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Impacts of hippocampal blood flow on changes in left ventricular wall thickness in patients with chronic heart failure

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ABSTRACT

Background: Although depressive symptoms increased mortality and hospitalization in chronic heart failure (CHF) patients, the underlying mechanism remains unclear. The aim of this study was to investigate whether an alteration in hippocampal perfusion, which is the neural substrate of depressive symptoms, is associated with changes in cardiac structures and/or functions in CHF patients.
Methods: We used baseline data of 70 CHF patients (66.8 ± 8.9 yrs, 32.5% women), including cerebral blood flow (CBF) in the hippocampus, geriatric depression scale (GDS) scores and echocardiographic parameters, in the Brain Assessment and Investigation in Heart Failure Trial (B-HeFT) (UMIN000008584). Echocardiography was repeated at 3.1 ± 0.5 years after the baseline evaluation. We first tested voxel-wise regression model with hippocampal CBF as dependent variable and each of echocardiographic parameter change as independent variable, adjusted for age and sex. Structural equation modeling was used to test a mediation effect of cognitive test scores on associations between hippocampal perfusion and changes in cardiac structures and/or functions.
Results: Baseline anterior hippocampal CBF was negatively correlated with changes in left ventricular posterior wall thickness (PWT) ($P < 0.05$ with family-wise error corrections). An existence of depressive symptoms was positively correlated with the baseline anterior CBF and negatively with the PWT changes ($P < 0.05$, both). There were both direct effects of the baseline anterior hippocampal CBF on PWT thinning and effects mediated through the depressive symptoms ($P < 0.05$, both).
Conclusions: This study provides the first evidence that the alteration in hippocampal perfusion may lead to changes in cardiac structures via increase in depressive symptoms in CHF patients.

1. Introduction

Patients with chronic heart failure (CHF) have a high prevalence of depression and cognitive impairment [1,2]. These neuropsychological disturbances in CHF are highly related to structural changes in the brain [3]. One of the neural substrates for depression and cognitive impairment is the hippocampus, which is the important brain region for emotion and memory [4,5]. The hippocampus is one of the regions most vulnerable to hypoxia [6–8] and also is affected by CHF [9–11]. Our previous animal study demonstrated that ischemic CHF causes structural abnormalities of the hippocampus, including changes in neurogenesis, neurite outgrowth and astrocytes number [9]. Hippocampal atrophy and hypoperfusion are correlated with depressive symptoms and memory impairment in CHF patients [10,11]. These evidence indicate that CHF may lead to depression and cognitive impairment via abnormalities of the hippocampus.

Oppositely, depression and cognitive impairment are associated with worse prognosis of CHF. People with depression had more than a 2-fold higher risk of developing heart failure relative to those without it [12]. Increased mortality and hospitalization are noted in CHF patients with depression or cognitive decline [2,13]. Thus, there may be a heart-brain axis between CHF and depression and/or cognitive impairment, where the one side exacerbates the other and vice versa [14]. However, the mechanism of worse CHF outcomes from depression and cognitive impairment, which relate to hippocampal abnormalities [10,11], remains unclear.

Our previous Brain Assessment and Investigation in Heart Failure Trial (B-HeFT) acquired cross-sectional data of brain MRI, psychological tests and echocardiography to show the involvement of hippocampal abnormalities in depression and cognitive impairment in CHF patients [8,11,15]. This study used longitudinal follow-up data of echocardiography acquired in B-HeFT2 to investigate whether hippocampal CBF was

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associated with changes in cardiac structures and/or functions in CHF patients, and if so, to test whether this association was mediated by depressive symptom and/or cognitive impairment.

2. Methods

2.1. Study participants

We enrolled 40 Stage B and 40 Stage C CHF patients aged 45–90 years from August 2012 to April 2013 as described previously [11]. At baseline, CBF, psychological test scores, echocardiographic parameters and plasma BNP levels were acquired within 6 months in all patients. Echocardiography (N = 70) and plasma BNP measurement (N = 64) were repeated at 3.1 ± 0.5 years after the baseline evaluation. The study protocol was approved by the ethical committee of the Tohoku University Graduate School of Medicine (#2012-2-31, #2015-1-578) and was registered in the University Hospital Medical Information Network as B-HeFT (UMIN000008584) and B-HeFT2 (UMIN000020355).

