Atrophy of the parahippocampal gyrus is prominent in heart failure patients without dementia

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Abstract

Aims The exacerbation of heart failure (HF) induces brain damage and cognitive impairment (CI), which frequently attenuates the effects of treatment. However, it is not clear whether HF patients without clinical dementia demonstrate increased risk of CI. We examined whether local atrophy in the parahippocampal gyrus, a potential predictor of CI, is prominent in HF patients without clinical dementia.

Methods and results Twenty stable HF patients with a history of admission due to decompensated HF or presentation of apparent pulmonary congestion following chest X-ray and 17 controls were enrolled in this observational, analytical, cross-sectional, case-control study. Patients with dementia were excluded from this study based on the results of cognitive assessment. Three-dimensional T1 weighted magnetic resonance image analysis was performed to evaluate the severity of local brain atrophy using software based on statistical parametric mapping. Z-score values were calculated to evaluate the severity of atrophy in the total brain and parahippocampal gyrus. The severity of total brain atrophy was similar between HF patients (8.0 ± 2.9%) and controls (6.5 ± 3.1%). However, the Z-score was significantly higher in the HF group (1.12 ± 0.49) in comparison with the control group (0.63 ± 0.36, P = 0.002). The Z-score value did not correlate with age, ejection fraction, left atrial dimension, left ventricular dimensions, or brain natriuretic peptides in the HF group but did correlate with the Clinical Frailty Scale.

Conclusions Local atrophy in the parahippocampal gyrus was prominent in HF patients without clinical dementia. This finding showed that HF patients without dementia feature a potential risk for developing CI.

Keywords Heart failure; Cognitive function; Frailty; Brain atrophy; MRI

Introduction

Heart failure (HF) is a progressive disease that incorporates a cycle of repetitive exacerbation, hospitalization, and recovery. During this malignant cycle, patients experience both physical and mental impairments, including depression and various cognitive deficits.[1] Because HF and cognitive impairment (CI) frequently overlap, particularly within ageing populations, HF patients demonstrate a high rate of comorbidity with dementia and CI.[2] HF patients with comorbid CI experience issues with regard to memory, concentration, decision-making, and learning. CI typically reduces adherence, which attenuates the effects of treatment and exacerbates HF, thereby worsening patient's prognosis.[3] However, it remains unclear whether HF patients without a history of CI demonstrate increased risk of developing the condition.

Recent quantitative magnetic resonance imaging (MRI) studies have demonstrated that the volume of the medial temporal lobe, which includes the parahippocampal gyrus, is reduced in patients with CI, especially in Alzheimer's disease.[4] The severity of atrophy in the parahippocampal gyrus increases with the duration of CI. Accordingly, previous publications have indicated that hippocampal atrophy predicts conversion from CI to Alzheimer's disease.[5] Atrophy within the medial temporal lobe and putamen,[6] including the parahippocampal gyrus,[7] has been observed in HF patients with comorbid CI. If morphological changes in the parahippocampal gyrus are detected in HF patients,

particularly those without history of dementia, a future risk of dementia or mild CI (MCI) is possible. However, previous studies have not focused heavily on this matter. Therefore, HF patients without clinical dementia might be at risk of developing the condition.

The aim of this study was to investigate whether local atrophy in the parahippocampal gyrus, a potential predictor of CI, is prominent in HF patients without clinical dementia.

