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Cerebral cortical microinfarcts: A novel MRI marker of vascular brain injury in patients with heart failure

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ABSTRACT

Background: Patients with heart failure (HF) are at risk for vascular brain injury. Cerebral cortical microinfarcts (CMIs) are a novel MRI marker of vascular brain injury. This study aims to determine the occurrence of CMIs in patient with HF and their clinical correlates, including haemodynamic status.
Methods: From the Heart-Brain Study, a multicenter prospective cohort study, 154 patients with clinically stable HF without concurrent atrial fibrillation (mean age 69.5 ± 10.1, 32% female) and 124 reference participants without HF (mean age 65.6 ± 7.4, 47% females) were evaluated for CMIs on 3 T MRI. CMI presence in HF was tested for associations with vascular risk profile, cardiac function and history, MRI markers of vascular brain injury and cognitive profile.
Results: CMI occurrence was higher in patient with HF (17%) than reference participants (7%); after correction for age and sex OR 2.5 [95% CI 1.1–6.0] $p = .032$; after additional correction for vascular risk factors OR 2.7 [1.0–7.1] $p = .052$. In patients with HF, CMI presence was associated with office hypertension (OR 2.7 [1.2–6.5] $p = .021$) and a lower cardiac index (B = -0.29 [−0.55−−0.04] $p = .023$ independent of vascular risk factors), but not with cause or duration of HF. Presence of CMIs was not associated with cognitive performance in patients with HF.
Conclusions: CMIs are a common occurrence in patients with HF and related to an adverse vascular risk factor profile and severity of cardiac dysfunction. CMIs thus represent a novel marker of vascular brain injury in these patients.

1. Introduction

Heart failure (HF) is associated with an increased risk for vascular brain injury [1]. Patients with HF are reported to have a 2- to 3-fold increased risk of symptomatic stroke [2,3], while clinically "silent" vascular brain lesions – increasingly observed on MRI – are even more prevalent [4,5].

Recently, cerebral cortical microinfarcts (CMIs) have attracted attention as a novel marker of vascular brain injury. CMIs are small ischemic lesions detectable on neuropathological evaluation and MRI [6]. They are associated with vascular risk factors and manifestations of cerebral small vessel disease and thromboembolic stroke [6]. CMIs have shown to predict accelerated cognitive decline in memory clinic [7] and stroke patients [8] emphasizing their potential clinical value.

The occurrence of CMIs in patients with HF has not yet been explored. Yet, compromised cerebral hemodynamics and hypoperfusion - both known symptoms of HF- are confirmed risk factor for CMIs [9]. Moreover, CMIs were shown to relate to biomarkers of (sub)clinical cardiac disease in memory clinic patients [10].

Therefore this study investigated the occurrence of CMIs in patients with HF compared to reference participants without HF. Among patients with HF, we explored the relation between CMIs presence and vascular risk profile, measures of cardiac functions and cardiac history, MRI markers of vascular brain injury and cognitive performance.

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2. Material and methods

2.1. Population

The Heart-Brain Study (HBS) is a multicenter prospective cohort study that recruited patients with HF and reference participants between May 2014 and December 2017 through four academic medical centers (UMCs) in the Netherlands: Leiden UMC (LUMC), Maastricht UMC (MUMC), Utrecht UMC (UMCU) and VU UMC (VUMC) [11]. HF patients and reference participants were eligible to participate if they were 50 years or older, able to undergo cognitive testing and independent in daily life (operationalized as being capable to come to the hospital and undergo the study protocol, including the MRI). Additional enrollment criteria for patients with HF was a HF diagnosis according to the European cardiology society (ESC) guidelines [12], including (1) typical symptoms (breathlessness at rest or on exercise, fatigue, tiredness, ankle swellings), signs (tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly) and (2) objective evidence of a structural or functional abnormality of the heart at rest on routine echocardiography. Moreover, patients with HF had to be clinically stable for at least 6 months in order to participate. Additional enrollment criterion for reference participants was the absence of a diagnosis of heart failure (based on medical history). Exclusion criteria for both HF patients and reference participants were (1) current atrial fibrillation (AF), since AF may lead to unpredictable hemodynamic changes which might impact cardiac-MRI. Of note, a history of (paroxysmal) AF or AF detected during study participation were not considered exclusion criteria. (2) Current premature ventricular contractions (PVCs) exceeding 10% of total number of heartbeats, (3) a life-threatening disease other than HF with life-expectancy less than three years, (4) clinical evidence of a neurodegenerative disease other than vascular cognitive impairment of Alzheimer's disease (such as frontotemporal dementia, Lewy Body disease, or hypokinetic rigid syndrome), (5) other neurological or psychiatric diagnosis that affects cognitive performance or testing, such as severe traumatic brain injury or substance abuse. HF patients were recruited from cardiology outpatient clinics from the LUMC, MUMC, VUMC and general practices in the region of South Holland, the Netherlands. The reference participants were selected by active recruitment among spouses of patients and through advertising leaflets in the hospital and by advertisements in local newspapers through the UMCU VUMC, LUMC and MUMC.