2.2. Echocardiography

Echocardiography was performed according to the previous study [11]. Left ventricular ejection fraction (LVEF) was assessed using the Simpson's biplane method. LV diastolic diameter (LVDd) and LV posterior-wall thickness (PWT) were obtained from the end-diastolic parasternal long-axis view. Inter- and intra-observer variabilities were 2.07 ± 1.66% and 1.64 ± 1.51% for LVEF, 5.47 ± 2.42% and 1.30 ± 0.89% for LVDd, and 5.54 ± 3.25% and 5.08 ± 2.65% for PWT, respectively. In addition, we also acquired LV systolic diameter (LVDs) and left-atrial diameter (LAD) from the parasternal long-axis view and early to late ventricular filling velocity ratio (E/A), tricupsid regurgitation peak gradient (TRPG) and right-ventricular diameter (RVD) from the apical 4-chamber view.

2.3. Psychological tests

Psychological tests were conducted as the previous study [11,15]. Briefly, the patients underwent the 15-item Geriatric Depression Scale (GDS) and the logical memory subtest of the Wechsler Memory Scale-revised (WMS-R) for assessment of depressive symptoms and memory impairment, respectively. An existence of depressive symptoms and that of memory impairment were defined as 5 or more in GDS score [16] and 11 or less in delayed task score of WMS-R [17].

2.4. Brain MRI recording and pre-processing

CBF images were constructed from pseudocontinuous arterial spin labeling perfusion images (3D fast spin-echo acquisition) using a 1.5-T whole-body MRI system (Signa HDxt, GE Medical Systems, Milwaukee, WI, USA) and an 8-channel NVArray coil (coil selection using head-A) with the following parameters: post-label delay 1.525 s, TR 4.587 s, TE 10.5 ms, spiral readout of 8 arms × 512 samples, axial thickness 4.0 mm, 32 sections, effective resolution 3.49 × 3.49 mm, FOV 240 mm, reconstructed matrix 128 × 128, NEX 3, and acquisition time 4 min 26 s. Each CBF map was normalized to the standard Montreal Neurological Institute space to perform voxel-wise statistical analyses as described previously [11]. The normalized CBF maps were smoothed with an isotropic Gaussian kernel by convolving a 10 mm full width at half maximum and then to produce whole-brain CBF maps. Hippocampal CBF maps were created by excluding regions out of the hippocampus, which was defined according to the Wake Forest University PickAtlas toolbox [11,18], from the whole-brain CBF maps.

2.5. Statistical analysis

To test a possible association between baseline hippocampal CBF and changes in cardiac structures and/or functions, we mapped hippocampal regions, where their baseline CBF was correlated with echocardiographic parameter changes. A voxel-wise regression analysis was conducted using CBF of each voxel inside the hippocampal maps as independent variable and the change in each echocardiographic parameter or plasma BNP level as dependent variable, adjusting for age and sex. We showed both regions exceeding a lenient threshold of $P < 0.05$ uncorrected for multiple comparisons and a conservative threshold of $P < 0.05$ with family-wise error (FWE) corrections. Absolute values of baseline hippocampal CBF within regions of interests (ROIs) ($P < 0.05$ FWE corrected) were calculated and used to depict its scatter plots and regression line with the PWT changes, which showed a significant correlation in the voxel-wise regression analysis.

To investigate whether a possible association of baseline hippocampal CBF with changes in cardiac structures and/or functions was mediated by depressive symptom and/or cognitive impairment, we first tested multivariable models using stepwise variable selection identifying each of the hippocampal CBF in the ROI or the change in echocardiographic parameter or plasma BNP level as the best subset of the covariates associated with cognitive test scores. Statistical significances were set at $P < 0.05$ corrected for multiple testing (uncorrected crude $P < 0.0028$).