Methods

Subjects

We conducted an observational, analytical, cross-sectional, case–control study at Kaken Hospital. Twenty consecutive HF patients who had previously undergone MRI analysis and had a stable clinical condition were recruited for the present study. All HF patients were diagnosed according to the Framingham criteria.[8] In addition, 17 healthy controls with existing MRI data were recruited for the study at outpatient clinic. Healthy controls denied symptoms and a history of HF and had normal left ventricular function (ejection fraction >0.6). HF patients were required to meet a number of inclusion criteria, including (i) a history of admission due to decompensated HF, or presentation of apparent pulmonary congestion following chest X-ray and (ii) a stable clinical condition. Exclusion criteria were based on (i) active systemic inflammation, (ii) malignant tumour, (iii) active myocarditis, (iv) clinical dementia, (v) moderate to severe CI (Mini-Mental State Examination <24), (vi) mental impairment, (vii) admission to nursing home, and (viii) inability to receive MRI examination. For example, we excluded patients with claustrophobia, implanting metal including implantable cardioverter defibrillator, and artificial pacemaker.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the local institution review board. All patients provided informed consent prior to participating in the study. All patients received optimized standard medical therapy for HF throughout.

MRI analysis

Three-dimensional MRI was employed to analyse morphological changes in the parahippocampal gyrus, using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD)[4]—an MRI analysis technique used to support the diagnosis of Alzheimer's disease by quantifying the severity of atrophy in the parahippocampal gyrus. Three-dimensional T1 weighted, T2 weighted, and diffusion weighted images of the whole brain were obtained using a 1.5 T MRI scanner (EXCELART Vantage, Toshiba medical systems, Japan). The 3D volumetric acquisition of a T1 weighted echo sequence produced a gapless series of thin sections. The acquired images were reformatted to gapless 1.5 mm thick transaxial images. Image analysis was performed to evaluate the severity of local grey matter atrophy using 2 mm voxel-based morphometry with VSRAD-based software (VSRAD plus) based on statistical parametric mapping. Eighty healthy subjects were used as internal controls for VSRAD.

Voxel-based specific regional analysis system for Alzheimer's disease was used to calculate the severity of neural atrophy using a two-step protocol. First, 3D images of each case were normalized in shape and size to standard brain images to adjust for the structural differences of each brain. During the second stage, the images were divided into grey matter, white matter, and cerebrospinal fluid components. The grey matter signal intensity of each voxel was then used to calculate the Z-score with the following equation:

$$Z\text{-score value of each voxel} = ((\text{internal control mean intensity}) - (\text{intensity of each voxel}))/(\text{standard deviation of internal control intensity}).$$

The Z-score of each voxel was used to calculate the severity of local atrophy. The average Z-score of voxels in the volume of interest (VOI) was used to index the severity of atrophy in each region. Selecting the bilateral parahippocampal gyrus as the target VOI, VSRAD was used to evaluate the severity of atrophy in patients. Furthermore, the severity of atrophy in the whole brain was quantified to calculate the total percentage of voxels affected by neuronal atrophy (Z-score > 2). A Z-score map was created from VSRAD data to illustrate the distribution of atrophic regions and the severity of atrophy on normalized brain slices.

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) was performed as a screening test for cognitive function.[9] Originally, the MMSE was developed for the evaluation of cognitive status but is now widely used as a screening test for dementia and other related disorders. The MMSE is designed to evaluate a range of cognitive processes, including orientation of time and place, registration, attention and calculation, recall of name, three-stage command, reading and writing, and construction copying, with a full score of 30. A score under 23 indicates CI. To exclude clinical dementia, only patients with an MMSE score ≥24 were recruited for this study.

Frailty Scale

Frailty, a clinical feature with increased vulnerability result from ageing, associates with CI. Therefore, frailty may

correlate with the severity of neural atrophy in parahippocampal gyrus. The frailty of HF patients and controls was evaluated to clarify the relationship between the severity of neural atrophy and frailty. Frailty was evaluated using the Canadian Study of Health and Aging (CSHA) Frailty Scale[10] (category 1: very fit—robust, active, energetic, well-motivated and fit; category 2: well—without active disease but less fit than people in category 1; category 3: well, with treated comorbid disease—disease symptoms are well controlled compared with those in category 4; category 4: apparently vulnerable—although not frankly dependent, these people commonly complain of being 'slowed up' or have disease symptoms; category 5: mildly frail—with limited dependence on others for instrumental activities of daily living; category 6: moderately frail—help is needed with both instrumental and non-instrumental activities of daily living; category 7: severely frail—completely dependent on others for the activities of daily living, or terminally ill). Using this scale, clinicians can rapidly define the degree of frailty with regard to one of seven phases, wherein a score of 1 indicates that the patient is very fit, and a score of 7 indicates that the patient is severely frail. Patient frailty was evaluated during an interview at the outpatient clinic.