This study was approved by the Medical Ethics Review Committee of the LUMC and local boards of the participating UMCs. The study was performed in accordance with the declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). Written informed consent was obtained from all participants prior to research related procedures.

For both HF patients and reference participants a core clinical dataset was collected, including vascular risk factors, detailed neurologic, cardiac and medical history including medication use. In addition, all subjects attended an examination day that included neuropsychological tests, cardiac and brain MRI, and blood samples.

For the current study we included all HF patients and reference participants who successfully underwent brain MRI. Of the 162 HF patients and 128 reference participants, 2 HF patients were excluded due to poor scan quality, and 6 HF patients and 3 reference participants due to lacking of MRI sequences. In addition, 1 reference participant appeared to meet the ESC criteria of HF after inclusion and was excluded from the current analysis. This resulted in a study population of 154 HF patients and 124 reference participants.

2.2. Vascular risk factors

The following vascular risk factors were recorded for both HF patients and reference participants. Hypertension was defined as presence in the medical history. Current office hypertension was defined as a mean systolic tension > 140 mg/Hg or diastolic tension > 90 mm/Hg measured on the research day. Hypercholesterolemia was defined as presence in the medical history or use of cholesterol lowering medication. Diabetes was defined as presence in the medical history. Body surface area (BSA) was calculated in m^2 according to the following formula: $BSA = 0.007184 \times W^{0.425} \times H^{0.725}$, in which W refers to the weight in kg and H to the height in cm [13]. Obesity was defined as a body mass index over 30. Smoking was defined as current or previous smoking. Vascular claudication was defined as presence in the medical history. History of stroke was defined as previous clinical ischemic of hemorrhagic stroke. For patients with HF use of antiplatelet, direct or oral anticoagulant medication was recorded.

2.3. MRI protocol

Cardiac and brain MRI were acquired at 3 T on Ingenia or Achieva scanners (Philips, Best, the Netherlands). The cardiac protocol included short-axis multislice cine steady-state free precision (TR 3.1 ms; TE 1.55; flip angle 45°; 40 heart phases; 67 phase percentage; breath-hold; number of slices dependent on size of LV (range 12–16 slices), resolution $1.5 \times 1.6 \times 8.0$ mm^3). The brain MRI protocol included 3D T1-weighted images (TR 8.2 ms; TE 4.5 ms; shot interval 3000 ms; flip angle 8°; inversion delay 990 ms, resolution $1.0 \times 1.0 \times 1.0$ mm^3), fluid-attenuated inversion recovery (FLAIR) images (TR 4800 ms; TE 313 ms; TI 1650 ms; TSE factor 182, resolution $1.11 \times 1.11 \times 1.11$ mm^3) and susceptibility-weighted imaging (SWI) (3D gradient echo, TR 45 ms, TE 31 ms, flip angle 13°, EPI factor 3, resolution $0.8 \times 0.8 \times 1.6$ mm^3). ASL scans were acquired using a pseudo-continuous arterial spin labeling (pCASL) sequence with a label duration of 1800 ms and a postlabeling delay of 1800 ms (resolution $3 \times 3 \times 7$ mm^3).

