THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Impact of Intravenous Agitated Saline Contrast Echocardiography on Subclinical Neuronal Injury Determined By Neuron-Specific Enolase

ORIGINAL INVESTIGATION

ABSTRACT

Background: Patent foramen ovale (PFO) is a congenital defect of the interatrial septum with 25%-30% prevalence. Diagnostic echocardiography involves the injection of agitated saline, and microbubble passage from the right to the left atrium is monitored. The reliability of this method has been questioned in case series, with a low incidence (0.062%) of generally transient, mild clinical cerebrovascular events. This study aimed to examine whether transthoracic echocardiography, which was performed on patients with PFO and atrial septal aneurysm (ASA) without neurological history, and healthy controls can cause silent neuronal injury by evaluating neuron-specific enolase (NSE) with saline contrast echocardiography (SCE).

Methods: Fifty-two patients who underwent SCE for color flow through the interatrial septum or prominent interatrial septal aneurysm and were diagnosed with PFO were included. Fifty-one control patients without PFO or ASA were included. Serum samples were collected from the patients before and 12 hours after the SCE test, and NSE levels were measured by Enzyme Linked Immunosorbent Assay (ELISA).

Results: Median baseline NSE levels were 6.4 (2.8-9.6) ng/mL in the PFO/ASA group and 5.3 (3.6-9.1) ng/mL in controls. At 12 hours, median NSE levels remained similar (6.6 (3.8-11.5) vs. 5.8 (4.6-9.6) ng/mL; $P = .90$). The median change in NSE (ΔNSE) did not differ between groups [1.19 (−1.01 to 2.23) vs. 0.73 (−1.16 to 2.25) ng/mL; $P = .58$]. There was no relationship between age, presence of interatrial septal aneurysm, mitral annulus calcification, number of bubbles passed in the SCE test, and baseline and 12-h change in NSE levels ($P = .926$). Neuron-specific enolase level changes were found to be correlated between groups ($P < .001$).

Conclusion: This study is the first to evaluate whether SCE causes silent neuronal injury. It is suggested that when evaluated with NSE, the SCE method is safe and does not cause silent neuronal injury in patients without underlying neuronal susceptibility.

Keywords: Contrast echocardiography, neuron specific enolase, paradox embolism, patent foramen ovale, silent cerebral ischemia

INTRODUCTION

Foramen ovale is an opening in the interatrial septum during the fetal period that allows blood to bypass the non-functional lungs. In most individuals, it closes after birth, but in 15%-35% of the population, it remains open, known as patent foramen ovale (PFO).[1,2] Although it is often asymptomatic, PFO can be associated with conditions like cryptogenic stroke and systemic arterial embolism.[2,3] Patent foramen ovale can allow blood clots to travel from the venous to arterial system, increasing the risk of paradoxical strokes.[2] Transthoracic echocardiography (TTE) is commonly used to diagnose PFO but has limited sensitivity. Contrast echocardiography, using agitated saline, is more accurate, while transesophageal echocardiography remains the gold standard.[4-6] Saline contrast echocardiography (SCE) is generally considered safe, although rare ischemic events have been reported.[1,2]

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Received: September 11, 2025
Accepted: January 5, 2026
Available Online Date: February 20, 2026

Cite this article as: Korkmaz K, Kaya CT, Us E, Tutar DE. The impact of intravenous agitated saline contrast echocardiography on subclinical neuronal injury determined by neuron-specific enolase. *Anatol J Cardiol.* 2026;30(6):363-368.

DOI:10.14744/AnatolJCardiol.2026.5809

 Anatol J Cardiol 2026; 30(6): 363-368

Enolase is a cytosolic enzyme that plays a central role in glycolysis. Neuron-specific enolase (NSE) is the isoform that is found in neurons and neuroendocrine cells. When neuronal damage occurs and cell membranes are disrupted due to trauma, ischemia, or hypoxia, NSE is released into the extracellular space, cerebrospinal fluid, and bloodstream.[7] Due to it being relatively specific to neurons and being released after neuronal injury, it is used as a biomarker for neuronal damage. It has been studied in various ischemic and cardiac conditions such as stroke, traumatic brain injury, cardiac arrest, heart failure, and percutaneous coronary interventions.[8-12] Various studies have shown that levels of NSE are concordant with the level of damage determined by magnetic resonance imaging (MRI) findings as lesion burden or infarct size.[13-15] It can also determine silent neuronal injury, which is neuronal injury without overt clinical symptoms.[10,12] Although clinically silent, silent neuronal injuries are not benign. Even small neuronal injuries, especially if recurrent, can contribute to decreased neuronal reserve and decline in cognitive function.[16,17]

