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Cognitive Deficits and Related Brain Lesions in Patients With Chronic Heart Failure

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ABSTRACT

OBJECTIVES This study sought to determine the spectrum of brain lesions seen in heart failure (HF) patients and the extent to which lesion type contributes to cognitive impairment.

BACKGROUND Cognitive deficits have been reported in patients with HF.

METHODS A total of 148 systolic and diastolic HF patients (mean age 64 ± 11 years; 16% female; mean left ventricular ejection fraction 43 ± 8%) were extensively evaluated within 2 days by cardiological, neurological, and neuropsychological testing and brain magnetic resonance imaging (MRI). A total of 288 healthy, sex- and age-matched subjects sampled from the Austrian Stroke Prevention Study served as MRI controls.

RESULTS Deficits in reaction times were apparent in 41% of patients and deficits in verbal memory in 46%. On brain MRI, patients showed more advanced medial temporal lobe atrophy (MTA) (Scheltens score) compared to controls (2.1 ± 0.9 vs. 1.0 ± 0.6; $p < 0.001$). The degree of MTA was strongly associated with the severity of cognitive impairment, whereas the extent of white matter hyperintensities was similar in patients and controls. Moreover, patients had a 2.7-fold increased risk for presence of clinically silent lacunes.

CONCLUSIONS HF patients exhibit cognitive deficits in the domains of attention and memory. MTA but not white matter lesion load seems to be related to cognitive impairment. (J Am Coll Cardiol HF 2018;6:583–92)

Chronic heart failure (HF) constitutes a serious health care problem with increasing incidence and prevalence. In particular, improved survival after myocardial infarction has contributed to the rise in the prevalence of left ventricular systolic dysfunction (1). Longer-term outcome, quality of life, and health care costs depend not only on left ventricular function but also on the severity of secondary impairment of other organ systems, including the brain (1).

There is consistent evidence that HF patients frequently develop cognitive deficits as disease evolves (2–5). Such impairment may interfere with disease control because HF treatment and monitoring both require a high degree of comprehension, self-control, and adherence to treatment recommendations. In stable HF outpatients, lower left ventricular ejection fraction (LVEF) and deficits in various cognitive domains predicted 1-year mortality risk (3).

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ABBREVIATIONS AND ACRONYMS

6-MWT = 6-min walk test

AF = atrial fibrillation

CI = confidence interval

HF = heart failure

LVEF = left ventricular ejection fraction

MRI = magnetic resonance imaging

MTA = medial temporal lobe atrophy

OR = odds ratio

PVH = periventricular hyperintensity

WMH = white matter hyperintensity

To date, information on the prevalence, type, and severity of cognitive impairment in HF patients is limited. Data on the spectrum of brain lesions that contribute to cognitive dysfunction are particularly sparse (6–9).

In this study we report on the associations between cognitive performance and brain lesions at baseline among patients followed in the prospective Cognition.Matters-HF study. Moreover, the extent of medial temporal lobe atrophy (MTA), white matter hyperintensities (WMHs), and clinically silent lacunes in HF patients were compared with those of an age-matched healthy population sampled from the ASPS (Austrian Stroke Prevention Study) and ASPS-Fam (Austrian Stroke Prevention Family Study) trials (10,11).

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METHODS

STUDY DESIGN AND ETHICAL CONSIDERATIONS. The Cognition.Matters-HF study is an investigator-initiated, prospective monocentric follow-up study. The study protocol was approved by the local ethics committee and complies with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

PATIENT SELECTION CRITERIA. Patients with clinically confirmed chronic HF were eligible. HF was defined according to established criteria in the guidelines of the European Society of Cardiology at the time of study entry (12). Patients with de novo or acutely decompensated HF were not eligible. Other exclusion criteria were a history of clinical stroke, apparent psychiatric disease (including depression or dementia), carotid artery stenosis >50%, or any implant or device impeding brain magnetic resonance imaging (MRI) (Online Table 1).

STUDY FLOW. Figure 1 shows the time schedule of study-related investigations. Echocardiography was used as the initial screening procedure. Baseline investigations (and iterative follow-up examinations after 12, 36, and 60 months) comprised comprehensive evaluation by a cardiologist, neuropsychologist, neurologist, and neuroradiologist. Care was taken to complete all diagnostic procedures per visit within 2 days.

DIAGNOSTIC PROCEDURES. Cardiological evaluation and laboratory. Clinical examination, electrocardiography, echocardiography, 24-h Holter electrocardiography, 24-h blood pressure measurement, and 6-min walk test (6-MWT) were all performed according to standard operating procedures at the Comprehensive Heart Failure Center Würzburg. Blood samples for routine clinical chemistry investigations were tested at the certified facility of the University Hospital Würzburg.

