Impaired Frontal Brain Activity in Patients With Heart Failure Assessed by Near-Infrared Spectroscopy

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Background—The prevalence of depression and/or anxiety disorders is reported to be higher in patients with heart failure (HF) than in the general population, and patients with HF also have coexisting cognitive problems. Recently, the development of near-infrared spectroscopy (NIRS) has enabled noninvasive measurements of regional cerebral blood volume and brain activity, in terms of cerebral oxyhemoglobin in the cerebral cortex, with a high time resolution. The aim of the current study was to determine the associations between frontal brain activity and depressive symptoms, anxiety status, and cognitive function in patients with HF.

Methods and Results—We measured and compared frontal brain activity determined by NIRS during a verbal fluency task in patients with HF (n=35) and control subjects (n=28). The Center for Epidemiologic Studies Depression Scale for assessment of depressive symptoms, State-Trait Anxiety Inventory for assessment of anxiety status, Mini-Mental State Examination for assessment of cognitive function, and NIRS were simultaneously conducted. NIRS showed that frontal brain activity was significantly lower in the HF group than in the control subjects (28.5 versus 88.0 mM-mm; P<0.001). Next, we examined the associations between frontal brain activity and the findings of Center for Epidemiologic Studies Depression Scale, State-Trait Anxiety Inventory, Mini-Mental State Examination, and verbal fluency task. There were significant correlations between frontal brain activity and State-Trait Anxiety Inventory (R=−0.228, P=0.046), Mini-Mental State Examination (R=0.414, P=0.017), and verbal fluency task (R=0.338, P=0.007), but not with Center for Epidemiologic Studies Depression Scale (R=−0.160, P=0.233).

Conclusions—Frontal brain activity assessed by NIRS is reduced and is associated with high anxiety status and low cognitive function in patients with HF. (J Am Heart Assoc. 2020;9:e014564. DOI: 10.1161/JAHA.119.014564.)

Key Words: anxiety • cognitive function • dementia • depression • heart failure

The prevalence of depression and/or anxiety disorders has been reported to be several times higher in patients with heart failure (HF) than in the general population, and a substantial proportion of patients with HF also have coexisting cognitive problems. Comorbid mood disorders are associated with increased morbidity, mortality, and medical costs in patients with HF but are underdiagnosed and undertreated. Cognitive impairment is one of the most common comorbidities in patients with HF and is associated with poor quality of life and self-care, as well as increased morbidity and mortality.

It has been recently reported that reduced cerebral blood flow (CBF) may be associated with altered autonomic, mood, cognitive, and language and speech regulation sites in HF patients. The neural damage appears on examination by several magnetic resonance imaging (MRI) procedures and is reflected as regional loss of tissue or injury, as measured by manual assessment, voxel-based morphometry, quantitative T2-relaxometry, and diffusion tensor imaging procedures.

Recently, the development of near-infrared spectroscopy (NIRS) has enabled noninvasive and bedside measurements of regional cerebral blood volume in terms of relative concentrations of oxyhemoglobin and deoxyhemoglobin, with a high time resolution. The concentrations of oxyhemoglobin and deoxyhemoglobin are assumed to reflect the regional cerebral blood volume. In addition, oxyhemoglobin increases and deoxyhemoglobin decreases in NIRS have been shown to reflect cortical activation by simultaneous measurements with other methodologies, NIRS presents cerebral perfusion, and...
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Clinical Perspective

What Is New?
- Frontal brain activity assessed by near-infrared spectroscopy was reduced in patients with heart failure.

What Are the Clinical Implications?
- Impaired frontal brain activity was associated with high anxiety status and low cognitive function.

is used as functional brain monitoring. A positive correlation has been confirmed between oxyhemoglobin concentration by NIRS and blood-oxygen-level-dependent signaling by functional MRI. Further, NIRS has recently been used to investigate the neurocognitive processes associated with neurological (Alzheimer disease, Parkinson disease, epilepsy, and traumatic brain injury) and psychiatric disorders (depression, bipolar disorder, anxiety disorders, and schizophrenia). The frontal NIRS signal has been proposed as a supportive tool in assisting the diagnosis of major psychiatric disorders with depressive symptoms in addition to evaluation of brain activity. Compared with positron emission tomography, single-photon emission computed tomography, and functional MRI, NIRS has the advantages of requiring minimal equipment and being easy to use.

