# Relation of Acute Decompensated Heart Failure to Silent Cerebral Infarcts in Patients With Reduced Left Ventricular Ejection Fraction

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**Heart failure (HF) is a prothrombotic state with increased rate of thromboembolic events. Magnetic resonance imaging studies demonstrated increased rate of silent cerebral infarcts (SCI) in this patient group and SCIs were shown lead to dementia, cognitive decline, and depression. We aimed to show acute decompensated phase is associated with increased rate of recent SCI in reduced ejection fraction HF patients. HF patients with sinus rhythm hospitalized for acute decompensation were studied. Neuron specific enolase (NSE), a sensitive neuronal ischemia marker, was used to detect recent SCI. Decompensated and compensated phase blood samples for NSE were collected on the day of admission and on the third day of compensation, respectively. One hundred and forty seven patients with mean age of 72 were studied. There were significantly more patients with positive NSE levels at decompensated state (29% vs 4%, p <0.001). Multivariate predictors for recent SCI were smoking, new onset atrial fibrillation, spontaneous echo contrast of left ventricle, and aneurysmatic apex. Statin use was found to be protective against NSE elevation. In conclusion, our data reveal that decompensated HF is significantly associated with increased levels of NSE suggestive for silent neuronal injury.**  **(Am J Cardiol 2019;123:1835−1839)**

Heart failure (HF) patients are known to have a prothrombotic state and disturbed coagulation system. All 3 components of the Virchow triad (endothelial dysfunction, stasis, and hypercoagulability) are altered in HF, especially at the acute decompensated state.[1,2] There are magnetic resonance imaging (MRI) studies demonstrating that nearly 1/3 of the HF patients have silent cerebral infarcts (SCI), defined as the evidence of neuronal injury in the absence of clinically apparent stroke or transient ischemic attack.[3−5] These lesions were shown to associate with atrial fibrillation, cardiomyopathies, and transcatheteter interventions in cardiology.[6,7] Silent neuronal damage can be detected mainly by means of imaging modalities, but an acute event can also be detected by serum neuron specific enolase (NSE), a sensitive neuronal ischemia marker detectable in the serum in 2 to 4 hours and remain positive for about 3 days.[8−10] Our hypothesis was that acute decompensated HF state is associated with increased rate of new onset SCI.

## Methods

Consecutive patients hospitalized for acute decompensated HF were evaluated. Exclusion criteria were (1) left ventricular ejection fraction (EF) >40%, (2) acute coronary syndrome or recent percutaneous intervention in previous 4 weeks, (3) hemodynamic instability like cardiogenic or septic shock and patients who needed cardioversion or cardiopulmonary resuscitation, (4) newly diagnosed HF, (5) atrial fibrillation, (6) use of anticoagulants for any reason, (7) end-stage renal failure (glomerular filtration rate <15 ml/min/1.73 $m^2$) or dialysis patients, (8) mitral stenosis, (9) known apical or left atrial thrombus, (10) history or new onset transient ischemic attack, stroke or known carotid artery disease, (11) cerebral trauma, tumor or central degenerative disease, and (12) patients with known infection. Our study complies with the Declaration of Helsinki. All patients gave written informed consent and local ethics committee approved the study protocol.

Decompensated state was diagnosed according to the modified Framingham Criteria.[11] Patients were managed according to recent HF management guideline of European Society of Cardiology (ESC).[12] All patients received low molecular weight heparin (LMWH) treatment at prophylactic doses during the hospital stay. Blood samples for NSE were collected on the day of hospitalization, before prophylactic LMWH has been injected. Compensated phase was defined as absence of any signs of decompensation with complete tapering of intravenous medication, stable on oral medications without congestion and judgment was done by the attending physician. Levels of NSE were reevaluated at the third day following the compensation criteria had been reached.

Neuron-specific enolase analysis was performed on immunologic automated analyzer by h-NSE kits (Diametra, Foligno, Italy) with direct immunoenzymatic colorimetric method. Intra- and interassay coefficient variables were

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≤4.4% and 11.2%, respectively, and 0.12 μg/L was defined as the upper limit of normal for NSE by the manufacturer. Patients with levels of serum NSE >0.12 μg/L (12 ng/mL) were defined to have a recent SCI.