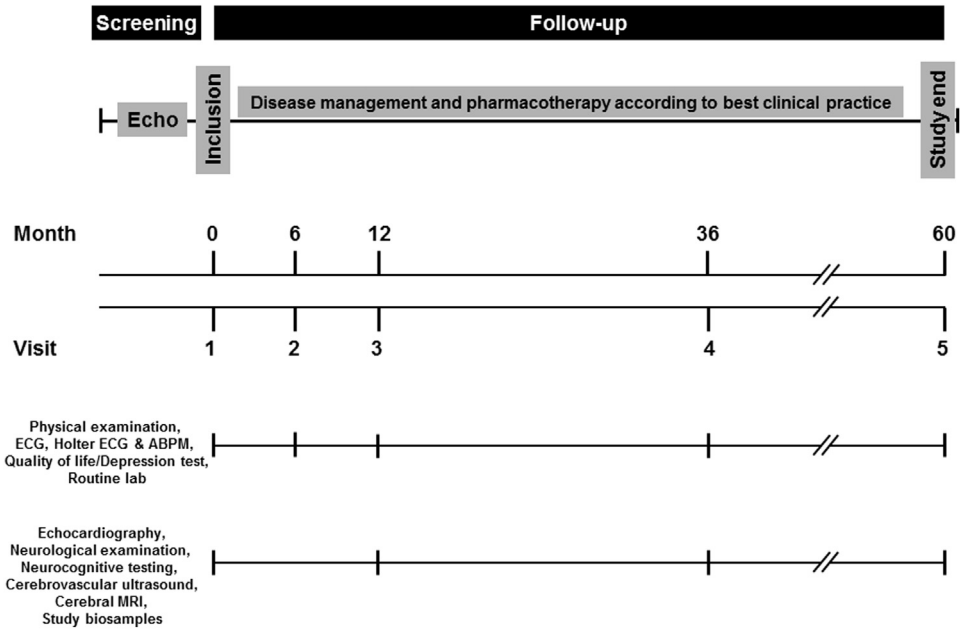
Neuropsychological test battery. All patients completed a comprehensive neuropsychological test battery, which was performed between 9 AM and 11 AM. A detailed description of the test battery is provided in the Online Methods and Online Table 2. The modifying effect of age, sex, and educational level had been investigated in validation studies of these tests in healthy volunteers. Respective influencing factors per test were then considered in the test outputs, which were given by T-standardized values (mean = 50, SD = 10 as mean reference comparator). As such, a T ≤40 indicates performance below average according to the test-specific control group. Reliability of tests ranged between 0.60 and 0.99 (13). Selection of tests was based on taxonomy of attention dimensions from Sturm et al. (14). The applied sequence prevented learning effects by arranging attention tests at the beginning and avoiding the overlap of memory spans and contents. Verbal and visual performances were measured separately within the domains of memory and executive functions.

Neurological examination. The neurological evaluation included clinical examination, Barthel index (15), modified Rankin scale (15), National Institutes of Health Stroke Scale (16), Mini-Mental State Examination (17), and cerebrovascular ultrasound (18) (for details, see the Online Methods).

Cerebral MRI. ***Image acquisition.*** Brain MRI was performed on a 3-T scanner (Siemens MAGNETOM Trio, Siemens Healthcare, Erlangen, Germany) using a 12-channel head coil involving T_1W FLASH, T_1W 3D TFL, T_2W FLAIR, T_2W TSE, DWI, localizers, SV spectroscopy, and ASL perfusion (for detailed protocol and definition of terms, see the Online Methods and Online Table 3).

Image analysis. MRI analysis was performed according to the study protocols of ASPS and ASPS-Fam (10,11). ASPS, commenced in 1991, and its extension ASPS-Fam are prospective single-center community-based studies on the cerebral effects of vascular risk factors in the normal elderly population of Graz, Austria. Images from HF patients were read and documented by an expert neuroradiological reader (B.A.) focusing on brain atrophy, white matter lesions, and brain infarctions. The findings were formally approved by a second senior

FIGURE 1 Study Flow



Time schedule of study flow and examinations of the long-term Cognition.Matters-HF study. ABPM = ambulatory blood pressure monitoring; ECG = electrocardiogram; MRI = magnetic resonance imaging.

neuroradiologist (L.S.) and then compared with the available imaging data of healthy controls.

Cerebral atrophy was rated visually for the inner and outer cerebrospinal fluid space on a scale ranging from 1 to 8. Global cerebral atrophy was defined as the mean of the inner and outer atrophy. Regional MTA, including that of the hippocampus, was rated using the Scheltens score previously established for this purpose, on a scale ranging from 0 (normal) to 4 (severe atrophy) (19,20). For statistical analyses, the mean of both sides (left and right) of the MTA score was used. Mean MTA ≥1.5 in patients younger than 75 years and mean MTA ≥2 in patients older than 75 years were considered pathological (19,20).

To visually quantify lesion load with WMH, we applied the Fazekas and periventricular hyperintensity (PVH) scores ranging from 0 to 3 for both periventricular and deep WMH for each subject on fluid-attenuated inversion recovery sequences (21).

Finally, clinically silent lacunar, hemodynamic, and territorial infarcts were counted. A *clinically silent* infarct was defined as a lesion in a patient without a history of cerebrovascular events, who had a normal neurological examination at study entry.