In the present study, we aimed to (1) evaluate and compare frontal brain activity using NIRS in patients with HF and control subjects, and (2) determine the associations between frontal brain activity and depressive symptoms, anxiety status, and cognitive function.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects and Study Protocol

This is a cross-sectional study with 28 age-matched control subjects and 35 patients with HF who came to Fukushima Medical University Hospital between May 2018 and June 2019. The diagnosis of HF was made by several cardiologists on the basis of the HF guidelines. Study subjects underwent echocardiography, carotid artery ultrasonography, laboratory testing, psychological testing, and NIRS. The verbal fluency task (VFT) is used to test frontal region function and is commonly used with NIRS analysis. The control subjects were without past history of HF, physical signs of HF, or structural cardiac abnormalities, which were detected by echocardiography. The study protocol was approved by the ethical committee of Fukushima Medical University (no. 823), and the investigation conforms to the principles outlined in the Declaration of Helsinki. All subjects provided written informed consent to participate in the study. Patients with carotid artery stenosis, cerebral infarction, or dementia, or patients receiving treatment for schizophrenia, depression, or bipolar disorder were excluded. We evaluated several comorbidities that often coexist and are associated with adverse prognosis in patients with HF. Regarding the psychological testing, the Center for Epidemiologic Studies Depression Scale (CES-D) was used to evaluate depressive symptoms, the State-Trait Anxiety Inventory–State (STAI-S) and Trait (STAI-T) were used to evaluate anxiety status and trait, and the Mini-Mental State Examination (MMSE) was used to evaluate cognitive function.

We compared the findings of CES-D, STAI-S, MMSE, VFT, and NIRS findings between the patients with HF and control subjects and determined the associations between frontal brain activity and depressive symptoms, anxiety status, and cognitive ability.

Blood samples were obtained from all subjects at Fukushima Medical University Hospital. B-type natriuretic peptide levels were measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan).

Echocardiography and carotid artery ultrasonography were performed blindly by experienced sonographers using standard techniques. The left ventricular ejection fraction was calculated using Simpson’s method in a 4-chamber view. All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc, Mountain View, CA). In the present study, HF with left ventricular ejection fraction ≥45% was defined as HF with preserved ejection fraction, and HF with left ventricular ejection fraction <45% was defined as HF with reduced ejection fraction.

Measurement of NIRS

A VFT was widely used as an activating task during NIRS analysis, as previously reported. In the current study, oxyhemoglobin, deoxyhemoglobin, and total hemoglobin were measured with a 52-channel NIRS machine (Hitachi ETG4000, Hitachi Medical Corp., Tokyo, Japan) using 2 wavelengths of near-infrared light (695 and 830 nm). NIRS measurement was performed by attaching 52 channels to the head. The 52-channel device was connected symmetrically around the prefrontal cortex. The main measured channels were as follows: right temporal lobe (channels 1–3, 11–14, 22–24, 32–35, and 43–45), left temporal lobe (channels 8–10, 18–21, 29–31, 39–42, and 50–52) and frontal region (channels 25–28, 36–38, and 46–49). Especially, an increase in cerebral oxyhemoglobin concentration in the frontal region in response to the VFT is considered as a marker of frontal brain activity. Most of the lower and forward channels were placed along the line connecting T3-Fpz-T4,
based on the international 10-20 system. Compliance with the scalp measurement sites of the international 10-20 system allows prediction of the measurement sites on the brain surface with relatively high accuracy. NIRS signal changes were measured during a 10-second pretask baseline period, a 60-second activation period, and a 55-second posttask baseline period. The sampling rate of oxyhemoglobin concentration data was 0.1 second. The obtained data were analyzed using the “integral mode”: The pretask baseline was set as the mean over a 10-second period just before the task period, and the posttask baseline was fixed as the mean over the last 5 seconds of the posttask period. Linear fitting between the pre- and posttask baselines was applied to the data between the 2 baselines. The average oxyhemoglobin concentration during the VFT that was performed for 60 seconds was used for the analysis. A previously reported algorithm was used to automatically reject data with artifacts. Data are expressed as waveforms and topographic maps. The intraclass correlation coefficient of the mean oxyhemoglobin concentration during the task segment was calculated for the 52 channels. The single-measure intraclass correlation coefficient was 0.5309, and the average measure intraclass correlation coefficient was 0.6936, which are both reliable, as previously reported. NIRS analyses were performed using MATLAB R2011 (Math Works Inc, Natick, MA), and Prism 6.0 software (GraphPad Software, Inc, San Diego, CA).

Activation Task, VFT
An outline of the VFT procedure is as follows. Changes in hemoglobin oxygenation occur in people performing the VFT. Artifacts must be eliminated by having the subject sit in a chair, relax, and move as little as possible during the test. The subject is first prompted by a voice saying, “Start /a/, /i/, /u/, /e/, /o/” to repeat the utterance “/a/, /i/, /u/, /e/, /o/” for 30 seconds. The baseline activity recorded during this meaningless utterance is used to remove the effect of vocalization on brain activity from the data. The subject is next prompted by a voice to vocalize as many words as possible that start with a certain letter. This is done in three 20-second sets. The subjects are verbally prompted to vocalize words starting with a certain letter to increase the difficulty of the task. The exercise is scored by recording the number of words uttered every 20 seconds. Finally, the subject is prompted by a voice saying, “Stop /a/, /i/, /u/, /e/, /o/” to stop the task and repeat “/a/, /i/, /u/, /e/, /o/” for 70 seconds.