2.4. Cardiac parameters

For both HF and reference participants the following parameters were derived from cardiac MRI using a semi-automatic contour detection with manual correction by an experienced reader: Left ventricular-end diastolic volume (LV-EDV) and left ventricular end-systolic volume (LV-ESV) in L. Left ventricular stroke volume (LV-SV) in L was calculated according to the formula: *LV-EDV − LV-EDV*. Cardiac output was calculated in L/min according to the formula: *LV-SV × heart rate* (heart rate was derived from the DICOM header) and cardiac index was expressed in L/min/m^2 according to the formula: *LV-SV × pulse rate / BSA*. Left ventricular ejection fraction (LVEF) was calculated according to the formula: *LV-SV / LV-EDV × 100%*. LVEF was used to categorize patients with HF according to the ESC guidelines [12] into HF- reduced ejection fraction (LVEF < 40%), HF- mid-range ejection fraction (LVEF 40–49%) and HF-preserved ejection fraction (LVEF > 50%).

For both HF patients and reference participants a history of paroxysmal AF, myocardial infarction, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) was recorded. Additionally, for HF patients, cause and duration of heart failure, presence of valvular heart disease and cardiac arrhythmias were recorded.

2.5. Cerebral MRI-markers including CMIs

The following cerebral MRI-markers were rated by an experienced neuroradiologist according to the STRIVE-criteria [14]: Microbleeds, infarcts (cortical and non-lacunar subcortical infarcts; lacunar infarcts), enlarged perivascular spaces and white matter hyperintensities (WMHs) according to the Fazekas scale [15]. Cerebral small vessel disease score was constructed for each patient according to a previously developed scale [16]. Brain volumetrics, including gray matter, white matter and WMH volume were calculated using an automated pipeline (Quantib brain, Rotterdam, the Netherlands) after manual segmentation

of infarcts and other pathologies. Cerebral blood flow (CBF) of the normal appearing gray matter (GM) was quantified in mL/100 mg/min. Post-processing included motion-correction and partial volume correction [17].

CMIs were rated by visual inspection according to established criteria on 3 T MRI [6]. In short, CMIs had to be <4 mm, strictly intracortical and hypointense on T1-weighted imaging, cavitated, hyperintense or isointense on FLAIR and iso- or hyperintense on SWI. CMIs had to be visible in at least two planes (eg, sagittal, transversal, coronal) and distinct from enlarged perivascular spaces, arterioles, venules and microbleeds. Lesions neighboring a larger infarct (i.e., <1 cm in the same gyrus) were disregarded [6,18]. Ratings were performed in an in-house developed tool in MeVisLab (MeVis medical solutions, Bremen, Germany) by three experienced raters, blinded to the clinical condition of the subjects. Interrater agreement was very good (interclass correlation 0.97 in a subset of 31 scans).

2.6. Blood samples

Blood samples were drawn to determine hemoglobin (mmol/L), hematocrit (L/L) and C-reactive protein (CRP) mg/L using standard methods.

2.7. Cognitive testing

The educational level was rated according to the 7-point Verhage criteria [19]. Subjects underwent standardized neuropsychological testing, including a Dutch version of the mini-mental state examination (MMSE) [20] and a extensive neuropsychological test battery covering four cognitive domains including memory, language, attention/psychomotor speed and executive functioning [11]. Neuropsychological tests used per cognitive domain are documented in appendix 1. A composite z-score of all cognitive domains was created, corrected for age, sex and education and with reference participants as reference. Additionally, patients were classified as 1) cognitively normal (no cognitive domains impaired), 2) minor cognitive impairment (one domain impaired) or 3) major cognitive impairment (more than one domain impaired). Of note, a cognitive domain was considered impaired when the score was −1.5 SD below the mean age, sex and education-adjusted mean z-score.

2.8. Statistical analysis

Differences between HF patients and reference participants, and HF patients with and without CMIs were compared with linear regression (for normally distributed data), logistic regression (for proportions) and Mann-Whitney *U* tests (for non-parametric data). Occurrence rate of CMI between HF and reference participants was subsequently corrected for age, sex and vascular risk factors in a logistic regression model. Brain volumetrics were corrected for age, sex and intracranial volume. For the cognitive tests results were standardized as age, sex and education-adjusted z-scores. An exploratory mediation analysis was performed using the PROCESS v3.3 macro (http://processmacro.org/index.html) [21] in SPSS to test the mediation effect of CBF in the relationship between cardiac index and CMI presence with 5000 bootstrapping samples and 95% confidence interval (CI). We also performed exploratory analyses on reference participants with and without CMIs using linear and logistic regression. All statistical analyses were carried out using IBM SPSS v 25 and a p-value < 0.05 was considered statistically significant.

