



## Impaired frontal brain activity in patients with heart failure assessed by near-infrared spectroscopy

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**Impaired frontal brain activity in patients with heart failure assessed by near-infrared spectroscopy.**

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## **Abstract**

**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 HF patients 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 HF patients.

**Methods and Results:** We measured and compared frontal brain activity determined by NIRS during a verbal fluency task (VFT) in HF patients (n = 35) and control subjects (n = 28). The Center for Epidemiologic Studies Depression Scale (CES-D) for assessment of depressive symptoms, State-Trait Anxiety Inventory (STAI-S) for assessment of anxiety status, and Mini-Mental State Examination (MMSE) 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 vs 88.0 mM·mm,  $P < 0.001$ ). Next, we examined the associations between frontal brain activity and the findings of CES-D, STAI-S, MMSE and VFT. 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 ( $R=-0.160$ ,  $P=0.233$ ).

**Conclusion:** Frontal brain activity assessed by NIRS is reduced, and is associated with high anxiety status and low cognitive function, in HF patients.

## **Introduction**

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,<sup>1-4</sup> and a substantial proportion of HF patients also have coexisting cognitive problems.<sup>5-8</sup> Comorbid mood disorders are associated with increased morbidity, mortality, and medical costs in HF patients,<sup>9-15</sup> but are underdiagnosed and undertreated.<sup>16</sup> Cognitive impairment is one of the most common comorbidities in patients with HF,<sup>8</sup> and is associated with poor quality of life and self-care, as well as increased morbidity and mortality.<sup>7,17</sup>

It has been recently reported that reduced cerebral blood flow (CBF) may be associated with altered autonomic, mood, cognitive regulatory sites, and language and speech regulation sites in HF patients.<sup>18-20</sup> 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,<sup>21</sup> voxel-based-morphometry,<sup>18</sup> quantitative T2-relaxometry<sup>19</sup> and diffusion tensor imaging<sup>22</sup> 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 (oxy-Hb) and deoxyhemoglobin (deoxy-Hb),

with a high time resolution. The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume.<sup>23-25</sup> In addition, oxy-Hb increases and deoxy-Hb decreases in NIRS have been shown to reflect cortical activation by simultaneous measurements with other methodologies,<sup>24</sup> presenting cerebral perfusion and is used as functional brain monitoring.<sup>23</sup> A positive correlation has been confirmed between oxy-Hb concentration by NIRS and blood-oxygen-level-dependent signaling by functional MRI.<sup>26,27</sup> Further, NIRS has recently been used to investigate the neurocognitive processes associated with neurological (Alzheimer's disease, Parkinson's disease, epilepsy, and traumatic brain injury) and psychiatric disorders (depression, bipolar disorder, anxiety disorders, and schizophrenia).<sup>28</sup> 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.<sup>24,29,30</sup> Compared to 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 HF patients 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 HF patients who came to Fukushima Medical University Hospital between May 2018 and June 2019.

The diagnosis of HF was made by several cardiologists based on the HF guidelines.<sup>31,32</sup>

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.<sup>33,34</sup> The control subjects were without history of HF, physical findings of HF, or structural cardiac abnormalities which were detected by echocardiography. The study protocol was approved by the ethical committee of Fukushima Medical University (#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, 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 HF patients.<sup>35</sup> Regarding the psychological testing, the Center for Epidemiologic Studies Depression Scale (CES-D) was used to evaluate depressive symptoms,<sup>36-38</sup> the State-Trait Anxiety Inventory-state (STAI-S) and STAI-trait (STAI-T) were used to evaluate anxiety status and trait,<sup>39</sup> and the Mini-Mental State Examination (MMSE) was used to evaluate cognitive function.<sup>40</sup> We compared the findings of CES-D, STAI-S, MMSE, VFT and NIRS findings between the HF patients 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 (BNP) 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.<sup>35,41</sup> The LVEF was calculated using Simpson's method in a four-chamber view.<sup>35,41</sup> All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc.,



Mountain View, CA, USA). In the present study, HF with LVEF  $\geq 45\%$  was defined as HFpEF, and HF with LVEF  $< 45\%$  was defined as HFrEF.