Blood sampling, echocardiography, and brachial-ankle pulse wave velocity measurement

Blood sampling for measuring brain natriuretic peptide (BNP) level, creatinine level, and blood thiamine level, routine two-dimensional echocardiography analysis for evaluating left ventricular function, and brachial-ankle pulse wave velocity (baPWV) measurements for evaluating arterial stiffness were performed as described previously.[11] These measurements were performed under steady-state conditions in patients following an optimized medication regime. Serum BNP level was measured to evaluate severity of HF. Serum creatinine level was measured to evaluate renal function that may be impaired by hypoperfusion and venous congestion. Estimated glomerular filtration rate (eGFR) was calculated by the equation as eGFR (mL/min/1.73 m^3) = 194 × [Age]$^{-0.287}$ × [serum creatinine]$^{-1.094}$ × 0.739 (if female patients). Blood thiamine level was assessed for subjects who did not take vitamin medication or supplements to elucidate whether brain atrophy in HF patients come from low thiamine level. The baPWV was measured to evaluate whether brain atrophy correlates with arterial stiffness. Type of medication was recorded to evaluate patient's background.

Statistics

For data with continuous variables and a normal distribution, values were displayed as mean ± standard deviation. For data with a non-normal distribution, values were displayed as the median and interquartile ranges. A Student's *t*-test was used for the comparison of data between two groups. When the distribution of the data was skewed, a non-parametric test (Wilcoxon rank-sum test) was used to analyse the results. Proportions were compared using the X^2 test and Fisher's exact test. Univariate regression test was performed to investigate the correlation between covariates and *Z*-score. Stepwise multiple regression test was performed to find covariate best predicted *Z*-score, index of brain atrophy. JMP10 software (SAS Institute) was used for statistical analysis. A value of *P* < 0.05 was considered significant.

Results

Patient characteristics

The clinical, laboratory, echocardiographic, and haemodynamic background of HF patients and controls are displayed in *Table 1*. No significant differences were detected with regard to age, gender, body mass index, systolic blood pressure (SBP), and heart rate. However, the HF group featured a lower pulse pressure (PP), left ventricular ejection fraction. and eGFR than the control group. The cardiovascular risk factors, diabetes mellitus, hyperlipidaemia, and smoking, were equally distributed between the groups. All HF patients belonged to the functional class of New York Heart Association II. HF aetiology included ischaemic heart disease (*n* = 3), hypertensive heart disease (*n* = 3), dilated cardiomyopathy (*n* = 8), valvular heart disease (*n* = 3), and three additional conditions.

MRI analysis and local atrophy in parahippocampal gyrus

As shown in the representative case, the distribution of atrophy was scattered throughout the brain (*Figure 1*A). The severity of total brain atrophy (TBA), that is the total percentage of voxels affected by neuronal atrophy (*Z*-score value >2) tended to be higher in the HF group but did not reach statistical significance (*P* = 0.1466, *Figure 1*B).

Local atrophy of the parahippocampal gyrus was prominent in HF patients compared with controls. As shown in the MR images of representative cases, local atrophy in the parahippocampal gyrus was stronger in the HF group (*Figure 2*A). The *Z*-score value for the target VOI (pink circle), in the parahippocampal gyrus (white arrows), was larger in the HF group (1.12 ± 0.49) in comparison with control group (0.63 ± 0.36, *P* = 0.002, *Figure 2*B). However, the *Z*-scores of the target VOI did not reach the levels detected in Alzheimer's disease (*Z*-score value >2). The percentage of voxels affected by atrophy (*Z*-score value >2) in the target VOI, (% voxel atrophy), was larger in the HF group