DATA ANALYSIS. Variables are expressed as mean ± SD for continuous variables and n (%) for categorical variables. Comparisons of independent groups were performed using the Student's *t*-test after analysis of variance or the Fisher exact test, as appropriate. Potential confounders were sought by examining the association of each variable reported in **Table 1** with the presence of neuropsychological outcomes and morphological MRI parameters. For selected comparisons between groups, the odds ratio (OR) with 95% confidence interval (CI) are presented.

The control population available for the matching procedure consisted of 1,378 individuals in total (995 from ASPS and 383 from ASPS-Fam). For each HF patient, 2 control subjects were randomly selected (without replacement procedure) from the control cohorts accounting for sex and age (±2 years). Matching was performed using the function Match from the R library called Matching. From logistic regression models accounting for the matching structure of the sample, conditional ORs with corresponding 95% CIs and p values are reported.

All tests were performed 2-sided, and $p < 0.05$ was considered statistically significant. No adjustment accounting for multiple testing was introduced.

TABLE 1 Baseline Characteristics of the Study Participants (n = 148)

	Study Participants (n = 148)	Controls (n = 284)	p Value
Age (yrs)	65 ± 11	65 ± 10	0.419#
Female	23 (16)	44 (16)	0.999**
Duration of heart failure (yrs)		–	
<2	39 ± 26		
2–5	48 ± 32		
>5	61 ± 41		
Predominant cause of heart failure			
Coronary artery disease	96 (65)		
Dilated cardiomyopathy	20 (14)		
Hypertension	8 (5)		
Other	24 (16)		
NYHA functional class			
I	41 (28)		
II	88 (59)		
III	19 (13)		
IV	0		
Blood pressure (mm Hg)			
Systolic	138 ± 20	143 ± 22	0.034††
Diastolic	81 ± 11	87 ± 10	<0.001††
Heart rate (beats/min)	65 ± 10	67 ± 11	0.012††
LVEF* (%)	43 ± 8		<0.001††
<35	25 ± 17	1.0 ± 0.5	<0.001**
35–44	58 ± 39	2.0 ± 1.0	
≥45	65 ± 44	194.0 ± 98.5	
6-MWT distance (m)	391 ± 99		
≤360	54 ± 38		
361–440	49 ± 35		
≥441	38 ± 27		
Medical history			
Current smoker	23 (16)	46 (16)	0.969**
Myocardial infarction	38 (26)	14 (5)	<0.001**

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Because of the explorative character of the study, we did not consider correction of p values for multiple testing. Therefore, significant results must be interpreted with caution and considered only as hints to possible underlying effects. Statistical analyses were performed using the software package R version 3.1.1 (22).

RESULTS

BASELINE CHARACTERISTICS. One hundred sixty patients were included in the study, but 12 subjects were excluded during baseline work-up because of normalization of LVEF in 2, neurological deficits in 5, neuropsychiatric deficits in 4, and MRI abnormalities in 1. Therefore, data analysis is based on 148 patients (Table 1).

Sixty-five percent of patients had ischemic HF and were moderately symptomatic with New York Heart Association functional class II (59%) or III (13%). Mean LVEF was 43 ± 8%, which is consistent with mild-to-moderate impairment. Mean 6-MWT distance was mildly reduced at 391 ± 99 m. Additional baseline characteristics according to occurrence of atrial fibrillation (AF) and cause of HF are provided in Online Tables 4 and 5, respectively.

Eighty-four percent of patients were receiving HF therapy according to established guidelines at study inclusion (12). Hypertension and diabetes were well controlled according to blood pressure and glycosylated hemoglobin measurements.

NEUROPSYCHOLOGICAL TESTING. A total of 147 patients completed the entire test battery. Table 2 gives the descriptive analyses of neuropsychological tests. Analysis of cofactors (according to Table 1) revealed the following significant results (full analysis provided in Online Table 6).

Attention. The mean T value for reaction time (combined area of *intensity* of attention) was 41.8 ± 7.5 in the total sample; 41% of patients performed below-normal average. In contrast, in the combined area of *selectivity* of attention, only 16% exhibited a below-average result. Worse performance in *intensity* of attention was associated with ischemic cause of HF ($p = 0.037$), higher New York Heart Association functional classification ($p = 0.010$), and shorter 6-MWT distance ($p = 0.027$). Worse performance in *selectivity* of attention was associated with older age ($p = 0.029$), higher prevalence of AF ($p = 0.022$), and higher intake of Coumadin derivatives or direct novel oral anticoagulants ($p = 0.026$).

Short- and medium-term memory. Testing for short- and medium-term memory demonstrated a difference between visual and verbal performance. *Visual* performance was close to the normal average; only 24% of patients performed below average. In contrast, *verbal* memory was slightly more compromised; in total, 46% of patients exhibited abnormal results. Women ($p = 0.04$) and patients with higher heart rate ($p = 0.013$) more frequently performed below average in the combined area of short- and medium-term memory.