The data that support the findings of this study are available from the corresponding author upon reasonable request, within the privacy legislation of the Netherlands and after permission of the Heart-Brain Connection (HBC) steering committee.

Table 1
Baseline characteristics and CMI presence in patients in HF and references.

	HF patients (n = 154)	References (n = 124)	p
Baseline characteristics			
Age (y)	69.5 ± 10.1	65.6 ± 7.4	0.001
Sex (female)	49 (32%)	58 (47%)	0.011
Education (7 levels)	5 [4–6]	6 [5–6]	0.007
Vascular risk factors			
Hypertension (medical history)	79 (52%)	30 (24%)	0.000
Current office hypertension[a]	57 (37%)	60 (48%)	0.062
Hypercholesterolemia	100 (66%)	37 (30%)	0.000
Diabetes	27 (18%)	2 (2%)	0.000
Smoking	107 (70%)	69 (56%)	0.014
Obesity	37 (24%)	18 (15%)	0.042
Paroxysmal AF	23 (15%)	0	0.000

Abbreviation: HF = Heart failure; AF = atrial fibrillation.
One missing in HF group for education and vascular risk factors, except hypertension (history) and obesity (2 missing).
[a] Current office hypertension: systolic tension > 140 mg/Hg or diastolic tension > 90 mm/Hg. Data are presented as mean ± SD, median (25th–75th percentile), or number (percentage).

3. Results

3.1. Baseline characteristics and occurrence of CMIs in patients with HF and reference participants

Patients with HF were older, proportionally less often female and had more vascular risk factors than reference participants (all except current office hypertension, $p < .05$, Table 1). Of the 154 patients with HF, 26 (17%) presented with at least one 1 CMI of whom 11 with multiple CMIs (max 5 CMIs per person). Of the 124 reference participants, 8 (7%) presented with at least 1 CMIs of whom 2 with multiple CMIs (max 7 CMIs per person). CMI occurrence was higher in patients with HF than reference participants after correction for age and sex (OR 2.5; 95% CI 1.1–6.0; $p = .032$; Model 1; Table 2). After additional correction for vascular risk factors the OR was not clearly attenuated, but the confidence interval widened (OR 2.7 [1.0–7.1]; $p = .052$; Model 4; Table 2). Additionally, the total number of CMIs per person was also

Table 2
Odds ratio of CMI presence in patients with HF compared to reference participants adjusted for covariates.

	OR of CMI presence [95% CI] in HF patients compared to references	p
Model 1: Unadjusted	2.9 [1.3–6.8]	0.011
Model 2: Adjusted for age & sex	2.5 [1.1–6.0]	0.032
Model 3: Adjusted for age, sex and individual vascular risk factors		
Adjusted for education	2.7 [1.1–6.4]	0.024
Adjusted for hypertension (medical history)	2.4 [1.0–5.8]	0.047
Adjusted for current office hypertension[a]	2.7 [1.2–5.9]	0.012
Adjusted for hypercholesterolemia	2.2 [0.9–5.4]	0.075
Adjusted for diabetes	2.3 [1.0–5.5]	0.062
Adjusted for current or previous smoking	2.5 [1.1–5.9]	0.035
Adjusted for obesity	2.3 [1.0–5.5]	0.056
Model 4: Adjusted for all vascular risk factors combined	2.7 [1.0–7.1]	0.052

CMI = cerebral cortical microinfarct; HF = Heart failure. Data presented as the odds ratio with 95% confidence interval of CMI presence in patients with heart failure compared to reference participants, both unadjusted (model 1), adjusted for age and sex (model 2) and adjusted for individual vascular risk factors (mode 3) and combined vascular risk factors (model 4).
[a] Current office hypertension: systolic tension > 140 mg/Hg or diastolic tension > 90 mm/Hg.

Table 3
Demographics, vascular risk factors, cardiac function and history in HF patients with and without CMIs.