Then, structural equation modeling was used to test a possible mediation effect of cognitive test scores on associations of the hippocampal CBF in the ROI with the PWT change. Goodness of model fits were evaluated using root mean square error of approximation, comparative fit index, and Tucker-Lewis index. Statistical significances were set at $P < 0.05$.

3. Results

Participant characteristics in this study are provided in Table 1. Baseline clinical characteristics, psychological test scores, echocardiographic parameters and plasma brain natriuretic peptide levels were comparable between included and excluded participants ($P > 0.05$, all), except for higher hypertensives in the included relative to the excluded group ($P < 0.05$).

3.1. Associations of hippocampal blood flow with cardiac remodeling

To support our primary hypothesis, baseline hippocampal blood flow was significantly associated with changes in PWT (Fig. 1). Baseline anterior hippocampal blood flow was negatively correlated with changes in PWT, while positive correlations of baseline posterior hippocampal blood flow also were found ($P < 0.05$ uncorrected for multiple comparisons, Fig. 1B, C). However, the negative correlations in only limited regions of the anterior hippocampus survived at a significance threshold of FWE-corrected $P < 0.05$ (Fig. 1B–E). A correlation coefficient between the baseline anterior hippocampal blood flow and the PWT changes was −0.452 ($P < 0.001$, Fig. 1F). There was no significant association between baseline hippocampal blood flow and changes in LVEF, LVD and plasma BNP levels (FWE-corrected $P < 0.05$).

3.2. Associations of cognitive test scores with hippocampal blood flow and cardiac remodeling

We next tested associations of baseline GDS and WMS-R scores with the baseline anterior hippocampal blood flow and changes in echocardiographic parameters and plasma BNP levels (Table 2). Of these, baseline higher GDS scores were positively correlated with the baseline anterior hippocampal blood flow and negatively with the PWT changes ($P < 0.05$, both).

Table 1
Participant characteristics.

	Included (N = 70)	Excluded (N = 10)	*P* value
Baseline clinical characteristics			
Age (years)	65.0 ± 10.0	71.5 ± 7.1	0.053
Female (%)	28.6	20.0	0.719
Stage C (%)	50.0	50.0	1.000
Education ≥12 years (%)	85.7	60.0	0.068
Ischemic heart failure (%)	54.3	50.0	1.000
Hypertension (%)	64.3	20.0	0.013
Diabetes (%)	30.0	10.0	0.270
Smoking (%)	61.4	80.0	0.314
Renin-angiotensin system-based inhibitor (%)	94.3	90.0	0.497
Beta-blocker (%)	94.3	90.0	0.497
Baseline psychological test scores			
Higher geriatric depression scale score (%)	32.9	60.0	0.157
Lower delayed recall task score (%)	34.3	40.0	0.734
Baseline echocardiographic parameters and plasma brain natriuretic peptide levels			
Left-ventricular ejection fraction (%)	51.3 ± 16.9	53.1 ± 21.5	0.761
Left-ventricular diastolic diameter (mm)	52.4 ± 7.7	56.1 ± 16.4	0.229
Left-ventricular systolic diameter (mm)	38.6 ± 10.3	41.6 ± 19.1	0.463
Posterior-wall thickness (mm)	9.7 ± 1.9	10.2 ± 2.1	0.409
Left-atrial diameter (mm)	40.5 ± 6.5	43.3 ± 9.1	0.233
Early to late ventricular filling velocity ratio	0.94 ± 0.40	0.94 ± 0.44	0.965
Right ventricular diameter (mm)	28.4 ± 5.4	27.8 ± 3.9	0.723
Tricupsid regurgitation peak gradient (mmHg)	25.9 ± 11.1	30.8 ± 11.9	0.204
Brain natriuretic peptide levels (pg/ml)	107.5 ± 127.5	125.8 ± 92.2	0.664
Changes in echocardiographic parameters and plasma brain natriuretic peptide levels			
ΔLeft-ventricular ejection fraction (%)	−0.1 ± 11.1		
ΔLeft-ventricular diastolic diameter (mm)	−1.2 ± 4.8		
ΔLeft-ventricular systolic diameter (mm)	−0.5 ± 6.2		
ΔPosterior-wall thickness (mm)	−0.2 ± 1.6		
ΔLeft-atrial diameter (mm)	0.7 ± 5.6		
ΔEarly to late ventricular filling velocity ratio	−0.01 ± 0.38*		
ΔRight ventricular diameter (mm)	1.6 ± 4.3		
ΔTricupsid regurgitation peak gradient (mmHg)	0.1 ± 12.4		
ΔBrain natriuretic peptide levels (pg/ml)	28.3 ± 163.6**		

A statistical significance was set at $P < 0.05$.
* N = 54.
** N = 64.