Statistical Analysis
Categorical variables are expressed as numbers and percent-ages. The chi-square test was used for comparisons of categorical variables and followed by Fisher’s exact test when appropriate. Normality was confirmed using the Shapiro-Wilk test in each group. Normally distributed variables are presented as mean ± SD, and non-normally distributed variables (eg, B-type natriuretic peptide, NIRS finding) are presented as a median and interquartile range. Normally distributed variables were compared using the Student t test, whereas non-normally distributed variables were compared using the Mann–Whitney U test. To compare continuous variables among the HF with reduced ejection fraction, HF with preserved ejection fraction, and control subjects, the Kruskal–Wallis test was used. Correlations between each NIRS finding and physiological questionnaire were assessed using Spearman’s correlation analysis. We used simple linear regression to identify potential confounding variables, and those with a P < 0.05 were included in the final multiple linear regression model. A P value of <0.05 was considered statistically significant for all comparisons. All analyses were performed using a statistical software package (SPSS version 24.0, IBM, Armonk, NY).

Results
The comparisons of clinical features between the control subjects and patients with HF in the present study are shown in Table 1. B-type natriuretic peptide was significantly higher, and hemoglobin, estimated glomerular filtration rate, and left ventricular ejection fraction were significantly lower in the patients with HF than in the control subjects. In addition, we found no significant difference in age, sex, percutaneous oxygen saturation, or medication, except for inotropic agents, between the 2 groups. Regarding psychological testing, VFT and MMSE were significantly lower, and STAI-S was significantly higher in the patients with HF than in the control subjects. In contrast, CES-D and STAI-T did not significantly differ between the groups.

Changes in mean oxyhemoglobin concentrations in the HF and control groups are shown in Figure 1. The horizontal axis represents time, and the vertical axis represents changes in mean oxyhemoglobin concentrations (mM-mm) during VFT. Figure 2 shows a topographic map of the differences in mean oxyhemoglobin concentrations. The mean oxyhemoglobin concentrations of right temporal lobe (channels 2, 13, 14, 32, 34, 35, 43, and 45), left temporal lobe (channels 8, 10, 18–21, 29–31, 39–42, and 50–52) and frontal region (channels 25–28, 36, 38, 46, 47, and 49) were significantly lower in the HF group than in the control subjects.

Next, we focused frontal and temporal brain activity (integral values of mean oxyhemoglobin concentrations in the frontal region and temporal lobes). Frontal and temporal brain activity was compared between the groups and are
presented in Figure 3. Frontal and temporal brain activity were significantly lower in both the HF with reduced ejection fraction and HF with preserved ejection fraction than in the control subjects. In the multiple regression analysis to determine brain activity confounding factors (Table 2), HF was independently associated with frontal brain activity (β=−0.556, \(P<0.001\)) and temporal brain activity (β=−0.499, \(P=0.003\)). In addition, as shown in Table 3, there were significant correlations between frontal brain activity and STAI-S (\(R=−0.228, \(P=0.046\)), MMSE (\(R=0.414, \(P=0.017\)), and VFT (\(R=0.338, \(P=0.007\)), but not with CES-D and STAI-T. On the other hand, there was no significant correlation between temporal brain activity and CES-D, STAI-S, or MMSE, except for VFT (\(R=0.330, \(P=0.008\)).

Table 1. Comparisons of Clinical Features Between the Control Subjects and Patients With Heart Failure