	HF CMI present ($n = 26$)	HF CMI absent ($n = 128$)	Odds ratio [95% CI]	p
Baseline characteristics				
Age (y)	71.3 ± 8.4	69.1 ± 10.3		0.306
Sex (females)	7 (27%)	42 (33%)	0.8 [0.3–1.9]	0.557
Body surface area (m^2)	2.0 ± 0.2	1.9 ± 0.2		0.312
Education (7 levels)	5 [4–6.5]	5 [4–6]		0.204
Vascular risk factors				
Hypertension (history)	16 (62%)	63 (50%)	1.6 [0.7–3.8]	0.286
Current office hypertension	15 (58%)	42 (33%)	2.7 [1.2–6.5]	0.021
Hypercholesterolemia	20 (77%)	80 (63%)	2.0 [0.7–5.2]	0.179
Diabetes	6 (23%)	21 (17%)	1.5 [0.5–4.2]	0.428
Smoking	20 (77%)	87 (69%)	1.5 [0.6–1.1]	0.396
Obesity	8 (31%)	29 (23%)	1.5 [0.6–3.8]	0.404
Vascular claudication	2 (8%)	6 (5%)	1.7 [0.3–8.9]	0.540
History of stroke	3 (12%)	5 (4%)	3.2 [0.7–4.3]	0.530
Medication				
Antiplatelet	17 (65%)	64 (50%)	1.8 [0.8–4.5]	0.156
(Direct) oral anticoagulants	7 (27%)	41 (32%)	0.8 [0.3–2.0]	0.609
Cardiac function				
Cause of HF[a]			1.4 [0.6–3.5]	0.374
Non-ischemic	8 (31%)	54 (42%)		
Ischemic	16 (62%)	66 (52%)		
Unknown	2 (7%)	7 (6%)		
Duration of HF[b]			1.6 [0.7–3.8]	0.273
≤5 years	12 (46%)	73 (58%)		
>5 years	14 (54%)	53 (42%)		
ESC HF criteria ($n = 147$)				
HF-reduced EF	13 (54%)	50 (41%)	1.7 [0.7–4.2]	0.224
HF-mid-range EF	9 (38%)	47 (38%)	1.0 [0.4–2.4]	0.948
HF preserved EF	2 (8%)	26 (21%)	0.4 [0.1–1.6]	0.161
			B [95% CI]	
LVEF (%) (n = 147)	40.5 ± 7.1	43.0 ± 10.0	−2.5 [−6.7–1.8]	0.253
Cardiac index (L/min/m^2)	2.49 ± 0.46	2.79 ± 0.59	−0.29 [−0.55−−0.04]	0.023
Cardiac output (L/min)	4.95 ± 1.22	5.40 ± 1.23	−0.45 [−0.9–0.10]	*0.105*
Pulse rate (beats/min)	58.5 ± 8.8	64.9 ± 12.6	−6.4 [−11.7−−1.1]	0.018
Cardiac history			OR [95% CI]	
Myocardial infarction	16 (64%)	60 (48%)	2.0 [0.8–4.8]	0.139
Valvular heart disease	2 (8%)	11 (9%)	0.9 [0.2–4.2]	0.872
Cardiac arrythmia	8 (32%)	32 (26%)	1.4 [0.5–3.5]	0.510
Paroxysmal AF	4 (16%)	19 (15%)	1.1 [0.3–3.4]	0.919
PCI	13 (50%)	38 (30%)	2.3 [1.0–5.4]	*0.058*
CABG	5 (19%)	25 (20%)	1.0 [0.3–2.8]	0.958

Abbreviation: HF = Heart failure; CMI = cortical microinfarct; ESC HF criteria = European society of cardiology Heart failure criteria; HF reduced EF = Heart failure with reduced ejection fraction (LVEF < 40%); HF-mid-range EF = Heart failure with midrange ejection fraction (LVEF 40–49%); HF preserved ejection fraction (LVEF > 50%); LVEF = Left ventricular ejection fraction; AF = atrial fibrillation. PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.
Data are presented as mean ± SD, median (25th–75th percentile), or number (percentage). OR or B with corresponding 95% confidence intervals represent differences between HF patients with and without CMIs.
One missing for education, cause of HF, cardiac valve disease, CABG and vascular risk factors (except hypertension (history) and obesity) 2 missing: hypertension (history) and obesity, duration of HF; 3 missing: PTA, myocardial infarction; 4 missing: cardiac arrhythmia. 7 missing: cardiac MRI derived measures (EF, cardiac index, pulse rate, cardiac output).
[a] Ischemic compared to non-ischemic HF on CMI presence.
[b] >5 years of HF vs ≤5 years of HF on CMI presence.

higher in HF patients (median 1, interquartile range [1–3] than reference participants (median 1, interquartile range [1–1.5], $p = .008$).