Statistical analyses were performed by using SPSS software package (version 20 for Windows, SPSS Inc., Chicago, IL). Discrete variables were expressed as numbers and percentages, continuous variables were expressed as mean ± standard deviation. Chi-square analysis or Fisher's exact test for the categorical variables, and Student's *t* test or Mann-Whitney U test for the continuous variables were performed to compare the NSE positive and NSE negative patients. Patients with NSE elevation at decompensated and compensated states were compared by using Mc Nemar test. A multivariable logistic regression analysis was performed to assess the independent predictors of NSE elevation. Gender, age, and variables with p <0.1 in the univariate analysis were subjected to multivariate analysis. A probability value of p <0.05 was considered significant.

## Results

Four hundred and twenty-nine patients hospitalized for acute decompensated HF were evaluated and 282 of them were excluded for following reasons: 118 patients had EF >40%, 108 patients had atrial fibrillation, 25 patients had acute coronary syndrome and underwent coronary angiography, and 31 patients withdrew informed consent. Finally, 147 patients (40% female) with mean age of 72 were studied.

Baseline characteristics of patients with acute decompensated HF according to presence of NSE elevation are given in Table 1. At admission, 43 patients (29%) were NSE positive. NSE elevation was significantly more prevalent among current smokers, patients with reduced glomerular filtration rate, and new onset atrial fibrillation during hospitalization. Echocardiographic evidence of spontaneous echo contrast at left ventricle, restrictive type of diastolic filling pattern and apical aneurysm of left ventricle were significantly associated with high NSE levels. Statin users were less likely to have NSE elevation. Antiplatelet use was not related with recent SCI (p = 0.39).

There were significantly less patients with positive NSE levels at compensation compared with the decompensated state (4% [7/147] vs 29% [43/147], p <0.001). NSE became negative in 40 of 43 patients, who were positive on initial evaluation (Figures 1 and 2). Compensated phase NSE level evaluation was done at 9 ± 3 days after admission.

Possible independent predictors of recent SCI were smoking (odds ratio [OR] 7.468; 95% confidence interval [CI] 1.728 to 32.272; p = 0.007), new onset atrial fibrillation (OR 22.357; 95% CI 3.326 to 150.280; p = 0.001),

Table 1
Baseline clinical characteristics of study patients

| Variable | Decompensated state: Silent cerebral infarct (+) (n = 43) | Decompensated state: Silent cerebral infarct (−) (n = 104) | p Value |
|---|---|---|---|
| Age, year mean ± SD | 72 ± 12 | 72 ± 11 | 0.78 |
| Women | 21 (49%) | 38(37%) | 0.16 |
| Body mass index (kg/m$^2$) | 30 ± 6 | 30 ± 6 | 0.60 |
| Hypertension | 28 (65%) | 56 (54%) | 0.11 |
| Diabetes mellitus | 31 (72%) | 65 (62%) | 0.26 |
| Current smoker | 14(33%) | 12(12%) | 0.002 |
| GFR (ml/min/1.73 m$^2$) | 42 ± 18 | 52 ± 20 | 0.001 |
| Prior myocardial infarction | 27 (63%) | 51 (49%) | 0.12 |
| Prior coronary bypass | 16 (37%) | 38 (37%) | 0.93 |
| New onset atrial fibrillation during hospitalization | 9 (21%) | 4 (4%) | 0.001 |
| History of TIA or stroke | 6 (%14) | 7(%7) | 0.16 |
| Peripheric vascular disease | 4 (9%) | 14(14%) | 0.48 |
| Dilated cardiomyopathy | 7 (16%) | 16 (15%) | 0.89 |
| Inotropic support during hospitalization | 8 (19%) | 16 (15%) | 0.63 |
| Patients with CRT | 4 (9%) | 11 (11%) | 0.81 |
| Left ventricular apical aneurysm | 24 (56%) | 12 (12%) | <0.001 |
| Spontaneous echo contrast in left ventricle (SEC) | 20 (47%) | 8 (8%) | <0.001 |
| Restrictive pattern of filling | 20 (47%) | 22 (21%) | 0.01 |
| Ejection fraction (%) | 28.8 ± 7.1 | 27.4 ± 7.8 | 0.31 |
| Pulmonary artery systolic pressure, mm Hg | 55.7 ± 15.8 | 54.7 ± 11.5 | 0.69 |
| Left atrium diameter (cm) | 4.6 ± 0.6 | 4.7 ± 0.6 | 0.20 |
| Medications on admission | | | |
| Antiplatelet therapy | 28 (65%) | 75 (72%) | 0.39 |
| Statin | 16 (37%) | 70 (67%) | 0.001 |
| Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers | 23 (52%) | 67 (64%) | 0.15 |
| Beta blocker | 37 (86%) | 75 (72%) | 0.36 |
| Aldosterone antagonist | 18 (41%) | 37 (36%) | 0.68 |

CRT, cardiac resynchronization treatment; GFR, glomerular filtration rate; LDL, low-density lipoprotein; NSE, neuron-specific enolase; TIA, transient ischemic attack; WBC, white blood cells.