|                         | Control Subjects (n=28) | Patients With Heart Failure (n=35) | \(P\) Value |
|-------------------------|-------------------------|-----------------------------------|-------------|
| Demographic data        |                         |                                   |             |
| Age, y                  | 70.5±9.3                | 70.6±8.8                          | 0.975       |
| Male sex, n (%)         | 22 (78.6)               | 21 (60.0)                         | 0.116       |
| NYHA Class 1/2/3/4, n (%)| ...                    | 21 (60.0)/14 (40.0)/0/0           |             |
| Ischemic/nonischemic, n (%)| ...                    | 17 (48.6)/18 (51.4)               |             |
| HFrEF/HFpEF, n (%)      | ...                    | 24 (68.6)/11 (31.4)               |             |
| Comorbidity             |                         |                                   |             |
| Hypertension, n (%)     | 22 (78.6)               | 21 (60.0)                         | 0.116       |
| Diabetes mellitus, n (%)| 9 (32.1)                | 19 (54.3)                         | 0.079       |
| Dyslipidemia, n (%)     | 23 (82.1)               | 27 (77.1)                         | 0.626       |
| Atrial fibrillation, n (%)| 12 (42.9)              | 11 (31.4)                         | 0.349       |
| Laboratory data         |                         |                                   |             |
| Left ventricular ejection fraction, % | 61.6±9.3                | 37.4±13.1                         | <0.001      |
| B-type natriuretic peptide, pg/mL* | 50.8 (12.1–108.2)       | 346.6 (133.7–650.9)              | <0.001      |
| Hemoglobin, g/dL        | 12.9±1.6                | 12.0±2.1                          | 0.045       |
| eGFR, mL/min per 1.73 cm² | 56.2±13.3              | 44.5±16.3                         | 0.003       |
| \(\text{SpO}_2\)        | 96.9±1.5                | 97.1±1.2                          | 0.412       |
| Medication              |                         |                                   |             |
| RAS inhibitor, n (%)    | 20 (71.4)               | 24 (68.6)                         | 0.806       |
| Calcium channel blocker, n (%) | 14 (50.0)             | 15 (42.9)                         | 0.572       |
| \(\beta\)-Blocker, n (%)| 18 (64.3)               | 24 (68.6)                         | 0.720       |
| Inotropic agent, n (%)  | 0                      | 11 (31.4)                         | <0.001      |
| Statin, n (%)           | 17 (60.7)               | 19 (54.3)                         | 0.608       |
| Antidiabetic agents, n (%)| 8 (28.6)               | 15 (42.9)                         | 0.242       |
| Antiplatelet agent, n (%)| 13 (46.4)              | 15 (42.9)                         | 0.777       |
| Anticoagulant, n (%)    | 11 (39.3)               | 18 (51.4)                         | 0.337       |
| Psychological testing   |                         |                                   |             |
| VFT                     | 11.1±4.6                | 8.6±2.9                           | 0.010       |
| CES-D                   | 10.2±9.6                | 11.6±8.0                          | 0.566       |
| STAI-S                  | 29.7±11.3               | 42.1±9.6                          | 0.043       |
| STAI-T                  | 39.0±9.3                | 40.5±10.7                         | 0.560       |
| MMSE                    | 28.4±1.4                | 26.4±3.0                          | 0.019       |

CES-D indicates Center for Epidemiologic Studies Depression Scale; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; MMSE, Mini-Mental State Examination; NYHA, New York Heart Association; RAS, renin-angiotensin- system; \(\text{SpO}_2\), percutaneous oxygen saturation; STAI-S, State-Trait Anxiety Inventory–State; STAI-T, State-Trait Anxiety Inventory–Trait; VFT, verbal fluency task.

*Data are presented as median (interquartile range).
Discussion

In the present study, NIRS was used to evaluate the brain activity of HF patients. NIRS showed that frontal and temporal brain activity (an increase in cerebral oxyhemoglobin concentration in the frontal region and temporal lobes in response to the VFT), cognitive function (MMSE), and language ability (VFT) were lower, and anxiety status (STAI-S) was higher in the patients with HF compared with the control subjects, despite no significant differences in SpO2 and depressive symptoms (CES-D) between the 2 groups. In addition, frontal brain activity was associated with STAI-S, MMSE, and VFT but not with CES-D and STAI-T. To the best of our knowledge, the current study appears to be the first to evaluate brain activity and psychological status in patients with HF using NIRS.

Regional CBF reduction in patients with HF appears in multiple brain sites, and those regions include vascular beds over the frontal, parietal, and occipital cortices, as well as the hippocampus, thalamus, and cerebellar areas; the majority of these brain sites also show brain tissue injury, as reported by previous studies using functional MRI. HF induces brain structural abnormalities that are associated with depressive symptoms and cognitive impairment. Multiple brain autonomic regulatory sites have been reported to show reduced CBF in patients with HF and include the hippocampus, thalamus, corona radiata, and cerebellar sites. The affected structures also show abnormal functional MRI signal responses to autonomic and cardiovascular challenges in HF. In the present study, with NIRS, mean oxyhemoglobin concentrations were lower in the HF group than in the control group in many of the 52 channels. The decrease in the mean oxyhemoglobin concentration in the frontal region was similar to the results seen in patients with depression. Frontal hypoperfusion and frontal dysfunction have been observed in patients with depression, which may be further associated with cognitive impairment.

With respect to mood disorder, brain sites associated with mood regulation include the prefrontal cortex, cingulate, insula,
hippocampus, amygdala, and cerebellar areas.19 These brain sites have been associated with injury in patients with depression only54; however, the majority of these areas also showed reduced CBF in HF patients.20 The amygdala is also involved in anxiety regulation, and the bilateral amygdalae showed reduced CBF.20 In addition, amygdala–prefrontal cortex functional connectivity (ie, impaired frontal brain activity and relative overactivity of the amygdala) are reported to be associated with anxiety symptoms.55,56 Reduced CBF in these regions likely contributes to tissue changes and thus has the potential to modify levels of depressive and anxiety symptoms in patients with HF. A decrease in the oxyhemoglobin concentration with NIRS reflects a decrease in frontal brain function in patients with depression or in a depressed state.48,49 Although we could not fully explain the reason why frontal brain activity determined by NIRS was associated with anxiety status (STAI-S) but not with depression (CES-D), diagnostic sensitivity of CES-D may have affected these results. Since patients with diagnosed

Figure 2. Topographic map of the differences in mean oxyhemoglobin concentration changes between the HF and control subjects. The mean oxyhemoglobin concentrations of right temporal lobe (channels 2, 13, 14, 32, 34, 35, 43, and 45), left temporal lobe (channels 8, 10, 18–21, 29–31, 39–42, and 50–52) and frontal region (channels 25–28, 36, 38, 46, 47, and 49) were significantly lower in the HF group than in the control subjects. HF indicates heart failure.