3.2. Clinical correlates of CMIs presence in patients with HF

Among the patients with HF, presence of CMIs was not associated with age, sex, use of antiplatelet medication or (direct) anticoagulants, or vascular risk factors, except for current office hypertension (Table 3). Regarding cardiac function, CMI presence was associated with an 11% lower cardiac index and a 10% lower in pulse rate (both $p < .05$ after correction for age, sex and vascular risk factors), while a trend was observed for an 8% lower cardiac output (after correction for age, sex and vascular risk factors $p = .080$). No relationship was observed between presence of CMIs and LVEF. HF patients with CMIs tended to more often have a medical history of PCI compared to HF patients without CMIs ($p = .058$).

With respect to cerebral MRI-markers (Table 4), CMI presence in HF patients was associated with a higher occurrence of larger cortical infarcts (>5 mm, $p = .012$) and a marginally decreased TBV (after adjustment for age, sex and TIV, $p = .068$), while no significant association was observed with MRI-markers of cerebral small vessel disease (e.g. WMH volume, lacunar infarcts, microbleeds or cerebral small vessel disease score). CMI presence in HF patients was accompanied with a marginally lower CBF of the GM, but this difference was not statistically significant. The relationship between CMI presence and cardiac index was not significantly mediated by CBF (B = -0.10; [−0.49–0.06], $p > .05$).

Blood biomarkers, including hemoglobin (4 missing), hematocrit and CRP (both 5 missing) were not related to CMI presence in HF patients (data not shown, $p > .05$).

Table 4
Cerebral MRI-markers in HF patients with and without CMIs.

	HF CMI present (n = 26)	HF CMI absent (*n* = 120)	B [95% CI]	*p*
TIV (ml)	1414.2 ± 115.7	1387.6 ± 136.0	19.9 [−28.3; 68.0]	0.417
TBV volume (ml)[a]	1090.7 ± 103.4	1092.3 ± 117.7	−15.8 [−32.8; 1.2]	0.068
GM volume (ml)[a]	650.1 ± 51.4	649.4 ± 66.9	−7.0 [−20.4; 6.3]	0.300
WMH volume (ml)[a,b]	2.2 [1.2–5.2]	1.6 [0.4–4.5]	0.28 [−0.28; 0.84]	0.331
CBF GM (ml/100 g/min)[c]	49.9 ± 10.7	54.8 ± 11.4	−4.9 [−10.1; 0.4]	0.124
			OR [95% CI]	
Cortical infarcts and non-lacunar subcortical infarcts	8 (31%)	12 (10%)	3.9 [1.3; 11.3]	0.012
Lacunar infarcts	11 (42%)	31 (26%)	1.9 [0.8; 4.7]	0.153
Microbleeds	4 (15%)	31 (26%)	0.4 [0.1; 1.2]	0.108
SVD score	1 [0–2]	0 [0–1]	–	0.603

Abbreviation: HF = Heart failure; CMI = cortical microinfarct; GM = gray matter; TIV; total intracranial volume; TBV = total brain volume; WMH = white matter hyperintensity; CBF = cerebral blood flow; GM = gray matter; SVD score = Small vessel disease score. Data are presented as mean ± SD, median (25th–75th percentile), or number (percentage). Differences between HF patients with and without CMI presented with OR or B and corresponding 95% confidence intervals. Eight missings for all cerebral MRI-markers.

[a] Brain volumetrics were corrected for age, sex and intracranial volume.

[b] WMH was log transformed.

[c] CBF was corrected for age, sex and partial volume.

Scores on the MMSE, composite z-score of the cognitive domains and the composite score of all cognitive domains (age, sex and education adjusted) was not associated with presence of CMIs in HF patients (Appendix 2). The proportion of patients with cognitive impairment also did not differ according to CMI presence.

3.3. Cardiac correlates of CMIs in reference participants

Presence of CMIs in reference participants was associated with sex, as females were less likely to have CMIs (13% females in CMI present vs 49% females in CMI absent, $p = .045$), but not with vascular risk factors. There was no relationship between CMI presence in and cardiac function (cardiac index B = -0.10 [−0.47–0.26] $p = .578$ and LVEF: B = -2.1 [−6.0–1.8] $p = .281$). None of the reference participants with CMIs had a history of AF, myocardial infarction or any cardiac interventions.