There is a theoretical concern that intravenous agitated SCE might lead to paradoxical air embolism, potentially causing acute ischemic stroke or transient ischemic attack (TIA).[11] Although clinical trials have generally not reported severe adverse events, MRI examinations of symptomatic patients have identified 3 cases of stroke and 2 cases of TIA.[1,11,18-20] In these reported cases, permanent sequelae were generally not observed, and, where present, the outcomes were mild. Trials on the reliability of SCE have primarily focused on neuronal damage detected by MRI in patients with clinical symptoms and signs of ischemic stroke.[1,19,20] According to current knowledge, no studies have assessed the impact of SCE on silent neuronal injury assessed by NSE levels. This study aims to investigate whether agitated saline contrast during PFO evaluation leads to silent neuronal injury by comparing NSE levels in patients with and without PFO.

METHODS

Patients aged 18 years and older who were presented to the outpatient clinics of the hospital between November 2021 and May 2023, underwent echocardiography and consented to participate in the study were included. Patients in whom a color flow favoring PFO was observed on color Doppler imaging in TTE, or patients with an atrial septal aneurysm (ASA) whose physician requested an intravenous agitated contrast saline study for the evaluation of PFO, were screened. In total, 91 patients with PFO and ASA detected on TTE were screened. Based on the evaluation, 52 patients without exclusion criteria were included in the PFO and ASA group, whereas 51 age- and sex-matched volunteers with normal echocardiographic findings were included in the control group.

Exclusion criteria included a recent cerebrovascular event history, recent acute coronary syndrome, patients under anticoagulant therapy and those with atrial fibrillation and mechanical heart valves due to an increased risk of embolism, brain or neuroendocrine tumors, degenerative central nervous system disease, recent head trauma, proven or suspected pregnancy.

HIGHLIGHTS

- Serum neuron-specific enolase (NSE) levels showed no significant difference between the patent foramen ovale/atrial septal aneurysm and control groups.
- Minimal numerical change in NSE values indicates that saline contrast echocardiography does not induce silent neuronal injury.
- Saline contrast echocardiography was found to be a safe and reliable diagnostic method.

Intravenous Agitated Saline Contrast Echocardiography Procedure

Prior to imaging, the procedure was explained to all participating patients in detail. Patients were instructed to take a deep breath and hold it in. Then, they should try to bear down forcefully and strain as if during a bowel movement while keeping their mouth and nostrils closed. They were asked to perform the maneuver for approximately 10 seconds until they were instructed to release by the operator. Confirmation was obtained from each patient to ensure adequate comprehension and cooperation.

Nine milliliter of 0.9% saline was mixed with 1 mL of air, and the mixture was agitated. The echocardiography system was prepared to record at least 20 cardiac cycles. The microbubble passage sequence between the heart chambers was evaluated in the recorded cycles after the patients performed the Valsalva maneuver. The adequacy of the Valsalva maneuver was determined by the presence of a transient leftward shift of the interatrial septum during release. 0-10 bubbles passing to the left atrium were classified as grade 1, 10-20 bubbles as grade 2, 20 or more bubbles without complete opacification as grade 3, and complete opacification during the passage as intense opacification. The passage of microbubbles to the left atrium during the first 3 cardiac cycles after the right atrium was opacified was considered a positive study.[21] Echocardiographic images during the test were obtained from the subcostal and apical 4-chamber views.

Estimation of Neuron-Specific Enolase

In cases of traumatic brain injury, serum NSE levels begin to rise within 2-12 hours, peak between 12 and 72 hours, and return to baseline within 3-5 days. In stroke, NSE levels typically peak at around 48 hours.[22,23] As a result, venous blood samples were drawn before the study and 12 hours after the contrast echocardiography study to determine the NSE levels. Serum samples were analyzed using the Elecsys NSE kit (Roche Diagnostics, Mannheim, Germany) according to the procedures specified by the ELISA method. The 95th percentile value is 16.3 ng/mL and 95% confidence range 15.7-17.0 ng/mL according to the manufacturer. In studies conducted with various kits, the pathological serum NSE threshold levels varied as 12, 18.9, 25.4, and 30 ng/mL.[10,24-26] In the study, the cut-off value of the assay used was 16.3 ng/mL.