Working memory. Combined working memory functions were below average in 25% of patients. Female sex ($p = 0.016$), higher diastolic blood pressure ($p = 0.026$), and shorter 6-MWT distance ($p = 0.028$) predicted abnormal performance in combined working memory functions.

Fluency. Test results for verbal fluency and flexibility and for visual fluency were in the lower normal range; 28%, 26%, and 23% of patients performed below normal average in verbal, visual, and composite variable of fluency, respectively. Patients with

higher systolic (p = 0.043) and diastolic (p = 0.005) blood pressure and shorter 6-MWT distance (p = 0.035) showed a tendency to perform worse in the composite variable of fluency. A lower percentage of abnormal results of domains compared with their composites is caused by selectivity of deficits within different tests.

Pre-morbid intelligence as control variable. Performance was normal or even above average in 94% of patients, indicating that poor performance in specific neuropsychological tests cannot be attributed to low premorbid intelligence.

In summary, the predominantly affected cognitive domains in HF patients at baseline were intensity of attention and verbal memory.

BRAIN IMAGING. Brain MRI could be obtained from 147 participants with HF; 142 patients were compared in a harmonized fashion with 284 age- and sex-matched healthy controls (age 65 ± 10 years; 16% female). For comparison of MTA, only 112 controls were available because of missing data (**Figure 2**). The association of cofactors with parameters given in **Table 1** is fully detail in Online Table 7; only significant influences are discussed here. Interestingly, intake of diverse blood thinners was not associated with structural brain changes.

Severity of MTA. Data on MTA were available for 96% of patients (n = 142) and in 39% of controls (n = 112). Because MTA assessment was available for a smaller group of controls only, we restricted analysis to case and control pairs with available information on MTA. After iterating the matching procedure for MTA assessment, 84 patients (59%) and 108 controls (38%) were available for comparison (24 1:2 and 60 1:1 matched cases and controls). Abnormal values for MTA were found in 63 patients (75%) and 23 controls (21%) (OR: 11.09; 95% CI: 5.64 to 21.78; p < 0.001). HF patients (2.1 ± 1.0) had higher Scheltens scores compared with controls (1.0 ± 0.6) (OR: 5.42; 95% CI: 3.31 to 8.88; p < 0.001). The proportion of abnormal MTA values (75%) as well as the Scheltens score values (2.1 ± 1.0) for all HF patients with available information on MTA were very consistent with these findings.

Older age (p < 0.001) and reduced 6-MWT distance (p < 0.001) were associated with more pronounced MTA in patients. Patients with AF (2.40 ± 0.81) had significantly higher MTA values compared with those without AF (1.96 ± 0.90; p < 0.001). However, when patients with AF were omitted from analysis, the difference in MTA between patients and controls remained (p < 0.001).

Presence and extent of WMH. The overall WMH volume did not differ between groups (OR: 1.01; 95% CI: 0.99 to 1.04; p = 0.429). Although no difference was observed for WMH load equal to Fazekas score of 2 or 3, the prevalence of WMH load of Fazekas score 1 was 2.4-fold higher in patients (OR: 2.35; 95% CI: 1.28 to 4.29; p = 0.006). Only 11.5% of patients versus 21.5% of controls were free of WMH (OR: 2.1; 95% CI: 1.16 to 3.8; p = 0.014).

Overall, older age (p < 0.001), higher systolic blood pressure (p < 0.001), and reduced 6-MWT distance (p = 0.011) were predictors of more pronounced WMH load in HF. Similarly, the prevalence of hypertension (p = 0.016), diabetes (p = 0.038), renal dysfunction (p = 0.021), and diuretic intake (p = 0.017) increased with higher Fazekas score.

Regarding the localization of WMH, however, we found a different distribution in the HF cohort compared with controls, with a relevant increase in PVH lesion load. There was a risk increase for PVH score of 1 by 8.67 (95% CI: 4.19 to 17.91; p < 0.001) and PVH score of 2 or more by 16.22 (95% CI: 6.92 to 37.99; p < 0.001) in patients compared with controls. Older age (p = 0.002), higher systolic blood pressure

TABLE 1 Continued

	Study Participants (n = 148)	Controls (n = 284)	p Value
Comorbidities			
Atrial fibrillation†	32 (22)	12 (4)	<0.001**
Peripheral vascular disease	14 (9)	7 (3)	0.003**
Hypertension‡	118 (80)	203 (72)	0.081**
Diabetes mellitus	44 (30)	35 (12)	<0.001**
HbA_{1c} in all patients (mmol/mol)	44.8 (13.0)	39.1 (8.5)	<0.001#
HbA_{1c} in diabetics (mmol/mol)	58.2 (16.15)	51.9 (14.0)	0.134††
Dyslipidemia	107 (72)	36 (13)	
COPD§	20 (14)		
Anemia‖	21 (14)	12 (4)	<0.001**
Renal dysfunction¶	54 (36)	57 (20)	<0.001**
Uncured malignancy	5 (3)	0 (0)	
Alcohol intake (dpw)	3.75 (6.50)	12.52 (16.70)	0.080††
Current medication			
ACE inhibitor and/or ARB	134 (91)	49 (17)	<0.001**
Beta-blocker	132 (89)	41 (14)	<0.001**
Aldosterone antagonists	55 (37)	2 (1)	<0.001**
Diuretics	99 (67)	25 (9)	<0.001**
Blood thinners			<0.001**
No	18 (12.2)	239 (84)	
Platelet aggregation inhibitors	85 (57.4)	36 (13)	
Coumadin or NOAC	45 (30.4)	9 (3)	