3.3. Modelling hippocampal blood flow, cognitive test score and cardiac remodeling

Finally, we used structural equation modeling to test associations between the baseline anterior hippocampal blood flow, the higher GDS scores and PWT changes (Fig. 2). Apart from a direct effect (standardized estimate 0.344 (95%CI 0.557, 0.123), $P = 0.002$), the association between baseline anterior hippocampal blood flow and LV posterior wall thinning was mediated by an indirect effect of the higher GDS scores (standardized estimate 0.111 (95%CI 0.219, 0.002), $P = 0.046$).

4. Discussion

We have explored hippocampal perfusion associated with echocardiographic changes in CHF patients. Negative correlations between baseline anterior hippocampal blood flow and PWT changes were discovered. The clinical significance of this correlation was supported by the observation that the association of differences in the anterior hippocampal blood flow with the PWT changes was mediated partly by higher GDS scores. Thus, this study indicates that the alteration in hippocampal perfusion, which is a neural substrate for depressive symptoms, may lead to changes in cardiac structures, which related to prognosis in CHF patients [19].

These hippocampal abnormalities were associated with depressive symptoms and cognitive impairment in CHF patients [10,11]. The correlation of lower CBF in the posterior hippocampus with depressive symptoms was found [11]. However, this study showed that higher CBF in the anterior hippocampus was correlated with higher GDS scores. Both the anterior and posterior hippocampus are associated with major depression [20,21]. The mixture of cerebral hyper- and hypoperfusion in depressed patients, including the hippocampal regions, was reported previously [22,23]. Brain hyperperfusion, including the anterior hippocampus, has a positive correlation with total Hamilton Depression Rating Scale score [22]. Inhaled carbon dioxide (CO_2) increases CBF in brain regions including the hippocampus in healthy volunteers [24], while this CO_2-induced cerebrovascular reactivity is impaired in CHF patients [25], which may lead to hippocampal hyperperfusion.

The association of anterior hippocampal hyperemia with PWT thinning was found at least partly through the mediation of depressive symptoms. Depression is an independent risk factor for increased mortality and hospitalization in CHF patients [13]. Associations of depressive symptoms with LV dysfunction and increase in the risk of heart failure onset also are reported in otherwise healthy people [13,26]. These evidence indicate that the hippocampus is a neural substrate for depressive symptoms in CHF patients, which may advance changes in cardiac wall thickness. However, the structural equation model showed that there is also a direct association between hippocampal blood flow and the PWT change without the involvement of depressive symptoms. One possible explanation is low blood levels of brain-derived neurotrophic factor (BDNF). BDNF is a molecule found in high concentration in the hippocampus and is crucial in memory formation, cell proliferation and synaptic plasticity [27]. Blood BDNF levels are positively correlated with hippocampal volume [27] and are associated with cognitive dysfunction in CHF patients [15]. CHF patients with low blood BDNF levels have higher death rate from any cause compared to those with high BDNF levels [28]. These suggest that reduction in blood BDNF levels, which may be associated with altered hippocampal CBF, cause cardiac remodeling in CHF patients. Increased hippocampal CBF is