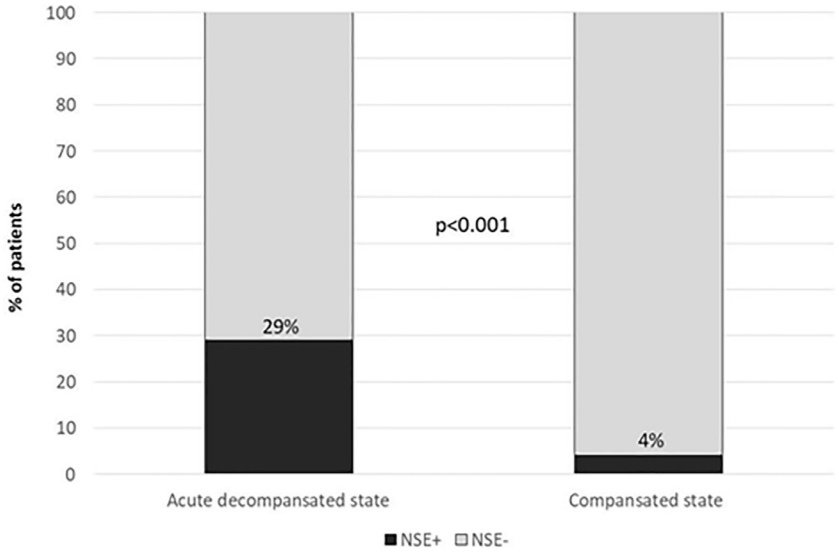


Figure 1. Comparison of neuron-specific enolase positivity at decompensated and compensated state of heart failure. NSE, neuron-specific enolase.

spontaneous echo contrast of left ventricle (OR 8.888; 95% CI 2.160 to 36.580; p = 0.002), and aneurysmatic apex (OR 11.339; 95% CI 3.204 to 40.127; p <0.001). Statin use was found to be protective against NSE elevation (OR 0.281; 95% CI 0.7086 to 0.912; p = 0.035; Table 2).

## Discussion

In this cohort of 147 patients hospitalized for acute decompensated HF with reduced EF and sinus rhythm, the prevalence of new onset SCI was 29%, which was only 4%

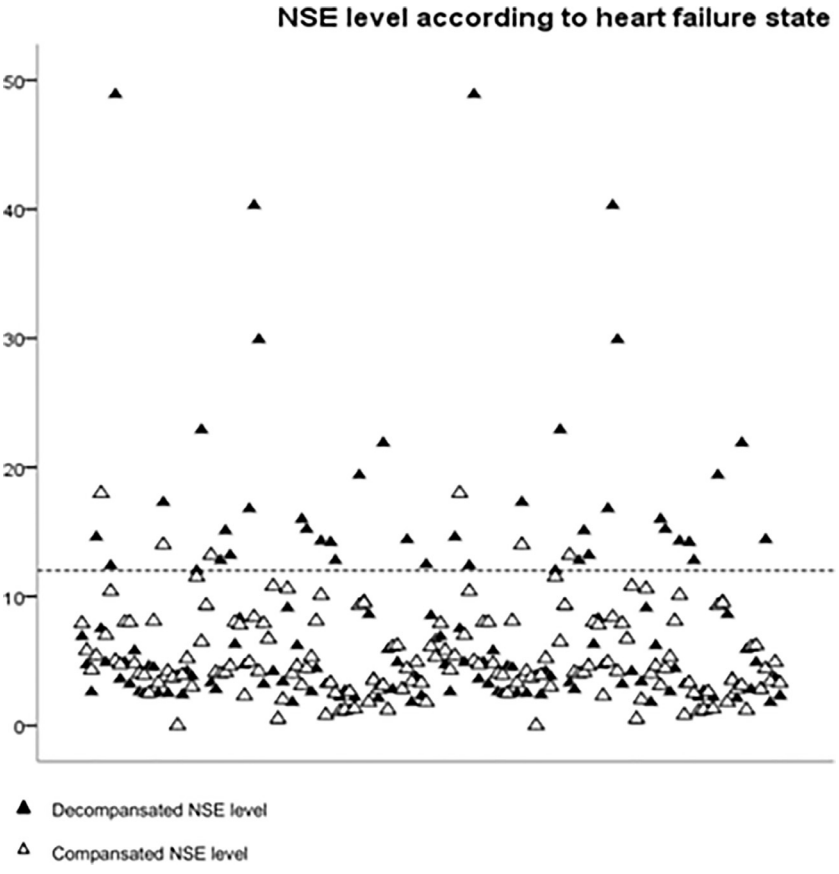


Figure 2. Neuron-specific enolase levels for each individual patient in decompensated and compensated states. Dotted line represents the cut-off value of 12 ng/ml. NSE, neuron-specific enolase.