Values are mean ± SD or n (%). *Left ventricular ejection fraction (LVEF) assessed in only 197 controls. †Atrial fibrillation was derived from electrocardiogram or 24-h Holter electrocardiogram. ‡Hypertension: sitting blood pressure >140/90 mm Hg or history of hypertension before the onset of heart failure. §Chronic obstructive pulmonary disease (COPD) according to current guidelines (27). ‖Anemia: hemoglobin <12 g/dl in women and <13 g/dl in men (28). ¶Renal dysfunction: estimated glomerular filtration rate <60 ml/min/1.73 m^2 (29). #Student's *t*-test. **Chi-square test. ††Wilcoxon Mann-Whitney *U* test.

6-MWT = 6-min walk test; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; dpw = drinks per week (1 drink = 0.25 l beer or 0.1 l wine or 2 cl spirits); HbA_{1c} = glycosylated hemoglobin; LVEF = left ventricular ejection fraction; NOAC = novel oral anticoagulant; NYHA = New York Heart Association.

TABLE 2 Neuropsychological Test Results

	T Value in All Patients (N = 148)	Patients With T Value ≤40
Intensity of attention	41.8 ± 7.5	60 (40.5)
TAP alertness md without signal	42.5 ± 8.4	55 (37.2)
TAP alertness md with signal	41.1 ± 7.2	70 (47.3)
Selectivity of attention	47.2 ± 6.7	22 (15.0)
TAP go/no-go	46.0 ± 7.7	31 (20.9)
TAP divided attention	44.4 ± 9.3	33 (22.3)
TAP incompatibility	51.1 ± 11.3	22 (15.0)
Memory (visual/verbal)	45.4 ± 7.9	41 (27.9)
VVM map short-term	48.6 ± 10.7	39 (26.4)
VVM text short-term	42.4 ± 9.9	67 (45.6)
VVM map medium-term	48.2 ± 9.6	26 (17.6)
VVM text medium-term	42.4 ± 10.5	61 (41.5)
Working memory	46.3 ± 8.5	37 (25.2)
WMS-R digit span	45.4 ± 9.8	36 (24.5)
WMS-R block tapping span	47.2 ± 11.2	44 (29.7)
Fluency (visual/verbal)	45.1 ± 7.2	34 (23.1)
RWT fluency	45.3 ± 9.4	41 (27.9)
RWT change of categories	44.3 ± 9.7	50 (34.0)
H5PT	45.5 ± 8.7	38 (25.7)
Pre-morbid intelligence	53.9 ± 8.7	9 (6.1)

Values are mean ± SD or n (%). T value ≤40 indicates performance below average according to test-specific control group.

H5PT = Hamasch 5-Point Test; md = median of the reaction time; RWT = Regensburger Word Fluency Test; TAP = Test Battery of Attentional Performance; VVM = Visual and Verbal Memory Test; WMS-R = Wechsler Memory Scale.

(p = 0.031), higher prevalence of hypertension (p = 0.025), and renal dysfunction (p = 0.002) were associated with higher PVH score in patients with HF.

Clinically silent lacunes and brain infarctions. Patients had a 2.7-fold increased risk (95% CI: 1.48 to 4.79; p = 0.001) for presence of clinically silent lacunes compared with controls.

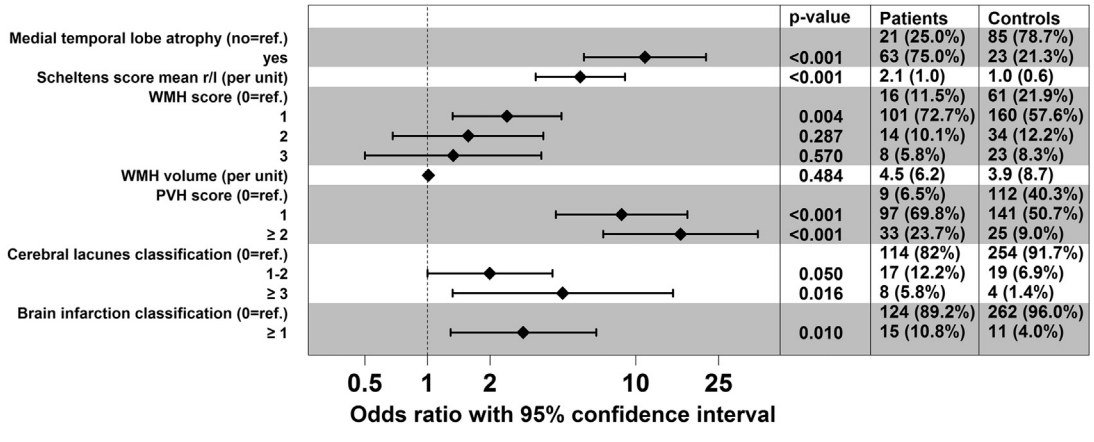
Cofactor analysis revealed that a longer duration of HF (p = 0.024), ischemic cause (p = 0.014), higher systolic blood pressure (p = 0.047), shorter 6-MWT distance (p = 0.041), prevalence of hypertension (p = 0.017), diabetes (p = 0.020), dyslipidemia (p = 0.033), and higher intake of diuretics (p = 0.004) were associated with the presence of lacunes in patients with HF.