Table 1 Baseline characteristics of heart failure patients and controls

	Control n = 17	Heart failure n = 20	P value
Age, years, median (IQR)	72 (69–80)	76 (66–81)	0.927
Female/male	11/6	7/13	0.1031
Body height, cm, mean ± SD	155.1 ± 12.6	161.8 ± 10.6	0.0855
Body weight, kg, median (IQR)	55 (49–66)	55 (46–77)	0.9514
BMI, kg/m^2, median (IQR)	23 (21.2–25.1)	23 (18.4–25.3)	0.4738
Systolic blood pressure, mmHg, mean ± SD	139.4 ± 15.5	128.0 ± 19.2	0.0586
Diastolic blood pressure, mmHg, mean ± SD	79.0 ± 9.7	77.0 ± 12.8	0.6021
Pulse pressure, mmHg, mean ± SD	60.4 ± 8.9	50.7 ± 12.4	0.0108
Heart rate, beats/min, mean ± SD	67.0 ± 10.8	72.2 ± 13.4	0.2068
baPWV, cm/s, median (IQR)	1764.5 (1480–2034)	1737.5 (1570–1904)	0.9549
eGFR, mL/min./1.73m^2, median (IQR)	72 (62–75)	47 (24–72)	0.0063
BNP, pg/mL, median (IQR)	34.3 (17.4–42.3)	170.5 (91.0–406.5)	0.0001
Blood thiamine level, ng/mL, mean ± SD	36.8 ± 7.9	34.8 ± 9.5	0.5171
Percentage of low blood thiamine level , %	0	21	
Echocardiographic data			
LVEF, %, median (IQR)	73.9 (63.9–78.9)	46.1(28.8–60.1)	<0.0001
LVEDD, mm, median (IQR)	46.0 (40.3–48.6)	53.1(47.0–57.2)	0.0098
LVESD, mm, mean ± SD	25.7 ± 4.7	39.7 ± 10.2	0.0001
LAD, mm, median (IQR)	37.4 (30.8–44.4)	47.4 (35.8–56.2)	0.0385
MMSE, median (IQR)	29 (27–30)	28 (27–30)	0.3477
Clinical Frailty Scale, median (IQR)	2 (2–3)	4 (3–5)	0.0008
Cardiovascular risk factors			
Smoker, %	29	45	0.4979
Atrial fibrillation, %	18	35	0.2876
Hypertension	94	75	0.1886
Diabetes mellitus, %	29	55	0.1845
Hyperlipidemia	59	45	0.5148
Medications			
Beta-blocker, %	18	80	0.0002
ACE-I or ARB, %	41	80	0.0152
CAB, %	82	45	0.0196
Diuretics, %	6	70	<0.0001
Antiarrhythmic, %	6	20	0.3479
Aldosterone receptor antagonist, %	12	20	0.6665

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BNP, brain natriuretic peptide; CAB, calcium channel blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MMSE, Mini-Mental State Examination; SD, standard deviation.

(11.77 ± 15.58 %) than in the control group (2.08 ± 3.58 %, P = 0.017). The ratio of % voxel atrophy in the target VOI to the total brain was also larger in HF patients (1.86 ± 3.13) than in controls (0.33 ± 0.57, P = 0.045).

Blood thiamine level and Mini-Mental State Examination

Mini-Mental State Examination scores were similar between the HF group and control group (Table 1). Because patients with clinical dementia or an MMSE score of <24 were excluded from the study, the mean MMSE score was 28 (range 26–30) in the HF group and 29 (range 26–30) in the control group. Only one subject scored <27 in the HF group and one in the control group. No difference was detected in blood thiamine levels between the HF and control group (Table 1). One HF patient taking vitamin supplements was excluded from thiamine assessment.

Canadian Study of Health and Aging Frailty Scale

Canadian Study of Health and Aging Frailty Scores (FS) were distributed between 1–4 in controls and 2–6 in HF patients. The mean FS of the HF group was significantly higher than the control group (Table 1). Therefore, frailty was more severe in the HF group compared with controls.