Figure 3. Comparisons of (A) frontal brain activity (integral values of mean oxyhemoglobin concentrations in the frontal region) and (B) temporal brain activity (integral values of mean oxyhemoglobin concentrations in the temporal lobes) between both HFrEF and HFpEF and control subjects. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Table 2. Multiple Regression Analysis to Determine Brain Activity Confounding Factors

| Factors                          | Univariate                  | Multivariate                |
|---------------------------------|-----------------------------|-----------------------------|
|                                 | B Coefficient | P Value | B Coefficient | P Value |
| Frontal brain activity          |               |         |               |         |
| Age                             | -0.109         | 0.413   |               |         |
| Male sex                        | 0.240          | 0.158   |               |         |
| Heart failure                   | -0.599         | -0.001  | -0.556        | <0.001  |
| Hypertension                    | 0.292          | 0.020   | 0.165         | 0.122   |
| Diabetes mellitus               | -0.118         | 0.357   |               |         |
| Dyslipidemia                    | 0.054          | 0.676   |               |         |
| Atrial fibrillation             | 0.128          | 0.316   |               |         |
| Left ventricular ejection fraction | 0.447     | -0.001  | 0.008         | 0.959   |
| B-type natriuretic peptide      | -0.231         | 0.071   |               |         |
| Hemoglobin                      | 0.142          | 0.267   |               |         |
| eGFR                            | 0.151          | 0.237   |               |         |
| SpO₂                            | 0.240          | 0.248   |               |         |
| RAS inhibitor                   | 0.086          | 0.500   |               |         |
| Calcium channel blocker         | 0.054          | 0.673   |               |         |
| β-blocker                       | 0.116          | 0.365   |               |         |
| Inotropics agent                | -0.153         | 0.231   |               |         |
| Statin                          | -0.058         | 0.649   |               |         |
| Antidiabetic agents             | -0.153         | 0.231   |               |         |
| Antiplatelet agent              | -0.138         | 0.280   |               |         |
| Anticoagulant                   | -0.102         | 0.427   |               |         |
| Temporal brain activity         |               |         |               |         |
| Age                             | -0.163         | 0.202   |               |         |
| Male sex                        | 0.206          | 0.106   |               |         |
| Heart failure                   | -0.523         | -0.001  | -0.499        | 0.003   |
| Hypertension                    | 0.258          | 0.041   | 0.149         | 0.192   |
| Diabetes mellitus               | -0.114         | 0.374   |               |         |
| Dyslipidemia                    | 0.125          | 0.331   |               |         |
| Atrial fibrillation             | 0.231          | 0.068   |               |         |
| Left ventricular ejection fraction | 0.381     | 0.002   | -0.014        | 0.930   |
| B-type natriuretic peptide      | -0.042         | 0.745   |               |         |
| Hemoglobin                      | 0.051          | 0.691   |               |         |
| eGFR                            | 0.151          | 0.239   |               |         |
| SpO₂                            | 0.136          | 0.517   |               |         |
| RAS inhibitor                   | 0.081          | 0.530   |               |         |
| Calcium channel blocker         | -0.103         | 0.422   |               |         |
| β-blocker                       | 0.114          | 0.373   |               |         |
| Inotropics agent                | -0.127         | 0.321   |               |         |
| Statin                          | 0.095          | 0.460   |               |         |
| Antidiabetic agents             | -0.124         | 0.332   |               |         |
| Antiplatelet agent              | -0.102         | 0.428   |               |         |
| Anticoagulant                   | -0.184         | 0.149   |               |         |

eGFR indicates estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; RAS, renin-angiotensin system; SpO₂, percutaneous oxygen saturation.
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A recent report showed that the degree of medial temporal lobe atrophy but not white matter lesion load seems to be related to cognitive impairment.59 Concordant with the present study, cerebral oxygenation is correlated with cognitive function assessed by the MMSE in patients with chronic kidney disease.65