Similarly, the risk of having silent brain infarctions increased 3.54-fold (95% CI: 1.62 to 7.71; p = 0.001) in patients versus controls. The number of brain infarctions was also strongly associated with the presence of HF (OR: 2.94; 95% CI: 1.41 to 6.14; p = 0.004).

Cofactor analysis revealed that higher systolic blood pressure (p = 0.011), prevalence of diabetes (p = 0.030), and intake of diuretics (p = 0.034) predicted the presence of silent brain infarctions in patients with HF. AF was not associated with the occurrence of silent lacunes (p = 0.80) or brain infarctions (p = 0.57).

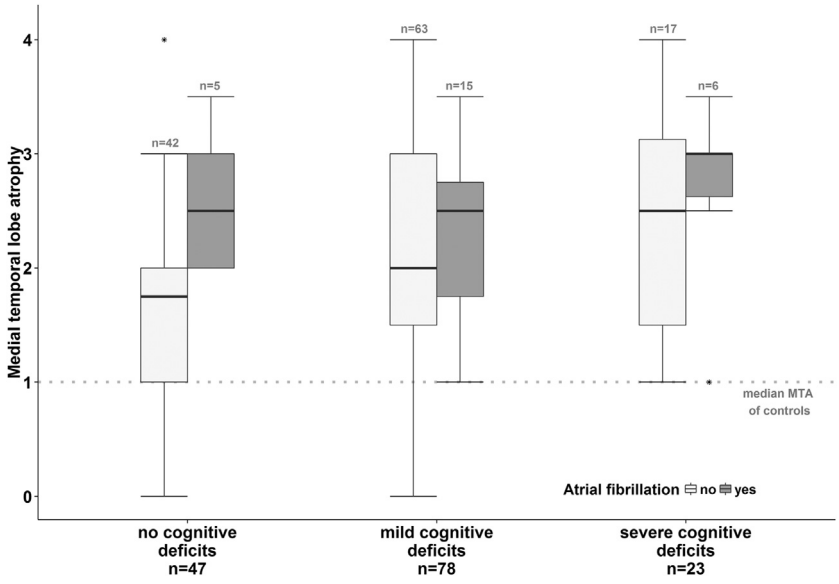
ASSOCIATION OF NEUROCOGNITIVE FUNCTION AND ALTERATIONS ON BRAIN MRI. To further investigate the interrelation between neuropsychological deficits and structural brain abnormalities in HF, we defined 3 groups according to their neuropsychological performance in 5 cognitive domains: group I without any deficits (n = 47 [32%]); group II with slight cognitive deficits performing below average in 1 or 2 domains (n = 78 [53%]); and group III

FIGURE 2 Comparison of Structural Brain Changes in HF Patients and Controls



Forest plot with odds ratio and 95% confidence interval for the presence of structural brain abnormalities in HF patients (n = 142) versus age- and sex-matched controls (n = 284). Reduced numbers are due to missing data in some evaluations. Values are mean ± SD or n (%). HF = heart failure; PVH = periventricular hyperintensity; WMH = white matter hyperintensity.

FIGURE 3 Association of Cognitive Dysfunction With MTA



Comparisons of MTA (box plots) in patients without (group I; n = 47 [32%]; neurocognitive test battery T ≥40 in all 5 domains), with slight (group II; n = 78 [53%]; underperformance in 1–2 domains), and with severe (group III; n = 23 [15%]; underperformance in >2 domains) cognitive deficits. Pronounced MTA was strongly associated with severity of cognitive impairment. This correlation remained unaffected by adjustment for the presence of atrial fibrillation (p = 0.005). *A data point that is located outside the "whiskers" of the boxplot (outside 1.5 times the interquartile range above the upper quartile and bellow the lower quartile). MTA = medial temporal lobe atrophy.

with severe cognitive deficits performing below average in more than 2 domains (n = 23 [15%]).

The extent of MTA advanced with increasing severity of cognitive impairment: mean MTA 1.8 ± 0.8 in group I, 2.1 ± 0.9 in group II, and 2.5 ± 0.9 in group III (p = 0.006). In particular, subnormal performance in the domain of selectivity of attention and visual/verbal memory was strongly associated with advanced MTA (p = 0.02 and p = 0.03, respectively). The correlation between cognitive impairment and the extent of MTA remained unaffected by adjustment for the presence of AF (p = 0.005) (**Figure 3**).