Statistical Analysis

The sample size was calculated based on the results of a preliminary study by the group where median NSE levels of control subjects were 7.9 and ASA subjects were 8.2 ng/mL. A hypothetical 20% increase from baseline in the PFO/ASA group was considered significant. For 80% power and a 2-sided alpha level of 0.05, the calculated sample size was 45 cases in each group. IBM SPSS Statistics 26 software was used for statistical calculations. Descriptive statistics included mean, standard deviation, median, tewnty-fifth and seventy-fifth percentiles, frequency, and percentage. Normality of continuous variables was assessed using the Shapiro–Wilk test. Most variables, including baseline, 12-hour and delta NSE levels, age, echocardiographic parameters, and laboratory measurements, were not normally distributed. Therefore, non-parametric statistical methods were applied where appropriate. The McNemar test was used to examine differences between categorical variables in dependent groups. In paired samples, within-group comparisons were performed using the Wilcoxon test. Agreement between 2 categorical variables was assessed with the Kappa coefficient. Spearman's correlation coefficient was used to determine the direction and strength of the relationships between variables. The relationship between multiple independent variables and NSE change was analyzed using linear regression analysis. Potential factors that could be associated with a twelfth hour NSE level ≥16.3 ng/mL were analyzed by a binary logistic regression analysis. A *P*-value of <.05 was considered statistically significant.

Ethics Committee Approval

The study was approved by the Research Ethics Committee with the decision number i9-579-21 on September 14, 2021.

RESULTS

Demographic, Clinical, and Echocardiographic Results

A total of 103 volunteers aged 19-66 years were included in the study, with 52 in the PFO and ASA group and 51 in the control group. Among the participants, 66 were female and 35 were male, with genders equally distributed between the groups. The mean age was 43.5 years in the PFO and ASA group and 40.94 years in the control group. The demographic and clinical characteristics of the study group are summarized at Table 1.

There was no statistically significant difference between the PFO/ASA and control groups in terms of demographic and clinical characteristics.

There were no statistically significant differences between the groups in terms of biochemical measurements and echocardiographic measurements (*P* > .05) (Table 1). Among the included patients, 10 (19.2%) had a medium PFO (grade 2 shunt), and 10 (19.2%) had a large PFO (grade 3 shunt).

Table 1. Baseline Demographic, Clinical, Laboratory, and Echocardiographic Characteristics

Variables	PFO/ASA (n = 52)	Control (n = 51)	*P*
Age, years	40.9 ± 10	43.5 ± 12	.329
Female sex, n (%)	36 (69.2)	30 (58.8)	.534
Diabetes mellitus, n (%)	5 (10)	1 (2)	.970
Hypertension, n (%)	8 (16)	7 (14.3)	.812
Hyperlipidemia, n (%)	0	3 (6.3)	.073
Current smoking, n (%)	10 (20)	12 (25)	.553
History of ASCVD, n (%)	1 (2)	0	.320
Creatinine, mg/dL	0.71 ± 0.16	0.75 ± 0.16	.313
LDL cholesterol, mg/dL	111 ± 37	113 ± 32	.842
Hemoglobin, g/dL	13.6 ± 1.7	13.9 ± 1.62	.519
Leukocytes (10^9/L)	7.8 ± 2.27	7.1 ± 1.45	.120
LVEF, %	59.3 ± 3.64	59.9 ± 0.72	.325
LA diameter, cm	3.8 ± 0.54	3.6 ± 0.34	.036

Values are presented as mean ± standard deviation or number (percentage).
ASCVD, atherosclerotic cardiovascular disease; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

Comparative NSE Levels and Relationships Between Subgroups

Baseline, twelfth-hour, and delta NSE levels were similar among the groups (Table 2). The increase in NSE levels after the SCE test was not found to be statistically significant (*P* = .77). The groups were similar regarding the number of patients with high NSE (≥16.3 ng/mL) levels both at baseline and after SCE. There were patients who had high baseline NSE levels both in the control and PFO/ASA groups. McNemar's test was performed to determine the proportion of patients who were classified as normal shifting to abnormal and vice versa; the *P* level for the control group was 1 and the PFO/ASA group was 0.757. These findings indicate that SCE did not increase the likelihood of NSE levels crossing to the abnormal range. Agreement between baseline and 12-hour NSE classification using a cut-off value of 16.3 ng/mL was moderate (Cohen's κ = 0.51) in the overall population. Group-specific analysis showed good agreement in the control group (κ = 0.65) and fair agreement in the PFO/ASA group (κ = 0.34), with no shift toward pathological NSE levels after SCE. Spearman's correlation analysis showed a significant correlation between baseline and 12th-hour NSE level changes in both the PFO and control groups (*P* < .001).

