-I [ $22.87$ (50.84) vs.  $5.30$ (36.41),  $p=0.009$ ] levels of SNI positive group were significantly higher compared to SNI- group. SNI was significantly higher among patients who underwent PCI (40.5% vs.17.1%,  $p=0.019$ ). CAVI values were higher in patients with SNI than those without SNI ( $10.36\pm 1.31$  vs.  $8.69\pm 1.18$ ,  $p<0.001$ ). While the CAVI values were positively correlated with the difference of NSE levels between basal and post catheterization values



**Figure 1. The correlation of CAVI with the difference of NSE levels before and 18 hours after the procedure was shown**

CAVI - cardio-ankle vascular index

( $p < 0.001$ ,  $r = 0.533$ ) (Fig.1), CK-MB ( $p = 0.001$ ,  $r = 0.371$ ) and troponin-I ( $p = 0.002$ ,  $r = 0.341$ ) and it was negatively correlated with LVEF ( $p < 0.001$ ,  $r = -0.393$ ) (Table 2).

**Independent predictors of SNI**

CAVI (OR= 2.992, 95% CI: 1.494-5.713,  $p = 0.002$ ), LVEF (OR= 0.911, 95% CI: 0.843-0.983,  $p = 0.017$ ) and undergoing PCI (OR=4.430, 95% CI: 1.034-18.97,  $p = 0.045$ ) were the independent predictors of SNI in logistic regression analysis (Table 3).

The cut-off value of CAVI to predict SNI was found 10.45 (sensitivity=71.8%, specificity=91.5%) in ROC curve analysis. The area under curve was 0.832 (95% CI: 0.746-0.918,  $p < 0.001$ , Fig. 2).

**Discussion**

We have found that 28.9% of patients presented with acute coronary syndrome developed SNI. CAVI, EF and undergoing PCI were the independent predictors of SNI in logistic regression analysis.

Procedural complications including stroke may occur during PCI (5, 6). Approximately 0.11-0.38% of patients developed stroke during PCI (7, 8). However, SNI after the CAG and PCI is inadequately evaluated. SNI is a precursor of symptomatic stroke and associated with dementia, deterioration of neuropsychological performance and decline in cognitive functions (25). SNI is quite common after cerebral angiography, it was shown that, 18.5-23% of patients had SNI after cerebral angiography (11, 12). However, there is limited data regarding the incidence of SNI after CAG. Moreover the data about the predictors and incidence of SNI in patients presented with ACS is lacking. Busing et al. (7) reported that SNI was common after PCI (23%) compared to CAG (11%), but it was not statistically significant. In their series total of 48

**Table 2. The correlates of CAVI**

Variable	R	P
Age	0.057	0.606 <sup>a</sup>
Male	0.081	0.469 <sup>b</sup>
Body mass index	-0.179	0.105 <sup>a</sup>
Hypertension	-0.001	0.493 <sup>b</sup>
Diabetes	-0.048	0.664 <sup>b</sup>
Hyperlipidemia	-0.072	0.519 <sup>b</sup>
Smoking	-0.143	0.196 <sup>b</sup>
Atrial fibrillation	-0.017	0.879 <sup>b</sup>
Mean arterial pressure	-0.007	0.951 <sup>a</sup>
Percutaneous coronary intervention	0.144	0.194 <sup>b</sup>
Estimated creatinine clearance	-0.047	0.674 <sup>a</sup>
Glucose	-0.019	0.865 <sup>a</sup>
Low density lipoprotein	-0.112	0.313 <sup>a</sup>
Total cholesterol	-0.142	0.199 <sup>a</sup>
Hemoglobin	0.055	0.625 <sup>a</sup>
Creatine kinase-myocardial band	0.371	0.001 <sup>a</sup>
Troponin-I	0.341	0.002 <sup>a</sup>
Left ventricular ejection fraction	-0.393	<0.001 <sup>a</sup>
Difference of NSE level	0.533	<0.001 <sup>a</sup>

<sup>a</sup>Pearson correlation analysis; <sup>b</sup>Spearman correlation analysis

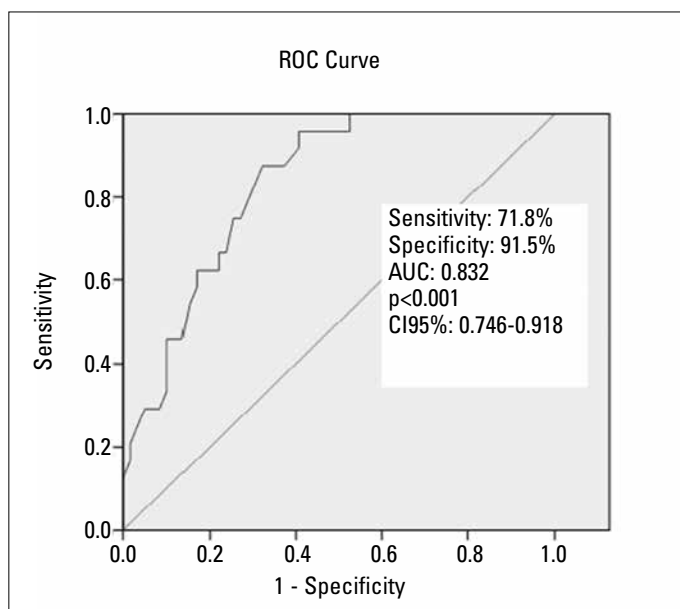
**Table 3. Results of logistic regression analysis**