No further associations between overall cognitive impairment and other brain abnormalities, including global cerebral atrophy, became apparent. Only marginal associations were seen between other brain abnormalities on MRI and single cognitive domains (Online Table 8).

DISCUSSION

This study concurrently investigated cognitive domains and brain lesions in patients with mild-to-moderate systolic HF. The principal findings are that HF patients exhibited selective deficits in the domains of attention and verbal memory, and MTA was identified as a probable structural correlate of cognitive impairment.

Cognitive impairment in HF patients as detected by a pathological mini-mental test has been associated with greater overall mortality risk (3). More detailed neuropsychological testing revealed that affected cognitive domains encompass early and delayed recall, learning, recognition, memory, and working memory (2–4). In a cross-sectional study of 50 HF patients and 50 healthy controls, the prevalence of cognitive impairment in HF patients was 46%, at least 4 times more frequent than in controls (4). In our cohort, only 32% of HF patients showed normal performance within all domains of cognition, whereas 16% had severe cognitive impairment. The most pronounced deficits were found in the domain of attention. Interestingly, underperformance in attention tests was strongly associated with severity of HF. In 912 HF outpatients age >70 years, memory impairment (assessed by the delayed-recall Memory Impairment Screen) was present in 46% of subjects and severe memory impairment in 23% (23). In our study, we consistently observed that severity of memory impairment increased with increasing

severity of HF. Coma et al. (24) reported that permanent AF was associated with cognitive impairment in HF. In our study, 22% of HF patients exhibited AF. Accordingly, MTA was on average more pronounced in our patients with AF, but the significant interrelation between MTA severity and cognitive impairment persisted after adjustment for presence of AF. This was also true for the extent of MTA in HF patients without AF compared with controls.

A major strength of our study is that HF patients were examined within 2 days by an interdisciplinary team, thus enabling concurrent investigation of heart and cognitive function as well as structural abnormalities on brain MRI, a methodological element that has been criticized in previous publications (5).

We determined MTA by visual rating applying the Scheltens score (19), which can differentiate between Alzheimer disease patients and control subjects, with sensitivity of 70% to 100% and specificity of 67% to 96% (19). In our study, 75% of HF patients had a pathological Scheltens score compared with only 21% of controls, which is a marked and clinically relevant difference in the average Scheltens score between HF patients and age- and sex-matched controls. Among patients, higher Scheltens scores were associated with worse performance on the 6-MWT, thus hinting at an important relationship among the severity of HF-related physical compromise, brain morphology, and cognitive impairment. Moreover, in our cohort of HF patients, advanced MTA was the only structural MRI parameter that was strongly associated with the severity of overall cognitive impairment, as well as deficits in the domains of selectivity of attention and visual/verbal memory. Interestingly, LVEF as an objective measure of HF severity was not related to cognitive deficits or structural brain changes, but there was a strong association with the clinical degree of HF.

Only a few studies on neuroimaging correlates of cognitive function in HF patients are available. Vogels et al. (25) performed neurocognitive testing in 58 HF patients and calculated correlations between MRI findings and cognitive measures. Similar to our findings, MTA correlated with memory disturbances, poor executive functions, and lower scores of the Mini-Mental State Examination. Interestingly, WMH did not correlate to cognitive measures but to depression and anxiety. We excluded HF patients with depression and anxiety from our study and thus were able to show that WMH did not account for cognitive decline in HF. Both in the study of Vogels et al. (25) and in our study, neither global cerebral atrophy nor PVH was related to overall cognitive impairment. Only impaired selectivity of attention was associated with advanced global cerebral atrophy in our HF patients. However, we cannot exclude that global cerebral atrophy occurred at smaller scales below detectability by visual inspection. Almeida et al. (6) described a relative loss of total gray matter in 35 HF patients compared with adults with ischemic heart disease but normal LVEF.

STUDY LIMITATIONS. Further comprehensive image analyses will be needed to define the extent and dynamics of global cerebral atrophy but were beyond the scope of this large interdisciplinary study, which included multiple clinical, functional, and structural dimensions of the heart and brain.

Older age, higher systolic blood pressure, and presence of renal dysfunction predicted higher PVH burden in our HF cohort. These brain alterations are similar to those described in patients with type 2 diabetes and have been ascribed to reduced cerebral blood flow velocities and decreased resistance in middle cerebral arteries by Novak et al. (26). However, higher PVH score is not the relevant structural MR correlate for cognitive decline in HF patients.

The ongoing Cognition.Matters-HF study will report on structured follow-up examinations after 1, 3, and 5 years and provide further data on the time course of cognitive impairment in HF. Prevention and treatment of this HF complication may improve the overall prognosis of this devastating disease.