Arterial stiffness and brachial-ankle pulse wave velocity

With regard to baPWV, which denotes the extent of arterial stiffness, no differences were detected between the HF and control group (Table 1). Ankle-brachial pressure index did not differ between HF patients and the control group. Because of atrial fibrillation, four patients in the HF group and one case in the control group were excluded from baPWV measurement.

Figure 1 (A) Scattered grey matter atrophy was detected throughout the whole brain (white arrows) in both heart failure patients and controls. (B) The extent of grey matter atrophy in the heart failure group (solid bar) was similar to that of the control group (open bar).
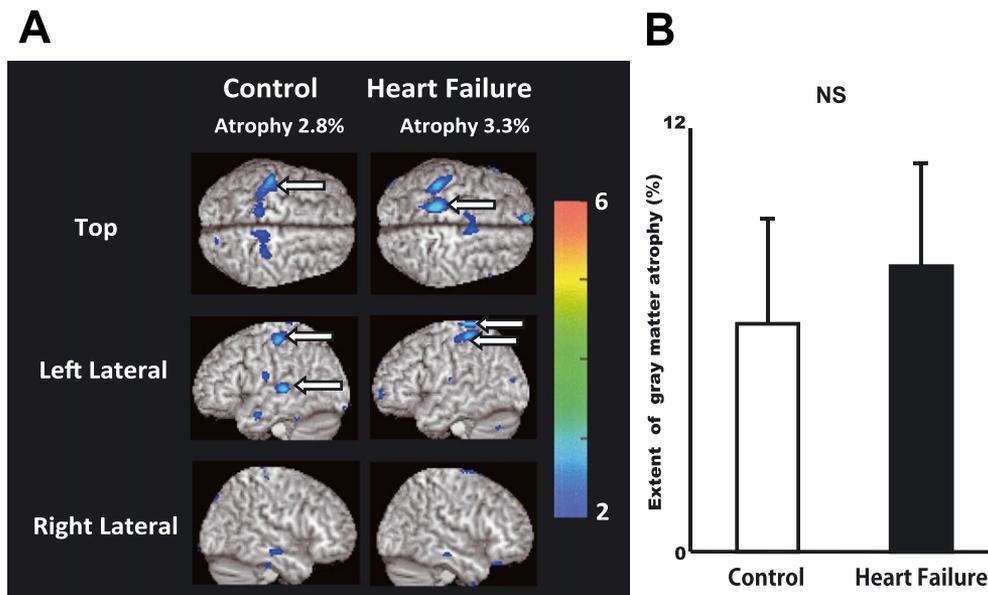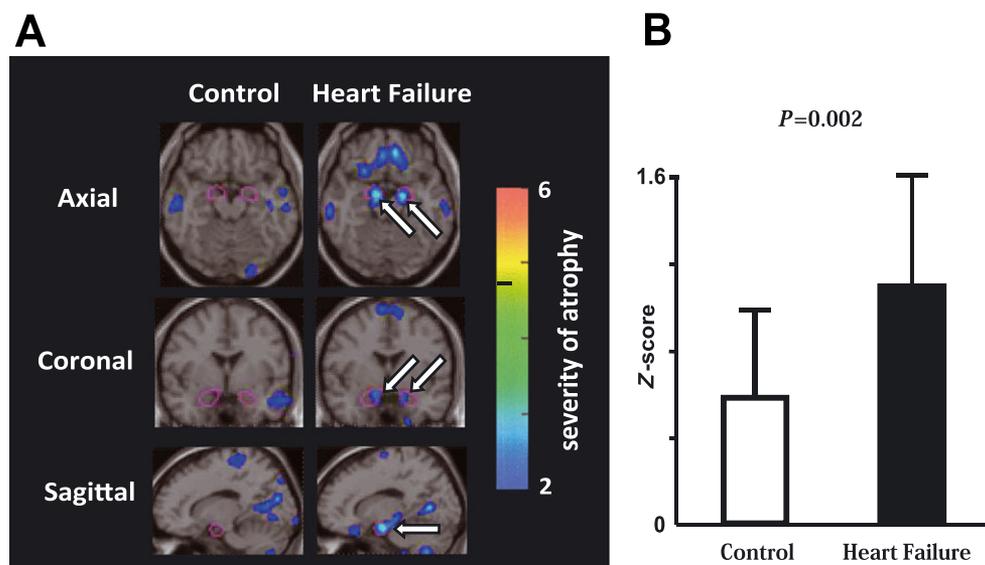