Table 3. Correlation Analyses With Integral Values of Mean Oxyhemoglobin Concentrations in the Frontal Region and Temporal Lobes and Physiological Parameters

|                          | Correlation (r) | P Value |
|--------------------------|----------------|---------|
| **Frontal brain activity (frontal region)** |                |         |
| VFT                      | 0.338          | 0.007   |
| CES-D                    | −0.160         | 0.233   |
| STAI-S                   | −0.228         | 0.046   |
| STAI-T                   | 0.001          | 0.995   |
| MMSE                     | 0.414          | 0.017   |
| **Temporal brain activity (temporal lobes)** |                |         |
| VFT                      | 0.330          | 0.008   |
| CES-D                    | −0.252         | 0.059   |
| STAI-S                   | −0.181         | 0.195   |
| STAI-T                   | −0.071         | 0.611   |
| MMSE                     | 0.077          | 0.578   |

CES-D indicates Center for Epidemiologic Studies Depression Scale; MMSE, Mini-Mental State Examination; STAI-S, State-Trait Anxiety Inventory–State; STAI-T, State-Trait Anxiety Inventory–Trait; VFT, verbal fluency task.

depression were excluded, and mean CES-D was low (ie, 10–11), CES-D might not be necessarily appropriate for evaluating depressive symptom in the present study subjects.

With respect to cognitive impairment, patients with HF exhibit patterns of cortical alterations that overlap with cortical atrophy observed in Alzheimer disease, including lateral temporal and parietal regions.45,57–61 Several brain sites including the hippocampus and prefrontal cortex regulate short-term memory and decision making. Higher white matter hyperintensity volume is a risk factor associated with dementia in older community-based residents.62 In subject without HF, increased left ventricular mass index corresponds to altered white matter microstructure, particularly among older adults with clinical symptoms of prodromal dementia.63 Cardiac function determined by compromised global longitudinal strain relates to worse episodic memory among older adults who are free of clinical dementia.64 In previous reports in patients with HF, CBF reductions appeared in the prefrontal cortex, a structure that plays critical roles in cognitive actions including executive decision making.7,8,17,57 HF shows cerebral gray matter loss and is associated with cognitive impairment.45,58 Hippocampal blood flow abnormality is associated with cognitive impairment in patients with HF.60,61 A recent report showed that the degree of medial temporal lobe atrophy determined by MRI was strongly associated with the severity of cognitive impairment, whereas the extent of white matter hyperintensities was similar in patients and controls.59 Medial temporal lobe atrophy but not white matter lesion load seems to be related to cognitive impairment.59 Concordant with the present study, cerebral

Study Limitations
The present study has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients, the present results may not be representative of the general population. Since VFT was used for NIRS testing, HF patients with New York Heart Association class III or IV were not enrolled. Although none of control subjects suffered from HF, most control subjects have hypertension, diabetes mellitus, dyslipidemia, or atrial fibrillation. Thus, patients with HF and control subjects in the present study might not be necessarily representative of a real-world cohort. Second, because NIRS can evaluate only a shallow layer of the brain, deep layers (eg, hippocampus) or detail of regional areas could not be evaluated. Although functional MRI is used to accurately evaluate regional CBF in patients with HF, high costs and a large-scale device or contraindication (eg, implantable device) in MRI interfere with simple and repeatable examination. NIRS is superior to MRI for easy-to-repeat measurements. Third, because of artifact, some NIRS signals in temporal areas could not be fully detected in some study subjects. NIRS signals during VFT may be influenced by skin blood flow. Fourth, although we excluded the presence of carotid artery stenosis or cerebral infarction, there may have been changes in cerebral oxyhemoglobin attributable to arteriosclerotic changes. Fifth, general condition may have affected the results of several physiological tests. Sixth, associations between brain activity determined by NIRS and each score of psychological testing (eg, depression, cognitive function, and anxiety) were roughly examined. These associations might be preliminary data. Therefore, the present results should be viewed as preliminary, and further studies with a larger population are needed.

Conclusions
Frontal brain activity assessed by NIRS was reduced and might be associated with high anxiety status and low cognitive function in patients with HF.

Disclosures
None.

References
1. Easton K, Coventry P, Lovell K, Carter LA, Deaton C. Prevalence and measurement of anxiety in samples of patients with heart failure: meta-analysis. J Cardiovasc Nurs. 2016;31:367–379.
2. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol. 2001;38:199–205.

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3. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006;48:1527–1537.

4. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. J Card Fail. 2005;11:455–463.

5. Angermann CE, Ertl G. Depression, anxiety, and cognitive impairment: comorbid mental health disorders in heart failure. Curr Heart Fail Rep. 2018;15:398–410.

6. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJ, Quinl CJ. Cognitive impairment and heart failure: systematic review and meta-analysis. J Card Fail. 2017;23:464–475.

7. Hajduk AM, Kief CJ, Person SD, Gore JG, Saczynski JS. Cognitive change in heart failure: a systematic review. Circ Cardiovasc Qual Outcomes. 2013;6:451–460.

8. Vogels RL, Scheltens P, Schroder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. Eur J Cardiol. 2007;9:440–449.

9. Alhurani AS, Dekker RL, Abed MA, Khalil A, Al Zaghal MH, Lee KS, Mudd-Martin G, Biddle MJ, Lennie TA, Moser DK. The association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. Psychosomatics. 2015;56:371–380.