### **Measurement of NIRS**

A VFT was widely used as an activating task during NIRS analysis as previously reported.<sup>33,34</sup> In the current study, oxy-Hb, deoxy-Hb, and total hemoglobin were measured with a 52-channels NIRS machine (Hitachi ETG4000, Hitachi Medical Corp., Tokyo, Japan) using two wavelengths of near-infrared light (695 and 830 nm). NIRS measurement was performed by attaching 52 channels to the head (**Figure 1**).<sup>29,30</sup> The 52-channel device attached to subjects' foreheads, and the most of lower and forward channels were placed along the line connecting T3-Fpz-T4, based on the international 10-20 system in a sitting position. This 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). 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. Especially, an increase in cerebral oxy-Hb concentration in the frontal region in response

to the VFT is considered as markers of frontal brain activity.<sup>30,42,43</sup> NIRS signal changes were measured during a 10-s pre-task baseline period, a 60-s activation period, and a 55-s post task baseline period. The sampling rate of oxy-Hb concentration data was 0.1 s. The obtained data were analyzed using the “integral mode”: the pre-task baseline was set as the mean over a 10-s period just before the task period, and the post-task baseline was fixed as the mean over the last 5 s of the post-task period. Linear fitting between the pre- and post-task baselines was applied to the data between the two baselines. The average oxy-Hb concentration during the VFT that was performed for 60 s was used for the analysis. An automatic artifact-rejection procedure was used and individual data were excluded when there were fewer than 6 remaining channels from frontal region and bilateral temporal lobes.<sup>30</sup> Data are expressed as waveforms and topographic maps. The Intraclass Correlation Coefficient (ICC) of the mean oxy-Hb concentration during the task segment was calculated for the 52 channels. The single-measure ICC was 0.5309, and the average measure ICC was 0.6936, which are both reliable, as previously reported.<sup>44</sup> 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.<sup>33,34</sup> 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 s. 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-s 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 s. 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 s.

### **Statistical analysis**

Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables and followed by Fisher’s exact test when/if appropriate. Normality was confirmed using the Shapiro-Wilk test in each group. Parametric variables are presented as mean  $\pm$  SD, and non-parametric variables (e.g.

BNP, NIRS finding) are presented as a median and interquartile range. Parametric variables were compared using Student's t-test, whereas non-parametric variables were compared using the Mann-Whitney U test. To compare continuous variable among the HFrEF, HFpEF and control subjects, Kruskal-Wallis test was used. We performed regression analysis to determine brain activity confounding factors. Correlations between each NIRS finding and physiological questionnaire were assessed using Spearman's correlation analysis. A P value of <0.05 was considered statistically significant for all comparisons. All analyses were performed using a statistical software package (SPSS ver. 24.0, IBM, Armonk, NY, USA).

## **Results**

The comparisons of clinical features between the control subjects and HF patients in the present study are shown in **Table 1**. BNP was significantly higher, and hemoglobin, estimated glomerular filtration rate, and left ventricular ejection fraction were significantly lower in the HF patients than in the control subjects. In addition, we found no significant difference in age, sex, percutaneous oxygen saturation or medication, except for inotropic agent, between the two groups. Regarding psychological testing, VFT

and MMSE were significantly lower, and STAI-S was significantly higher in the HF patients than in the control subjects. In contrast, CES-D and STAI-T did not significantly differ between the groups.