A multiple linear regression analysis was performed to assess if any echocardiographic or clinical variables influenced a change in NSE levels. In the multivariable model including age, ASA, mitral annulus calcification, shunt grade, and presence of PFO, none of the variables predicted a change in NSE levels (all *P* > .1).

Table 2. Comparision of NSE Changes Between Groups

	PFO and ASA Group (n = 52)	Control Group (n = 51)	*P*
Baseline NSE* (ng/mL)	9.1 ± 10.5 mean 6.4 (2.8-9.6)	12.7 ± 19 mean 5.3 (3.6-9.1)	.942
Twelfth hour NSE* (ng/mL)	9.8 ± 10.6 mean 6.6 (3.8-11.5)	12.7 ± 18 mean 5.8 (4.6-9.6)	.900
Delta NSE* (ng/mL)	0.75 ± 4.35 mean 1.19 (−1.01 to 2.23)	−0.03 ± 4.35 mean 0.73 (−1.16 to 2.25)	.580

*The values are given as mean ± SD and median (IQR).
NSE, neuron spesific enolase; PFO, patent foramen ovale.

Table 3. Binary Logistic Regression Analysis for Elevated NSE at Twelve Hours (≥16.3 ng/mL)

Predictor	Odds Ratio (OR)	95% CI	*P*
Age	1.00	0.95-1.05	.96
PFO	0.23	0.01-4.12	.32
ASA	3.53	0.25-50.38	.35
Shunt grade	1.31	0.64-2.66	.46

ASA, atrial septal aneurysm; PFO, patent foramen ovale.

An exploratory binary logistic regression analysis was also performed to identify potential factors that could be associated with a twelfth-hour NSE level ≥16.3 ng/mL. None of the variables were independently associated with elevated NSE levels at 12 hours (Table 3).

No significant relationship was found between shunt degree and the change in NSE levels in both groups, indicating that higher shunt severity did not result in higher NSE levels ($P = .926$).

DISCUSSION

Silent cerebral ischemia is an acute neuronal damage detected radiographically in the absence of clinical stroke or TIA, and it may lead to cognitive dysfunction, dementia, and increased mortality.[27] Although MRI imaging is generally the preferred technique to determine cerebral ischemia or injury, it is not universally available and is costly. Routine use of MRI for determination of subclinical ischemia in asymptomatic patients is not cost-effective. Moreover, microinfarctions are generally to small to be detected on conventional MRI imaging.[28] Therefore, biomarkers of neuronal injury might be useful in the detection of this clinically silent condition with potential adverse consequences.

According to the best of current knowledge, no studies have evaluated asymptomatic, silent neuronal injury due to SCE using either imaging or laboratory methods. This study is the first study to demonstrate the safety of SCE on silent neuronal injury using a biomarker-based approach.

In the literature, several studies have demonstrated that NSE is highly effective and prognostic in detecting cerebral injury, supported by comparative neuroimaging across various patient groups. In the imaging-supported analysis conducted by Mochetti et al, which reviewed 11 studies, NSE levels were reported to be significant predictors of the extent of neuronal damage and clinical outcomes.[15] Similarly, in the study by Seung-Un Oh et al, NSE was identified—through comparison with diffusion MRI—as an important predictor of both the severity of neuronal injury and the degree of clinical neurological deficit.[13] In a neonatal asphyxia study, the diagnostic value of NSE for neuronal injury was established through comparisons with EEG and MRI, while in patients undergoing aortic surgery, NSE levels were shown to correlate with neurological outcomes and the extent of ischemia when assessed alongside computed tomography (CT) or MRI findings.[29,30] Moreover, multiple studies have demonstrated that NSE levels predict silent cerebral ischemia following coronary interventions in patients with acute coronary syndrome, as well as in those undergoing percutaneous coronary intervention for chronic total occlusion.[12,30-32] In addition, NSE can predict poor clinical outcomes in out-of-hospital cardiac arrest.[11]

In this study, if SCE caused silent neuronal injury in patients with PFO, higher serum NSE levels at the twelfth hour and a significant difference from the baseline value compared with the control group were expected. The hypothesis was that the test is reliable and that the difference in NSE levels between the 2 measurements would not be significant compared with the control group. The statistical analysis revealed no significant difference between the PFO/ASA and control groups in the difference between the 2 NSE levels. Previous studies have reported varying pathological serum NSE threshold levels of 12, 18.9, 25.4, and 30 ng/mL.[9,24-26] The mean NSE levels in the control group were found to be slightly above even the smallest threshold level reported in previous studies, with baseline values of 12.7 ng/mL and the twelfth hour value also at 12.7 ng/mL. However, the median values were 5.3 ng/mL for the first NSE and 5.8 ng/mL for the second NSE. This suggests that acceptable levels for NSE measurements may vary widely. Although inter-kit variability may play a role, the use of a 12 ng/mL cutoff—and even values as high as 16.3 ng/mL—may still result in frequent false positives when compared with median concentrations observed in healthy individuals. Median values for both NSE measurements were higher in the PFO and ASA group, though not statistically significant. The minimal numerical change between the twelfth-hour NSE and baseline NSE values and the lack of a significant difference between the PFO/ASA and control groups suggest that SCE is generally a safe method.