	P value	OR	95% CI lower	95% CI upper
CAVI	0.002	2.992	1.494	5.713
EF	0.017	0.911	0.843	0.983
PCI	0.045	4.430	1.034	18.97
CK-MB	0.263	0.994	0.984	1.004
Troponin-I	0.335	1.009	0.991	1.027

CAVI - cardio-ankle vascular index; CI - confidence interval; CK-MB - creatinine kinase - myocardial band; EF - ejection fraction; OR - odds ratio; PCI - percutaneous coronary intervention

patients were included and PCI was performed to 13 patients. In contrary to their study we have found that PCI significantly increased the risk of SNI. Furthermore our study population was larger and PCI was performed to 42 patients.

SNI was evaluated by MRI in prior studies (7, 9, 10). MRI is the most sensitive non-invasive radiological method for the evaluation of cerebral anatomy. But MRI has some limitations as well. MRI could not analyze morphological abnormalities smaller than MRI pixel which is 1.8-2.0 mm<sup>2</sup>. Thus the cerebral injury after CAG may be underestimated in previous studies. As Lund et al. (10) reported that, microembolization to cerebral circulation was common in elective left heart catheterization. In their series cerebral microembolization (92.1% gaseous and 7.9% solid) was observed in all patients demonstrated by transcranial



**Figure 2. The ROC curve analysis showing the sensitivity and specificity of CAVI  $\geq 10.45$  for predicting the occurrence of SNI**

SNI - silent neuronal injury

Doppler ultrasonography. We used NSE for the determination of SNI in this study. Various biochemical markers are used for the evaluation neuronal injury. NSE is a sensitive and specific marker of neuronal injury and is effective in predicting neurological outcome and survival after cardiac arrest (17, 26). In patients with ischemic stroke, the release of NSE has been associated with neurological outcomes and infarct volume (17, 18, 27). Increased NSE level is significant associated with post-operative neurocognitive dysfunction (28).

CAVI is a novel arterial stiffness parameter which is independent of blood pressure. CAVI reflects the stiffness of all arterial tree. CAVI is an established marker of atherosclerosis and associated with major adverse cardiac events. Increased arterial stiffness is associated with stroke. Recently it was shown that CAVI is a valuable marker of cerebral small vessel disease (29, 30). We found that CAVI is independently associated with the development of SNI after CAG and PCI. This finding suggested that catheter manipulations may easily injure aorta during cardiac catheterizations in patients with stiffened arteries. As the patients with increased CAVI values also had arteriosclerosis of carotid arteries and cerebral small vessel disease, these patients are more prone to develop SNI after cardiac catheterization.

Saji et al. (30) studied 220 consecutive patients without history of transient ischemic attack or stroke in a healthy population and found that CAVI was significantly increased in patients with SNI. The cut-off value of CAVI for detection of SNI was 9.2 in their study (30). In opposed to Saji et al. (30) we studied the patients that underwent coronary angiography and intervention due to acute coronary syndrome and we found that, the cut-off value of CAVI for the development of SNI was 10.45 (sensitivity=71.8%, specificity=91.5%) in ROC analysis. CAVI is increased

in patients with established CAD therefore the higher cut-off value that is detected in our study may be due to the concomitant presence of CAD (31).

## Study limitations

The present study has several potential limitations. First, the study population included patients with acute coronary syndrome, who had significant atherosclerosis. The risk of SNI after PCI therefore may be overestimated. Second, MRI was not performed which is the gold standard diagnostic imaging modality for the evaluation of cerebravascular injury. NSE is affected by hemolysis thus catheterization related hemolysis may cause overestimation of SNI. Although heparin was administered during the procedure thrombosis of the catheter may also ensue. Air embolism may be another cause of SNI as well. Furthermore ACS is a hypercoagulable state thus the in situ thrombus formation in cerebrovascular tree could not be excluded in this study.

## Conclusion

Besides undergoing PCI and having low LVEF, measurement of CAVI may be a useful tool for predicting the development of SNI after percutaneous coronary angiography and intervention in patients with ACS.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - A.Ç.A.; Design - A.Ç.A.; Supervision - T.G.; Resource - A.Ç.A., İ.G., E.K., H.B.; Materials - A.Ç.A.; Data collection &/or processing - F.B., E.H.; Analysis &/or interpretation - A.Ç.A.; Literature search - T.T., A.Ç.A.; Writing - A.Ç.A.; Critical review - T.G., İ.G., H.B.; Other - E.A., R.B., T.T.

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