Figure 2 (A) The atrophy of the target volume of interest (pink circle) in the parahippocampal gyrus was prominent (white arrows) in heart failure patients compared with controls. (B) The heart failure group (solid bar) demonstrated more significant atrophy in the parahippocampal gyrus than the control group (open bar).

The correlation between severity of local brain atrophy and background factors

Univariate regression test showed that CSHA FS correlated with the Z-score in HF patients (*Table 2*). Frailty in particular was linked to neural atrophy in the parahippocampal gyrus. The Z-score did not correlate with age, left ventricular ejection fraction, left atrial dimension, left ventricular dimensions, eGFR, MMSE score, SBP, PP, thiamine level, baPWV, or BNP in the HF group. Multivariate stepwise regression analysis showed that FS was the best covariate to predict Z-score in HF patients (*Table 3*). Multivariate stepwise regression analysis showed that HR, left atrial dimension, left ventricular end-diastolic dimension, diastolic blood pressure, baPWV, MMSE, and blood thiamine level were significant covariate to predict Z-score in HF patients.

Table 2 Correlation between *Z*-score and parameters in heart failure patients

	R	*P* value
Age	0.319	0.170
Body height	0.235	0.318
Body weight	0.229	0.331
Body mass index	0.130	0.585
Systolic blood pressure	0.145	0.544
Diastolic blood pressure	0.274	0.243
Pulse pressure	0.037	0.876
Heart rate	0.268	0.254
baPWV	0.217	0.402
eGFR	0.251	0.286
Brain natriuretic peptide	0.308	0.186
Blood thiamine level	0.187	0.442
Echocardiographic data		
LVEF	0.134	0.574
LVEDD	0.031	0.896
LVESD	0.022	0.926
LAD	0.351	0.129
MMSE score	0.111	0.640
Clinical Frailty Scale	0.571	0.009

baPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MMSE, Mini-Mental State Examination.

Discussion

One of the most important findings in this study is that local atrophy of parahippocampal gyrus, a potential risk for CI, is prominent even in HF patients without clinical dementia. The averaged *Z*-score value, severity of atrophy, was higher in parahippocampal gyrus of HF patients than control. The

Table 3 Multivariate stepwise regression analysis of *Z*-score in heart failure patients

	F value	*P* value
Clinical Frailty Scale	328.931	0.00001
Blood thiamine level	222.983	0.00002
MMSE score	208.123	0.00003
Pulse pressure	122.662	0.00010
baPWV	114.382	0.00012
Diastolic blood pressure	36.826	0.00175
LVEDD	35.861	0.00186
LAD	16.238	0.01002
Heart rate	9.084	0.02962
Brain natriuretic peptide	2.995	0.14409
eGFR	2.117	0.21932
LVEF	1.783	0.25274
LVESD	0.941	0.38686
Body weight	0.195	0.68156
Age	0.132	0.73450
Systolic blood pressure	0.120	0.74685
Body height	0.014	0.91277
Body mass index	0.006	0.94184

baPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MMSE, Mini-Mental State Examination.

severity of TBA was generally higher in the HF group compared with the control group. In addition, the severity of atrophy in the parahippocampal gyrus increased with advance of frailty in HF patients. However, the severity of atrophy in the parahippocampal gyrus did not correlate with BNP or ejection fraction in steady-state condition.