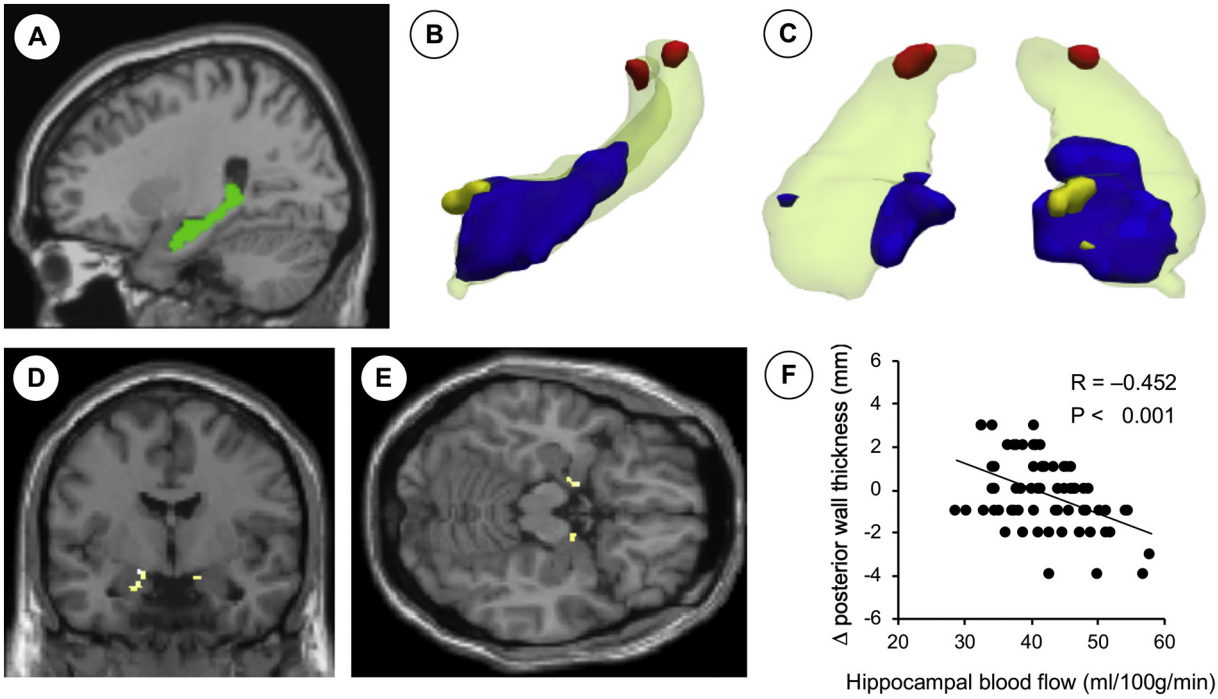

Fig. 1. Associations between baseline hippocampal blood flow and changes in left ventricular posterior wall thickness Representative picture of the hippocampus in a sagittal section (green area, A). D pictures of the hippocampus (green volumes) in lateral (B) and anterior (C) views, including volumes with baseline CBF negatively (blue volumes) and positively (red volumes) correlated with increase in PWT ($P < 0.05$, uncorrected for multiple comparisons). Yellow regions indicate anterior hippocampal regions with baseline CBF negatively correlated with increase in PWT at a significance threshold of $P < 0.05$ with FWE corrections for multiple comparisons in 3D lateral views (B, C) and coronal (D) and axial sections (E). Anterior hippocampal blood flow was negatively correlated with changes in PWT (F). N = 70. Abbreviations: CBF, cerebral blood flow; FWE, family-wise error; PWT, posterior wall thickness.

associated also with the onset of Takotsubo cardiomyopathy [29,30]. Another possible contributor is sleep apnea. Sleep apnea is found in more than half of CHF patients and is associated with worse prognosis [31,32]. Psychiatric disorders, including cognitive impairment and depression, are prevalent among patients with sleep apnea [33–36]. Sleep apnea is also associated with structural brain abnormalities including the hippocampus [37]. The hippocampal damage and cognitive impairment in patients with obstructive sleep apnea could be recovered by treatment with chronic positive airway pressure [38], indicating that these brain structural and functional deficits may be secondary to repetitive nocturnal intermittent hypoxemia. Moreover, electrical stimulation to the limbic structures including the hippocampus induces transient central apnea [39]. This bidirectional relationship between sleep apnea and the hippocampal abnormality may affect the associations among the hippocampal blood flow, depressive symptoms, and PWT changes found in the present study. The mechanism of cardiac structural and functional changes related to hippocampal CBF other than depressive symptoms should be investigated in the future study.