Changes in mean oxy-Hb concentrations in the HF and control groups are shown in **Figure 2**. The horizontal axis represents time, and the vertical axis represents changes in mean oxy-Hb concentrations (mM mm) during VFT. **Figure 3** shows a topographic map of the differences in mean oxy-Hb concentrations. The mean oxy-Hb 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 oxy-Hb concentrations in the frontal region and temporal lobes). Frontal and temporal brain activity was compared between the groups and are presented in **Figure 4**. Frontal and temporal brain activity were significantly lower both in the HF<sub>r</sub>EF and HF<sub>p</sub>EF 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 ( $\beta=-0.556$ ,  $p<0.001$ ) and temporal brain activity ( $\beta=-0.499$ ,  $p=0.003$ ). 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 correlations between temporal brain activity and CES-D, STAI-S, or MMSE, except for VFT ( $R=0.330$ ,  $P=0.008$ ).

## **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 oxy-Hb 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 HF patients compared to the control subjects, despite no significant differences in SpO<sub>2</sub> and depressive symptoms (CES-D) between the two 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 HF patients using NIRS.

Regional CBF reduction in HF patients 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.<sup>18-20</sup> HF induces brain structural abnormalities that are associated with depressive symptoms and cognitive impairment.<sup>18,45,46</sup> Multiple brain autonomic regulatory sites have been reported to show reduced CBF in HF patients, 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.<sup>47</sup> In the present study, with NIRS, mean oxy-Hb concentrations were lower in the HF group than in the control group in many of the 52 channels. The decrease in the mean oxy-Hb concentration in the frontal region was similar to the results seen in patients with depression.<sup>48,49</sup> Frontal hypoperfusion and frontal dysfunction have been observed in patients with depression,<sup>50,51</sup> which may be further associated with cognitive impairment.<sup>52,53</sup>

With respect to mood disorder, brain sites associated with mood regulation include the prefrontal cortex, cingulate, insula, hippocampus, amygdala, and cerebellar areas.<sup>19</sup> These brain sites have been associated with structure change in patients with depression only;<sup>54</sup> however, the majority of these areas also showed reduced CBF in HF patients.<sup>20</sup> The amygdala is also involved in anxiety regulation, and the bilateral amygdalae showed reduced CBF.<sup>20</sup> In addition, prefrontal cortex is related with amygdala

mutually, and might be associated with anxiety symptoms.<sup>55,56</sup> Reduced CBF in these regions likely contributes to tissue changes, and thus, has the potential to modify levels of depressive and anxiety symptoms in HF patients. A decrease in the oxy-Hb concentration with NIRS reflects a decrease in frontal brain function in patients with depression or in a depressed state.<sup>48,49</sup> 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 depression were excluded, and mean CES-D was low (i.e. 10-11), CES-D might not be necessarily appropriate for evaluating depressive symptom in the present study subjects.

With respect to cognitive impairment, HF patients exhibit patterns of cortical alterations that overlap with cortical atrophy observed in Alzheimer's disease, including lateral temporal and parietal regions.<sup>45,57-61</sup> Several brain sites including the hippocampus and prefrontal cortex regulate short-term memory and decision-making. Higher white matter hyperintensity volume is risk factors associated with dementia in older community-based residents.<sup>62</sup> 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.<sup>63</sup> Cardiac function determined by



compromised global longitudinal strain relates to worse episodic memory among older adults who are free of clinical dementia.<sup>64</sup> In previous reports in HF patients, CBF reductions appeared in the prefrontal cortex, a structure which plays critical roles in cognitive actions including executive decision-making.<sup>7,8,17,57</sup> HF show cerebral grey matter loss, and is associated with cognitive impairment.<sup>45,58</sup> Hippocampal blood flow abnormality associated with cognitive impairment in HF patients.<sup>60,61</sup> Resent report presented that the degree of medial temporal lobe atrophy determined by magnetic resonance imaging was strongly associated with the severity of cognitive impairment, whereas the extent of white matter hyperintensities was similar in patients and controls.<sup>59</sup> Medial temporal lobe atrophy but not white matter lesion load seems to be related to cognitive impairment.<sup>59</sup> Concordant with the present study, cerebral oxygenation is correlated with cognitive function assessed by MMSE in patients with chronic kidney disease.<sup>65</sup>

### **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. Second, since NIRS can evaluate only a shallow

layer of the brain, deep layers (e.g. hippocampus) or detail of regional areas could not be evaluated. Although functional MRI is used to accurately evaluate regional CBF in HF patients, high costs and a large-scale device or contraindication (e.g. 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 presence of carotid artery stenosis or cerebral infarction, there may have been changes in cerebral oxy-Hb due 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 (e.g. depression, cognitive function and anxiety) were roughly examined. These associations might be preliminary data. Mechanistic 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 HF patients.