Previous studies have found that HF patients frequently exhibit neural atrophy[12] and white matter hyperintensity[13] in multiple brain regions, both of which are typically associated with dementia.[14–16] In these studies, the recruited patients were relatively younger than those examined here, or otherwise included aged HF patients with impaired cognitive function. In contrast, the present study recruited aged HF patients who demonstrated no signs of clinical dementia or MCI, as assessed by the MMSE. The severity of local atrophy in the parahippocampal gyrus was quantified and compared between HF and control groups using the semiautomatic MRI analysis technique VSRAD. Aged HF patients with normal cognitive function were found to exhibit more severe local brain atrophy in the parahippocampal gyrus than controls.

Neural atrophy in the parahippocampal gyrus is known to affect cognitive function. Previous reports using VSRAD have demonstrated that in Alzheimer's type dementia, the *Z*-score of the parahippocampal gyrus reaches more than 2.0.[4] Because we excluded HF patients with dementia and CI, the average *Z*-score of the parahippocampal gyrus was under 2.0 in this study. However, the *Z*-score was significantly higher in the HF group compared with control patients. Previous longitudinal observation studies concerning patients with Alzheimer's disease demonstrated that the severity of atrophy in the parahippocampal gyrus is increased, while the MMSE score decreases with the duration of the disease, reflecting the progressive nature of Alzheimer's disease.[17] While the HF patients assessed did not present with clinical dementia during the study, prominent atrophy in the parahippocampal gyrus might indicate a future risk of dementia for HF patients.

The advantage of voxel-based specific regional analysis system for Alzheimer's disease

VSRAD plus software was used for quantifying the severity of atrophy in the parahippocampal gyrus, calculating the *Z*-score of this region semi-automatically. Because the investigator is unable to change the VOI from the default setting, inter-investigator differences were minimalized and the reproducibility of data was maintained in the present study. VSRAD was originally developed to aid the diagnosis of Alzheimer's disease, wherein previous publications have indicated that VSRAD can be accurately used to differentiate patients with Alzheimer's disease from normal populations.[4,18]

In clinical situations, several examinations are typically used to screen for CI or dementia. However, such

examinations are case sensitive, semi-quantitative, and unable to distinguish patients with an early stage of MCI from normal controls.[3,19] In this study, no significant differences were detected between the MMSE scores of HF patients and the control group. However, a significant difference in the severity of atrophy in the parahippocampal gyrus was found between the HF group and controls. These findings indicate that VSRAD is able to provide useful information for evaluating the potential risk of developing CI for HF patients.

Clinical Frailty Scale

The potential risk of developing CI was found to correlate with the risk of frailty in HF patients. The present study demonstrated that FS was higher in HF patients compared with controls. Moreover, the Z-score of patients with HF, the severity of atrophy in the parahippocampal gyrus, correlated with FS. Multivariate stepwise regression analysis showed that FS was the best covariate to predict Z-score in HF patients. Frailty is a state that typically includes increased vulnerability and loss of physiological reserve. In aged HF patients, physical activity and the activity of daily living are affected by both ventricular function and frailty. In HF patients, the 6-min walk test is useful for evaluating the severity of frailty and its link to cognitive function.[20,21] However, exercise tests including 6-min walk test cannot be performed for some frail patients with lower extremity pain or arthralgia. Although clinical frailty scale is qualitative, this scale might be useful to evaluate frailty of mobility limited HF patients. Previous publications and the present findings suggest that the severity of frailty is a functional consequence of brain atrophy and a potential risk factor for the development of CI in HF patients. Moreover, the present results indicated that HF patients with evidence of brain atrophy might feature a poorer prognosis. Because frailty is an independent predictor of readmission and prognosis,[22] Z-scores might predict the prognosis of HF patients. Further investigation is needed to assess this query.