In a retrospective trial conducted by Bommer et al[1] in 1984, the reported incidence of side effects after SCE was 0.062%. No residual side effects or complications were reported. This study was conducted retrospectively based on patient symptom inquiries during and after the procedure.

In a trial conducted by van Gent et al[19] in 2009, 281 patients underwent SCE for the diagnosis of pulmonary arteriovenous malformation, compared with CT. No adverse events related to SCE were observed.

In a trial by Romero et al[2] in 2009, a total of 3314 SCE procedures were reviewed to investigate the relationship between SCE and cerebral ischemic events. Magnetic resonance imaging findings were noted in 3 of the patients who experienced cerebral ischemic events. The findings were observed in small areas and were similar to cerebral damage caused by any mechanism rather than being specifically related to cerebral air embolism. Neurological deficits were temporary, and if permanent, were mild. One patient had a history of stroke recurrence, and 3 had a history of migraine attacks. The relationship between PFO and migraine has been previously reported, with both pathologies being associated with stroke. It was concluded that migraine vasospasm induced by microbubbles might have caused the ischemic event.[2]

In a 2015 study by Velthuis et al,[20] among 132 patients with hereditary hemorrhagic telangiectasia and grade 3 shunts who underwent SCE, only 3 experienced paresthesia and migraine, whereas no adverse events were observed in patients with shunts below grade 3. These episodes were transient and did not result in neurological sequelae, which has been interpreted as evidence of the reliability of CKE.

In a 2015 study by Gupta et al,[33] long-term observations of 100 patients revealed that even in patients with severe right-to-left shunts, no serious neurological events were detected.

There is a theoretical concern that intravenous agitated SCE might lead to paradoxical air embolism. Previous studies have generally been based on imaging findings following the detection of symptoms after SCE. In most cases, no neuronal injury was identified; in those where injury was detected, patients typically had underlying neurological conditions predisposing them to damage, and the neuronal findings were mild and transient. The study is the first to specifically investigate asymptomatic and silent neuronal injury, and consistent with previous studies, no silent neuronal injury was detected following SCE testing. Based on both the findings and previous research, the SCE test can be considered a reliable and safe diagnostic method.

In addition, the literature has demonstrated a statistically significant relationship between the degree of hemolysis in serum samples and the increase in NSE concentration during the sample collection phase. One study reported that each unit of hemolysis (equivalent to 1 mg/dL of free hemoglobin) resulted in an average increase of 0.29 ± 0.09 ng/mL in NSE levels due to release from erythrocytes.[22] In the study, all blood samples were processed and stored under identical conditions; however, this factor may still have influenced the results.

Study Limitations

The first limitation is that most patients underwent TTE, and due to patient selection and the SCE administration being conducted during the pandemic, not all patients could undergo transesophageal echocardiography. The second limitation is the number of patients. The study involves a small and limited population, many with relatively small shunts which have a lower risk of stroke. The findings need to be expanded and verified in larger, more comprehensive populations. The third limitation is the lack of imaging methods capable of evaluating silent ischemic lesions. The study could be improved by incorporating diffusion MRI.

CONCLUSION

In the study, which evaluated whether SCE causes silent neuronal injury in patients with PFO using the NSE biomarker, no statistically significant increase in NSE levels was found in the PFO and ASA group compared to the control group after the test. Therefore, it was concluded that the SCE method does not cause silent neuronal injury and can be applied safely.

Ethics Committee Approval: This study was approved by the Ankara University Clinical Research Ethics Committee (Approval number: i9-579-21, Date: September 14, 2021).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.T.K., K.K.; Design – C.T.K., K.K.; Supervision – C.T.K., D.E.T.; Resources – D.E.T.; Materials – C.T.K., E.U.; Data Collection and/or Processing – K.K., C.T.K.; Analysis and/or Interpretation – C.T.K., K.K.; Literature Search – K.K., C.T.K.; Writing – K.K.; Critical Review – C.T.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

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