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## **Figure legends**

### **Figure 1**

The 52-channel device attached to subjects' foreheads, and the most of lower and forward channels were placed along the line connecting T3-Fpz-T4, based on the international 10-20 system in a sitting position.

### **Figure 2**

Comparison of changes in mean oxy-Hb concentrations in the heart failure (red) and control subjects (blue).

### **Figure 3**

Topographic map of the differences in mean oxy-Hb concentration changes between the HF and control subjects. The mean oxy-Hb 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.

### **Figure 4**

Comparisons of frontal brain activity (integral values of mean oxy-Hb concentrations in the frontal region) and temporal brain activity (integral values of mean oxy-Hb concentrations in the temporal lobes) between both HFrEF and HFpEF, and control subjects.

**Table 1. Comparisons of clinical features between the control subjects and heart failure patients**

	<b>Control subjects (n=28)</b>	<b>Heart failure patients (n=35)</b>	<b>P-value</b>
<b>Demographic data</b>			
Age (years)	70.5 ± 9.3	70.6 ± 8.8	0.975
Male gender (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/ non-ischemic (n, %)	-	17 (48.6)/ 18 (51.4)	
HFrEF/ HFpEF (n, %)	-	24 (68.6)/ 11 (31.4)	
<b>Co-morbidity</b>			
Hypertension (n, %)	22 (78.6)	21 (60.0)	0.116
Diabetes (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
<b>Laboratory data</b>			
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/1.73 cm <sup>2</sup> )	56.2 ± 13.3	44.5 ± 16.3	0.003
SpO <sub>2</sub>	96.9 ± 1.5	97.1 ± 1.2	0.412
<b>Medication</b>			
RAS inhibitor (n, %)	20 (71.4)	24 (68.6)	0.806

Calcium channel blocker ( <i>n</i> , %)	14 (50.0)	15 (42.9)	0.572
Beta blocker ( <i>n</i> , %)	18 (64.3)	24 (68.6)	0.720
Inotropic agent ( <i>n</i> , %)	0	11 (31.4)	<0.001
Statin ( <i>n</i> , %)	17 (60.7)	19 (54.3)	0.608
Anti-diabetic agents ( <i>n</i> , %)	8 (28.6)	15 (42.9)	0.242
Antiplatelet agent ( <i>n</i> , %)	13 (46.4)	15 (42.9)	0.777
Anticoagulant ( <i>n</i> , %)	11 (39.3)	18 (51.4)	0.337

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**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

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NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate; SpO<sub>2</sub>, percutaneous oxygen saturation; RAS, rennin-angiotensin-aldosterone system; CES-D, The Center for Epidemiologic Studies Depression Scale; STAI-S, State-Trait Anxiety Inventory-state; STAI-T, State-Trait Anxiety Inventory-trait; MMSE, Mini-Mental State Examination; VFT, verbal fluency task.

§ Data are presented as median (interquartile range).