Table 2
Predictors of silent cerebral infarction in multivariate logistic regression analysis

| Variable | OR (95% CI) | p Value |
|---|---|---|
| Age | 1.016 (0.972-1.062) | 0.481 |
| Men | 0.746 (0.247-2.258) | 0.605 |
| Smoker | 7.468 (1.728-32.272) | 0.007 |
| Atrial fibrillation at hospital | 22.357 (3.326-150.280) | 0.001 |
| Glomerular filtration rate | 0.987 (0.937-1.198) | 0.057 |
| Statin use | 0.281 (0.086-0.912) | 0.035 |
| Apical aneurysm | 11.339 (3.204-40.127) | <0.001 |
| Spontaneous echo contrast of LV | 8.888 (2.160-36.580) | 0.002 |
| Restrictive filling pattern | 1.724 (0.565-5.265) | 0.339 |

CI, confidence interval; LV, left ventricle; OR, odds ratio.

after compensation. To the best of our knowledge, this is the first study of an association between decompensated HF and NSE elevation.

Numerous studies have shown that HF is a disease with prothrombotic state. Stasis of blood due to low output in dilated chambers, altered neurohormonal mechanisms and endothelial dysfunction are contributors leading to platelet aggregates and increased thrombin activation.[13–16] Clinical incidence of thromboembolic events in HF patients is estimated to be around 2% per year.[17] Acute decompensated HF patients with higher plasma norepinephrine concentrations and lower EF were shown to have more embolic events.[18,19] Recently, MRI studies demonstrated a high prevalence of asymptomatic infarcts in brain parenchyma. Kozdag et al showed that 39% of ischemic and 27% of nonischemic cardiomyopathy patients had SCI.[4] In a trial conducted with low EF (<20%) HF patients, SCI rate was detected to be 34%.[3] MRI is the gold standard technique for the diagnosis of SCI; however, it fails to clarify the timing of the event.[5] NSE is an ischemia-specific marker for neurons, cleared nearly in 3 days after the acute attack.[10] By using NSE in our trial, we had the opportunity to detect the new onset neuronal injury.

Accumulating evidence implies that SCIs may lead to dementia, cognitive decline, and depression.[20] Kindermann et al showed that patients with decompensated HF had poorer performance at cognitive function tests.[21] Even though contributing mechanisms could be multifactorial, cerebral infarctions were a highly possible cause. Atrial fibrillation is known to associate with cognitive impairment, even in patients without history of stroke, possibly by the same mechanism. Recently, it has been demonstrated that by the time atrial fibrillation is diagnosed, cognitive deficits had already started and SCIs can be detected by MRI.[22] In support of this data, our trial revealed that new onset atrial fibrillation during hospitalization was the strongest predictor of recent SCI.

In this trial of HF patients, new onset SCI was found to be more prevalent during decompensation period (29%). Relatively lower incidence of SCI (4%) in compensated state can be explained by the relief of prothrombotic mechanisms, such as congestion and neurohormonal activation. Besides, use of prophylactic LMWH during hospital stay could have been a protecting factor. On the basis of this finding, one may assume that the use of oral anticoagulants may have a protective role in the genesis of SCI. However, there is no evidence that oral anticoagulant therapy reduces the incidence of silent brain injury.[23,24] Indeed, recent guidelines do not recommend the use of oral anticoagulants or antiplatelets in reduced EF HF patients with sinus rhythm.[12]

This study has several limitations. First of all, NSE is a surrogate biomarker and the diagnosis of SCI was not confirmed by MRI, which is the gold standard method. However, NSE is suggested to be a valid biomarker that allows for quantification of the degree of neuronal injury.[10] Furthermore, NSE levels were shown to have a good correlation with MRI.[25,26] Another limitation was that it was a single-center trial with limited number of patients. Our results, therefore, should be interpreted with caution.

In conclusion, our data reveal that decompensated HF is significantly associated with increased levels of NSE suggestive for silent neuronal injury. Prognostic value of this finding needs further investigation.

## Disclosures

The authors have no conflicts of interest to disclose.


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