4. Discussion

We found that CMIs commonly occur in patients with HF. Among patients with HF, presence of CMIs was associated with hypertension and severity of cardiac-pump dysfunction, but did not relate to cognitive impairment. These results show that vulnerability for vascular brain injury in patients with HF extends to CMIs.

In this study of patients with HF without current AF, we observed a CMI occurrence of 17%, which is markedly higher than the CMI occurrence in reference participants in this study (7%) and healthy controls from previous studies (6–12%) [22–24]. The occurrence rate in HF patients seems to be comparable to that reported for patients with a primary vascular brain disease, such as patients with acute stroke (10–15%) [8,25] and vascular cognitive impairment (20%) [22]. These findings emphasize that patients with HF should indeed be considered a population at considerable risk for vascular brain injury, including CMIs.

The question is what underlying causes contribute to the high CMI occurrence in HF patients. The first cause to consider is shared vascular risk factors. Risk factors, such as hypertension, hypercholesterolemia and diabetes, have been related to CMIs in memory clinic [26] and population-based cohorts [27]. Vascular risk factors are clearly common in patients in HF [12] and are known contributors to risk of (silent) macroscopic infarcts in these patients [28]. We can therefore not rule out a role of previous exposure or current treatment of vascular risk factors in our findings. In particular adjusting for hypercholesterolemia and diabetes slightly attenuated the relation between CMIs and HF, although adjustment for all vascular risk factors combined did not affect the effect size. Moreover, we found no relation between vascular risk factors and CMIs in reference participants without HF in this study, but it should be noted that the sample size was small compared to previous population based samples that did observe a relation between hypertension and CMI occurrence [27].

Another possibility is that the condition HF is causally related to CMIs. Two pathophysiological mechanisms have been proposed that can lead to brain infarction in the context of HF. Firstly, thromboembolism, the risk of which is known to be elevated by a marked reduced cardiac output in HF combined with stasis of blood in the cardiac chamber and the pro-thrombotic state associated with HF [29]. Secondly, cerebral hypoperfusion, primarily related to low cardiac output. Especially in the presence of small vessel disease, when autoregulation of the small vessels may be impaired, the brain is likely to be more vulnerable to bouts of hypoperfusion [30]. Both thromboembolism and hypoperfusion have shown to contribute to the development of CMIs in the context of conditions other than HF [6,9].

A key finding in the current study is the relation between CMIs and a markedly reduced cardiac index indeed supports the presence of thromboembolic and cerebral hypoperfusion pathways. Moreover, we found that CMIs presence was related to large cortical infarcts on MRI, which also suggests a thromboembolic origin. Notably, we found no significant association between CMIs and LVEF, despite the strong physiological link between LVEF and cardiac output/index. This discrepancy could possibly be explained by the lack of standardization for BSA for LVEF. However, we found that cerebral perfusion (CBF) was not an obvious mediator in our exploratory mediation analysis on the cardiac index – CMI relationship. Although it might be argued that this is to some extent due to the lack of powering of this study for these relatively small effect sizes. Another option is that the relation between CMI does not solely dependent on the cardiac output status. It would certainly be of interest to observe the clinical correlates of CMIs in HF patients with preserved EF, in which other principal pathophysiological processes might play a role. Future studies are encouraged to explore this issue in selected population of HF patients with preserved EF and taking into account other variables of interest such as venous congestion.

An important clinical issue is the prognostic value of CMIs in patients with HF. We found that CMI presence in HF patients was not related to worse cognitive functioning. This is unexpected finding in the light of previous research, showing a relatively consistent, though sometimes modest relationship between CMIs and cognitive impairment across different populations [6,31]. It might be explained by the fact that HF patients in the current study were all in a clinically stable phase of HF. Additionally, the HF patients had a relatively low burden of concurrent vascular brain injury and on the whole relatively preserved cognition

(as they scored only 0.2 SD z-score below reference participants), limiting the threshold to detect subtle differences in cognitive functioning. Another potential clinical implication of CMIs is the risk future stroke, as acute microinfarcts have shown to be associated with a 3-fold increased risk of poor clinical outcome after 2 years [32]. Future studies addressing the prognostic value of CMIs on stroke and cognition in HF patients are therefore recommended.