10. Sayers SL, Hanrahan N, Kutney A, Clarke SP, Reis BF, Riegel B. Psychiatric comorbidity and greater hospitalization risk, longer length of stay, and higher hospitalization costs in older adults with heart failure. J Am Geriatr Soc. 2007;55:1585–1591.

11. Angermann CE, Gelbrich G, Stork S, Schowalter M, Deckert J, Ertl G. Haider P. Competence Network Heart Failure. Somatic correlates of comorbid major depression in patients with systolic heart failure. Int J Cardiol. 2011;147:66–73.

12. Faris R, Purcell H, Henein MY, Coats AJ. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. Eur J Heart Fail. 2002;4:541–551.

13. Jiang W, Krishnan R, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, Ferrante M, Martsberger C, Arias RM, Fulcher AH, Bonsignore MR, Rabinovici GD, Severson JT, Karlson BK, Poon CW, Konrad C, Ponsik PW; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology, 2012. Eur J Heart Fail. 2012;14:803–869.

14. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Dzau VJ, Facility Task Force on Practice Guidelines. American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–e239.

15. Fujiwara T, Kono S, Katakura K, Abe K, Takahashi A, Gunji N, Yokokawa A, Kawashima K, Suzuki R, Wada A, Miura I, Yabe H, Ohira H. Evaluation of brain activity using near-infrared spectroscopy in inflammatory bowel disease patients. Sci Rep. 2018;8:402.

16. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure: a review. Curr Heart Fail Rep. 2015;12:145–152.

17. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O’Connor CM, Adams KF Jr, Dupree CS, Waugh RA, Bensimhon DR, Gaulden L, Christenson RH, Koch GG, Hinderliter AL. Relationship of depression to death or hospitalization in patients with heart failure. Am J Cardiol. 2009;104:102–108.

18. Roy B, Wada MA, Wang DJJ, Fonarow GC, Harper RM, Kumar R. Reduced regional cerebral blood flow in patients with heart failure. Eur J Heart Fail. 2017;19:1294–1302.

19. Sato Y, Yoshishita A, Kimishima Y, Kiko T, Watanabe S, Kanno Y, Abe S, Miyata M, Sato T, Suzuki S, Okawa M, Kobayashi A, Yamaki T, Kuni H, Nakazato K, Ishida T, Takeishi Y. Subclinical hypothyroidism is associated with adverse prognosis in heart failure patients. Can J Cardiol. 2018;34:80–87.

20. Shaffer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. J Clin Psychol. 2006;62:123–146.

21. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.

22. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1977;106:203–214.

23. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, Califf RM, Krishnan RR, O’Connor CM. Correlates of cognitive impairment among patients with chronic heart failure (from the SADHART-CHF study). Am J Cardiol. 2011;107:545–551.

24. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, Califf RM, Krishnan RR, O’Connor CM. Relationship between depression symptoms and long-term mortality in patients with heart failure. Am J Heart Fail. 2010;15:142–148.

25. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O’Connor CM, Adams KF Jr, Dupree CS, Waugh RA, Bensimhon DR, Gaulden L, Christenson RH, Koch GG, Hinderliter AL. Relationship of depression to death or hospitalization in patients with heart failure. Arch Intern Med. 2007;167:367–373.

26. Celano CM, Villegas AC, Albanese AD, Mckell SE, Gagnon HK, Huffman JC. Depression and anxiety in heart failure: a review. Harv Rev Psychiatry. 2018;26:175–184.

27. Zuccala G, Marzetti E, Cesarì M, Lo Monaco MR, Antonica L, Cocchi A, Carbonin P, Maffeì S. Correlates of cognitive impairment among patients with heart failure: results of a multicenter survey. Am J Med. 2005;118:496–502.

28. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. J Appl Physiol. 2003;95:677–684.

29. Woo MA, Kumar R, Macey PM, Fonarow GC, Harper RM. Brain injury in autonomic, emotional, and cognitive regulatory areas in patients with heart failure. J Card Fail. 2009;15:214–223.

30. Roy B, Wada MA, Wang DJJ, Fonarow GC, Harper RM, Kumar R. Reduced regional cerebral blood flow in patients with heart failure. Eur J Heart Fail. 2017;19:1294–1302.

31. Sato Y, Yoshishita A, Kimishima Y, Kiko T, Watanabe S, Kanno Y, Abe S, Miyata M, Sato T, Suzuki S, Okawa M, Kobayashi A, Yamaki T, Kuni H, Nakazato K, Ishida T, Takeishi Y. Subclinical hypothyroidism is associated with adverse prognosis in heart failure patients. Can J Cardiol. 2018;34:80–87.

32. Shaffer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. J Clin Psychol. 2006;62:123–146.

33. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.

34. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1977;106:203–214.

35. Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, Blazing MA, Gaulden LH, Califf RM, Krishnan RR, O’Connor CM. Prognostic value of anxiety and depression in patients with chronic heart failure. Circulation. 2004;110:3452–3456.

36. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–198.

37. Yoshihisa A, Takiguchi M, Shinzui T, Nakamura Y, Yamauchi H, Iwasa Y, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Okawa M, Kobayashi A, Yamaki T, Sugimoto K, Kuni H, Nakazato K, Suzuki H, Saitoh S, Takeishi Y. Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. Am J Cardiol. 2014;64:256–264.

38. Takahashi A, Kono S, Wada A, Oshima S, Abe K, Inazumi H, Fujita M, Hayashi M, Okai K, Miura I, Yabe H, Ohira H. Reduced brain activity in female patients with non-alcoholic fatty liver disease as measured by near-infrared spectroscopy. PLoS One. 2012;7:e0174169.

39. Abe K, Wada A, Oshima S, Kono S, Takahashi A, Kanno Y, Inazumi H, Hayashi M, Okai K, Miura SI, Yabe H, Ohira H. Reduced frontal activation during verbal
fluency task in chronic hepatitis C patients with interferon-based therapy as measured by near-infrared spectroscopy. *Hepatol Res*. 2017;47:E55–E63.

44. Kakimoto Y, Nishimura Y, Hara N, Okada M, Tani H, Okazaki Y. Intrasubject reproducibility of prefrontal cortex activities during a verbal fluency task over two repeated sessions using multi-channel near-infrared spectroscopy. *Psychiatry Clin Neurosci*. 2009;63:491–499.

45. Almeida OP, Garrido GJ, Beer C, Lautenschlager NT, Arnolda L, Flicker L. Cognitive and brain changes associated with ischaemic heart disease and heart failure. *Eur J Heart Fail*. 2012;14:1769–1776.

46. Suzuki H, Sumiyoshi A, Matsumoto Y, Duffy BA, Yoshikawa T, Lythgoe MF, Yanai K, Taki Y, Kawashima R, Shimokawa H. Structural abnormality of the hippocampus associated with depressive symptoms in heart failure rats. *Neuroimage*. 2015;105:84–92.

47. Ogren JA, Macey PM, Kumar R, Fonarow GC, Hamilton MA, Harper RM, Woo MA. Impaired cerebellar and limbic responses to the Valsalva maneuver in heart failure. *Cerebrellum*. 2012;11:931–938.

48. Matsuo K, Kato T, Fukuda M, Kato N. Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy. *J Neuropsychiatry Clin Neurosci*. 2000;12:465–471.

49. Matsuo K, Kato N, Kato T. Decreased cerebral haemodynamic response to cognitive and physiological tasks in mood disorders as shown by near-infrared spectroscopy. *Psychol Med*. 2002;32:1029–1037.

50. Narita H, Odawara T, Iseki E, Kosaka K, Hirayasu Y. Psychological retardation correlates with frontal hyperperfusion and the Modified Stroop Test in patients under 60-years-old with major depression. *Psychiatry Clin Neurosci*. 2004;58:389–395.

51. Videbech P, Ravnkilde B, Gammelgaard L, Egander A, Clemmensen K, Alosco ML, Hayes SM. Structural brain alterations in heart failure: a review of the literature and implications for risk of Alzheimer’s disease. *Heart Fail Rev*. 2015;20:561–571.

52. Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V, Arai AE, Launer LJ. Cardiac hemodynamics are linked to structural and functional features of brain aging: the age, gene/environment susceptibility (AGES)-Reykjavik Study. *J Am Heart Assoc*. 2015;4:e001294. DOI: 10.1161/JAHA.114.001294.

53. Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B, Schmid E, Colonna I, Hofer E, Mullges W, Ertl G, Heuschmann P, Solymosi L, Schmidt R, Stork S, Stoll G. Cognitive deficits and related brain lesions in patients with chronic heart failure. *JACC Heart Fail*. 2018;6:583–592.

54. Suzuki H, Matsumoto Y, Ota H, Sugimura K, Takahashi J, Ito K, Miyata S, Furukawa K, Arih H, Fukumoto Y, Taki Y, Shimokawa H. Hippocampal blood flow abnormality associated with depressive symptoms and cognitive impairment in patients with chronic heart failure. *Circ J*. 2016;80:1773–1780.

55. Gold AL, Shechner T, Farber MJ, Spiro CN, Leibenluft E, Pine DS, Strauss. Response to learned threat: an fMRI study in adolescent and adult anxiety. *Am J Psychiatry*. 2013;170:1195–1204.

56. Britton JC, Grillon C, Lissek S, Norcross MA, Szuhany KL, Chen G, Ernst M, Nelson EE, Leibenluft E, Shechner T, Pine DS. Response to learned threat: an fMRI study in adolescent and adult anxiety. *Am J Psychiatry*. 2013;170:1195–1204.