One can point out that the coefficient R between clinical frailty score and the Z-score is low to express the correlation. Because we excluded HF patients with CI and dementia, degree of parahippocampal gyrus atrophy of our HF patients is distributed in narrow range. Those excluded HF patients would have developed more severe atrophy in parahippocampal gyrus. If so, the coefficient R (0.57) and R^2 (0.33) between clinical frailty score and the Z-score would have been increased. In this study, if we included HF patients with CI and dementia, the R^2 increased from 0.33 to 0.51 (data not shown). Further study using large population is needed to elucidate this query.

Potential mechanism of brain atrophy in HF

The mechanisms underlying the neural atrophy of the parahippocampal gyrus in HF patients were not identified in the present study. Previous reports have indicated that neural atrophy in HF patients might be linked to acute and/or chronic hypoperfusion.[23] This hypothesis was supported by observational studies, in which cognitive dysfunction was improved following the recovery of haemodynamics due to heart transplantation or cardiac resynchronization therapy in HF patients.[24,25]

In this study, none of the patients presented with either severe hypoxia, which usually requires mechanical ventilation, or cardiogenic shock. However, we detected reduced eGFR in the HF group. This might suggest evidence for hypoperfusion and venous congestion during acute HF events.[26] Hypoperfusion, which induces local damage with differing severity in various regions of brain, might explain the scattered distribution of atrophy observed in HF patients in this study. However, previous reports indicate the absence of ischaemic injury in the hippocampus of patients with acute hypoperfusion.[27] Therefore, haemodynamic changes, including hypoperfusion, hypoxia, and venous congestion might induce local atrophy in the parahippocampal gyrus.

Hypoperfusion might produce dementia or CI through several mechanisms.[28] In this study, TBA did not differ between HF patients and controls; however, local atrophy was prominent in the parahippocampal gyrus of HF patients. Therefore, these findings might reflect the pathological neural changes underlying the development of CI or dementia in HF patients. Further study is needed to support this.

Studies indicate that thiamine deficiency might also underlie neural atrophy. Because thiamine is a water-soluble vitamin, previous publications indicate that the long-term use of diuretics might reduce the blood levels of thiamine.[29] However, in this study, the average blood levels of thiamine were similar between the two groups. The normal thiamine level in healthy adults is over 24 ng/mL. In the present study, the percentage of patients with a low thiamine level tends to be higher in the HF group. Therefore, it was not possible to conclude that low thiamine levels were responsible for neural atrophy in all HF patients. Low thiamine levels might play a partial or additional role in the development of neural atrophy in some HF cases.

The present study found no link between arterial stiffness and the severity of neural atrophy in HF patients. Previous publications have suggested a relationship between arterial stiffness and CI, with studies reporting increased arterial stiffness in Alzheimer's type dementia.[30,31] To evaluate the severity of arterial stiffness, baPWV and PP were assessed between the control and HF groups. PP was decreased in the HF group, while baPWV was similar between the groups. These results might be explained by

depressed left ventricular function and relatively low SBP in the HF group.

Limitations

Because of the case-control study with small sample size, it was not possible to produce a precise profile for the HF group and control group in this study. In comparison of two groups, lack of significance for the P value does not mean a lack of difference. Moreover, HF studies using MRI are unable to evaluate patients who cannot undergo MRI evaluation. Therefore, we could not generalize our study results for HF patients with implanted defibrillator and pacemaker. Because patients with evidence of CI (based on MMSE score) were excluded, degree of parahippocampal gyrus atrophy of our HF patients is distributed in narrow range. Therefore, this study might have underestimated the severity of neural atrophy in HF patients. These factors limit the generalization of our findings to all HF patients.

Clinical implication

Because HF patients with CI frequently have a poor prognosis, this study might contribute to the identification of

potential high-risk HF patients using neuroimaging-based diagnostic methods.

Conclusions

In our study, local atrophy in the parahippocampal gyrus, a potential predictor of CI, was prominent in HF patients without clinical dementia. This finding showed that HF patients without dementia feature a potential risk for developing CI.

Conflict of interest

The authors declare no conflict of interest.

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