Strengths of this study are the well-defined cohort of HF patients and reference participants, the elaborate cerebral and cardiac MRI protocol and extensive cognitive testing. Moreover, by actively excluding patients with AF upon enrollment (the rationale of which was possible interference of AF with the cardiac MR protocol) we reduced the potential distortion of results by thromboembolic stroke. It must be acknowledged that since only patients with stable HF were eligible for inclusion this could have resulted in a bias of relatively healthy HF patients, thereby underestimating the found effects. Moreover, no data was available on clinical course including previous bouts of acute HF or AF, while it is likely that such episodes could have significantly contributed to structural brain injury. As expected, CMIs occurred in a minority of subjects, especially in reference participants. We could therefore not further stratify results according to causes of HF and the limited statistical power may contribute to the fact that we failed to find an association between CMIs and manifestations of cerebral small vessel disease despite OR over 1.5. Although detection of CMIs on 3 T MRI is practical on a large scale, it is well established that smaller CMIs (visible on 7 Tesla MRI or neuropathological evaluation) escape the detection limit, while these truly microscopic lesions may certainly also contribute to the cognitive decline [31].

5. Conclusion

We found that CMIs were common in patients with HF and CMIs were related to vascular risk factor profile and severity of cardiac dysfunction. This study thus identifies CMIs as a novel marker of vascular brain injury in these patients.

CRediT authorship contribution statement

D.A. Ferro: Conceptualization, Methodology, Formal analysis, Writing - review & editing, Writing - original draft, Investigation. **H. van den Brink:** Writing - review & editing, Investigation. **R.P. Amier:** Writing - review & editing, Investigation. **M.A. van Buchem:** Methodology, Funding acquisition. **J. de Bresser:** Writing - review & editing, Investigation. **E.E. Bron:** Writing - review & editing, Investigation, Data curation. **H.P. Brunner-La Rocca:** Methodology, Funding acquisition. **A.M. Hooghiemstra:** Project administration, Data curation. **N.G.H.M. Marcks:** Investigation. **A.C. van Rossum:** Methodology, Funding acquisition. **G.J. Biessels:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

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Declaration of competing interest

The authors report no disclosures.

Appendix A

A.1. Specification of neuropsychological tests used per cognitive domain:

Cognitive domain	Neuropsychological test	Test variable included
Memory	Rey Auditory Verbal Learning Test[1]	Total immediate recall Delayed recall Recognition
	Visual Association Test, short version[2]	Part A
Language	Visual Association Test	Part A
	Fluency (animals)[3]	Number correct in 1 min
Attention/psycho-motor speed	Trail Making Test[4]	Part A
	Stroop Color-Word Test[5]	Mean of cart 1 and 2
	Letter-Digit Substitution Test[6]	Number correct in 90 s
	Digit span[7]	Forward
Executive functioning	Trail Making Test	Part B/Part A
	Stroop Color-Word Test	Interference (card 3 / ([card 1 + card 2] / 2)
	Digit span	Backwards

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A.2. Cognitive performance and proportion of patient with global cognitive impairment in HF patients with and without CMIs

	HF CMI present (n = 26)	HF CMI absent (n = 127)	P
MMSE	28.9 ± 1.0	28.5 ± 1.5	0.149
Composite of all cognitive domains	−0.04 ± 0.46	−0.22 ± 0.58	0.133
Memory	0.02 ± 0.83	−0.29 ± 1.27	0.237
Language	−0.06 ± 0.45	−0.32 ± 0.95	0.186
Attention/speed	−0.22 ± 0.85	−0.28 ± 0.80	0.729
Executive functioning	−0.11 ± 0.53	0 ± 0.83	0.528
Global cognitive impairment			0.239
No	24 (92%)	101 (80%)	
Minor	1 (4%)	21 (17%)	
Major	1 (4%)	4 (3%)	

Abbreviation: HF = Heart failure; CMI = cortical microinfarct; MMSE = mini-mental state examination. Composite of cognitive scores are the mean z-score for all cognitive domains corrected for age, sex and gender in relation to the references. Global cognitive impairment: No = no impaired cognitive domains, Minor = one impaired cognitive domain; Major = more than one impaired cognitive domain. One missing for MMSE, two missings for composite cognitive scores and global cognitive impairment.

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