This study has limitations. First, this study had a possible selection bias as we used data of only 70 patients from a single centre. Second, the follow-up of echocardiographic parameters and plasma BNP levels was not designed prospectively [11]. Third, as the participants were recruited for our previous B-HeFT study [8,11,15], sample size calculation was not conducted for the analyses in this study. A future prospective study with a large number of CHF patients is needed to address this issue.

5. Conclusions

This study provided the first evidence that increased hippocampal perfusion is associated with changes in cardiac structures through the mediation of depressive symptoms. Hippocampal perfusion may be an objective imaging marker for the prognosis of CHF patients.

Table 2
Associations of cognitive test scores with anterior hippocampal blood flow and echocardiographic parameters.

	Geriatric depression scale			Delayed recall task		
	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
Associations with hippocampal blood flow						
Hippocampal blood flow (ml/100 g/min)	4.78	2.01, 7.54	0.001	2.56	−0.46, 5.57	0.095
Associations with echocardiographic parameters and brain natriuretic peptide level						
ΔLeft-ventricular ejection fraction (%)	2.50	−3.06, 8.06	0.373	−4.90	−10.2, 0.42	0.070
ΔLeft-ventricular systolic diameter (mm)	−3.10	−3.24, 2.61	0.833	1.28	−1.75, 4.31	0.402
ΔLeft-ventricular diastolic diameter (mm)	1.71	−0.67, 4.09	0.156	0.42	−1.96, 2.81	0.724
ΔPosterior-wall thickness (mm)	−1.25	−2.02, −0.48	0.002	−0.67	−1.46, 0.11	0.092
ΔLeft-atrial diameter (mm)	−0.35	−2.83, 2.13	0.781	−1.21	−3.81, 1.38	0.353
ΔEarly to late ventricular filling velocity ratio	−0.05	−0.28, 0.17	0.639	0.04	−0.18, 0.27	0.718
ΔRight ventricular diameter (mm)	0.92	−1.25, 3.09	0.401	−0.22	−2.38, 1.94	0.843
ΔTricupsid regurgitation peak gradient (mmHg)	2.23	−4.11, 8.58	0.484	−0.18	−6.77, 6.42	0.957
ΔBrain natriuretic peptide levels (pg/ml)	30.5	−57.8, 118.8	0.492	−67.4	−160.0, 25.1	0.150

A statistical significance was set at $P < 0.05$ corrected for multiple testing (uncorrected crude $P < 0.0028$).

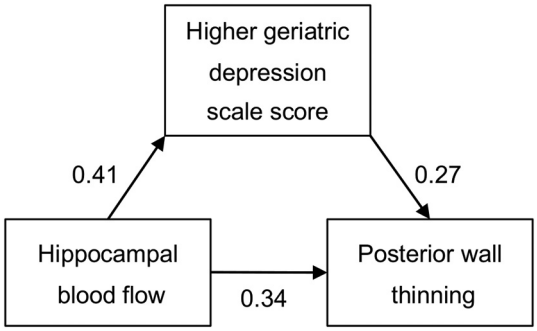

Fig. 2. Structural equation model illustrating associations among baseline anterior hippocampal blood flow, baseline depressive symptoms and left-ventricular posterior wall thinning. Standardized correlation coefficients are shown ($P < 0.05$, all). Root mean square error of approximation < 0.001, comparative fit index = 1.000 and Tucker-Lewis index = 1.000.

CRediT authorship contribution statement

Hideaki Suzuki: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization, Funding acquisition. **Yasuharu Matsumoto:** Resources, Writing - review & editing, Supervision. **Koichiro Sugimura:** Resources. **Jun Takahashi:** Resources. **Satoshi Miyata:** Methodology, Validation. **Yoshihiro Fukumoto:** Resources. **Yasuyuki Taki:** Methodology, Resources, Supervision. **Hiroaki Shimokawa:** Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

None declared.

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