**Table 2. Multiple regression analysis to determine brain activity confounding factors**

<b>Frontal brain activity</b>	Univariate		Multivariate	
	$\beta$ coefficient	p value	$\beta$ coefficient	p value
Age	-0.109	0.413		
Male gender	0.240	0.158		
Heart failure	-0.599	<0.001	-0.556	<0.001
Hypertension	0.292	0.020	0.165	0.122
Diabetes	-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		
SpO <sub>2</sub>	0.240	0.248		
RAS inhibitor	0.086	0.500		
Calcium channel blocker	0.054	0.673		
Beta blocker	0.116	0.365		
Inotropic agent	-0.153	0.231		
Statin	-0.058	0.649		
Anti-diabetic agents	-0.153	0.231		
Antiplatelet agent	-0.138	0.280		
Anticoagulant	-0.102	0.427		
<b>Temporal brain activity</b>	Univariate		Multivariate	
Factors	$\beta$ coefficient	p value	$\beta$ coefficient	p value
Age	-0.163	0.202		
Male gender	0.206	0.106		
Heart failure	-0.523	<0.001	-0.499	0.003
Hypertension	0.258	0.041	0.149	0.192
Diabetes	-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
SpO <sub>2</sub>	0.136	0.517
RAS inhibitor	0.081	0.530
Calcium channel blocker	-0.103	0.422
Beta blocker	0.114	0.373
Inotropic agent	-0.127	0.321
Statin	0.095	0.460
Anti-diabetic agents	-0.124	0.332
Antiplatelet agent	-0.102	0.428
Anticoagulant	-0.184	0.149

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NYHA, New York Heart Association; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate; SpO<sub>2</sub>, percutaneous oxygen saturation; RAS, rennin-angiotensin-aldosterone system.



**Table 3. Correlation analyses with integral values of mean oxy-Hb concentrations in the frontal region and temporal lobes and physiological parameters**

<b>Frontal brain activity (frontal region)</b>	<b>Correlation</b>	<b>P value</b>
VFT	R=0.338	P=0.007
CES-D	R=-0.160	P=0.233
STAI-S	R=-0.228	P=0.046
STAI-T	R=0.001	P=0.995
MMSE	R=0.414	P=0.017
<b>Temporal brain activity (temporal lobes)</b>	<b>Correlation</b>	<b>P value</b>
VFT	R=0.330	P=0.008
CES-D	R=-0.252	P=0.059
STAI-S	R=-0.181	P=0.195
STAI-T	R=-0.071	P=0.611
MMSE	R=0.077	P=0.578

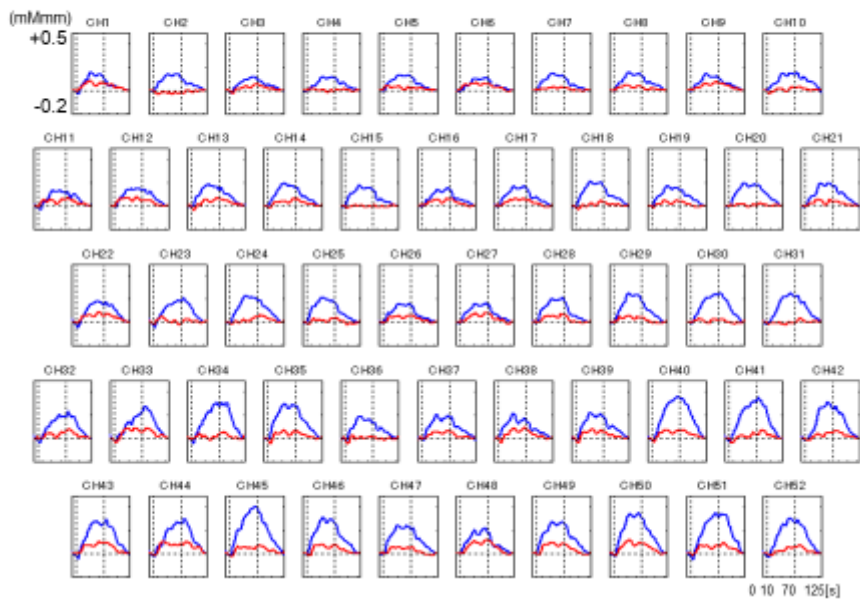
CES-D, The Center for Epidemiologic Studies Depression Scale; STAI-S, State-Trait Anxiety Inventory-state; MMSE, Mini-Mental State Examination; VFT, verbal fluency task.