CONCLUSIONS

Patients with chronic HF exhibit selective cognitive deficits in the domains of attention and verbal memory. Concomitant MRI suggests MTA is a probable structural correlate of cognitive impairment.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: MTA but not WMH is related to cognitive deficits in patients with HF. Temporal lobe structures are essentially involved in memory and attention, which are predominantly affected in HF. The occurrence of cognitive deficits in HF patients should prompt intensified patient training and supervision programs to enhance adherence to medication.

TRANSLATIONAL OUTLOOK 1: The predefined 3-year follow-up analysis of the Cognition.Matters-HF cohort will provide important information on the dynamics of cognitive decline and concomitant brain alterations in HF patients over time, who already exhibit significant abnormalities at baseline as shown here.

TRANSLATIONAL OUTLOOK 2: An increased knowledge of the dynamics of cognitive decline, its relation to the degree of HF, and the brain areas involved may help to elucidate underlying pathomechanisms and open avenues for treatment of this important comorbidity.

REFERENCES

1. Agrinier N, Thilly N, Briancon S, et al. Prognostic factors associated with 15-year mortality in patients with hospitalized systolic HF: Results of the observational community-based EPICAL cohort study. Int J Cardiol 2017;228:940–7.

2. Festa JR, Jia X, Cheung K, et al. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. Arch Neurol 2011;68:1021–6.

3. Pressler SJ, Kim J, Riley P, Ronis DL, Gradus-Pizlo I. Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. J Card Fail 2010;16:750–60.

4. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. J Card Fail 2009;15:1–10.

5. Hajduk AM, Kiefe CI, Person SD, Gore JG, Saczynski JS. Cognitive change in heart failure: a systematic review. Circ Cardiovasc Qual Outcomes 2013;6:451–60.

6. 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 Heart J 2012;33:1769–76.

7. Almeida OP, Garrido GJ, Etherton-Beer C, et al. Brain and mood changes over 2 years in healthy controls and adults with heart failure and ischaemic heart disease. Eur J Heart Fail 2013;15:850–8.

8. Alosco ML, Brickman AM, Spitznagel MB, et al. Independent and interactive effects of blood pressure and cardiac function on brain volume and white matter hyperintensities in heart failure. J Am Soc Hypertens 2013;7:336–43.

9. Alosco ML, Penn MS, Brickman AM, et al. Preliminary observations on MRI correlates of driving independence and performance in persons with heart failure. Int J Neurosci 2015;125:424–32.

10. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F, Austrian Stroke Prevention Study. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003;361:2046–8.

11. Seiler S, Pirpamer L, Hofer E, et al. Magnetization transfer ratio relates to cognitive impairment in normal elderly. Front Aging Neurosci 2014;6:263.

12. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

13. Schellig D, Drechsler R, Heinemann D, Sturm W. Handbuch neuropsychologischer Testverfahren. Gottingen, Germany: Hogrefe Verlag; 2009.

14. Sturm W, Herrmann D, Wallesch C. Lehrbuch der klinischen Neuropsychologie: Grundlagen, Methoden, Diagnostik, Therapie. Heidelberg, Germany: Spektrum Akademischer Verlag; 2000.

15. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke 1999;30:1538–41.

16. Lyden P, Lu M, Jackson C, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke 1999;30:2347–54.

17. Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. Appl Nurs Res 2000;13:209–13.

18. Uceyler N, He L, Kahn AK, Breunig F, Mullges W, Sommer C. Cerebral blood flow in patients with Fabry disease as measured by Doppler sonography is not different from that in healthy individuals and is unaffected by treatment. J Ultrasound Med 2012;31:463–8.

19. Scheltens P, van de Pol L. Impact commentaries. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 2012;83:1038–40.

20. van de Pol LA, Scheltens P. Medial temporal lobe atrophy scores translated to clinical practice: editorial comment on 'influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs'. J Intern Med 2014;275:331–3.

21. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351–6.

22. Team RC. R: a language and environment for statistical computing. Available at: http://www.R-project.org/. Accessed April 18, 2018.

23. Hanon O, Vidal JS, de Groote P, et al. Prevalence of memory disorders in ambulatory patients aged >/ = 70 years with chronic heart failure (from the EFICARE study). Am J Cardiol 2014;113:1205–10.

24. Coma M, Gonzalez-Moneo MJ, Enjuanes C, et al. Effect of permanent atrial fibrillation on cognitive function in patients with chronic heart failure. Am J Cardiol 2016;117:233–9.

25. Vogels RL, Oosterman JM, van Harten B, et al. Neuroimaging and correlates of cognitive function among patients with heart failure. Dement Geriatr Cogn Disord 2007;24:418–23.

26. Novak V, Last D, Alsop DC, et al. Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. Diabetes Care 2006;29:1529–34.

27. Global Initiative for Chronic Obstructive Lung Disease. From the Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available at: http://goldcopd.org/. Accessed October 5, 2017.

28. Adams EB. Nutritional anaemias. Br J Clin Pract 1968;22:501–4.

29. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.

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APPENDIX For an expanded Methods section as well as supplemental tables, please see the online version of this paper.