Figure 1: The setting of NIRS measurement



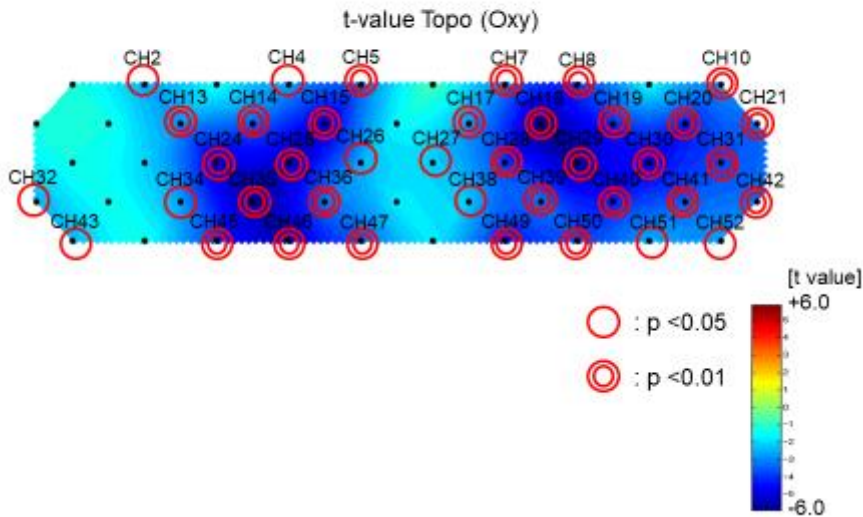
The 52-channel device attached to subjects' foreheads, and the most of lower and forward channels were placed along the line connecting T3-Fpz-T4, based on the international 10-20 system in a sitting position.

Figure 2: Comparison of changes in mean oxy-Hb concentrations in the HF and control subjects Control subjects Heart failure



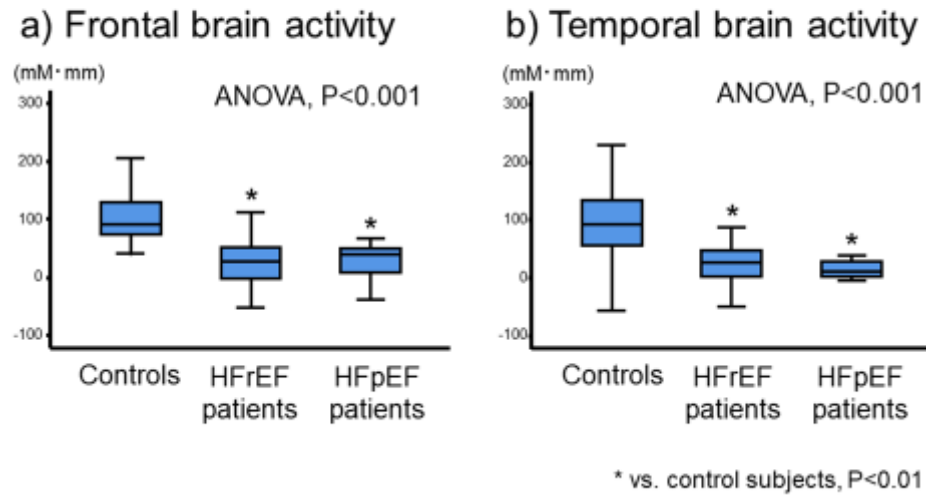
Comparison of changes in mean oxy-Hb concentrations in the heart failure (red) and control subjects (blue).

Figure 3: Topographic map of the differences in mean oxy-Hb concentration changes between the HF and control subjects



Topographic map of the differences in mean oxy-Hb concentration changes between the HF and control subjects. The mean oxy-Hb 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.

Figure 4:  
Comparison of frontal and temporal brain activity  
between HF patients and control subjects



Comparisons of frontal brain activity (integral values of mean oxy-Hb concentrations in the frontal region) and temporal brain activity (integral values of mean oxy-Hb concentrations in the temporal lobes) between both HFrEF and HFpEF, and control subjects.