Circulation: Heart Failure

ORIGINAL ARTICLE

Microvascular Dysfunction as a Possible Link Between Heart Failure and Cognitive Dysfunction

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BACKGROUND: Microvascular function in the brain and heart may play an important role in the course of patients with heart failure (HF), but its relationship with ventricular and cognitive function is not well understood. We hypothesized that microvascular function in HF is closely related to both, cardiac and cognitive function.

METHODS: In healthy controls and symptomatic patients with HF (New York Heart Association functional class II or III), we used oxygenation-sensitive magnetic resonance imaging during a standardized breathing maneuver to determine the cerebral oxygenation reserve and the myocardial oxygenation reserve (MORE) as markers for microvascular function. A stepwise multivariable linear regression was performed to determine the variables that best predict changes in cerebral oxygenation reserve and MORE. We also measured cognitive function using the Montreal Cognitive Assessment test.

RESULTS: Twenty patients with HF (age 64.4±8.3 years; 50% female sex), and 21 healthy controls (age 55.0±5.1 years; 62% female sex) were included in the analysis. In patients with HF, cerebral oxygenation reserve and MORE were lower than in healthy controls (MORE, −0.1±3.3 versus 5.0±4.2, cerebral oxygenation reserve: 0.43±0.47 versus 1.21±0.60, respectively) as were Montreal Cognitive Assessment score results (HF, 23.9±3.7; healthy, 27.8±1.5; P=0.002). The Montreal Cognitive Assessment score in patients was correlated with cardiac output (r=0.55, P=0.011) and MORE (r=0.46, P=0.040). In addition to the presence of HF, significant predictors of cerebral and myocardial oxygenation reserve were cardiac output and end-diastolic volume, respectively.

CONCLUSIONS: Our results indicate that heart failure is an independent predictor of coronary and cerebral microvascular dysfunction as defined by a reduced response to a vasodilatory breathing maneuver. This impaired response was associated with reduced cognitive function.

Key Words: brain ■ cognition ■ coronary artery disease ■ heart failure ■ magnetic resonance imaging

Heart Failure (HF) is a significant global health problem with a 1 in 5 lifetime risk of developing HF after 40 years of age.[1,2] With advances in clinical management and associated improved survival of patients with HF <80 years,[3] cognitive dysfunction is increasingly encountered as a clinical problem in patients with heart failure.[4] Specifically, patients with HF develop cognitive impairment at younger ages than those without HF and suffer from a decreased quality of life, and a higher mortality risk.[5] Although the underlying pathophysiology of HF is heterogenous and remains incompletely understood, many overlapping pathophysiologic mechanisms have been proposed for the HF-associated development of cognitive impairment, including chronic cerebral hypoperfusion or decreased cerebrovascular reactivity through endothelial dysfunction, arterial hypertension, and systemic inflammation.[6–8] Endothelial dysfunction and chronic cerebral hypoperfusion have been associated with an accelerated cognitive decline and are suggested to play a major role in the cause of cognitive impairment, vascular dementia, and Alzheimer disease.[9–12]

Cardiovascular magnetic resonance imaging (CMR) is the prime diagnostic imaging modality in the diagnostic workup of patients with HF, due to its ability to quantify

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WHAT IS NEW?

- Oxygenation-sensitive magnetic resonance imaging and breathing maneuvers can be used to assess microvascular function in 2 different vascular beds.
- The method appears particularly useful because of its safety (no contrast agents, no radiation or radioactive materials, no stress) and repeatability.
- Furthermore, it can track dynamic changes of tissue oxygenation, a direct, downstream biomarker, instead of surrogate markers such as tracer or contrast media kinetics.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The apparent relationship between the 2 vascular beds, coronary and cerebral, may reflect a common pathway by which heart failure leads to microvascular dysfunction and thus may serve as risk indicators for the other vascular bed, even in the absence of associated symptoms.
- The relationship between microvascular function and cognitive function indicates that cognitive dysfunction as observed in patients with impaired function may be due to microvascular dysfunction and thus offer another avenue for a more specific prevention or treatment of cognitive dysfunction in these patients.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance imaging
CORE	cerebral oxygenation reserve
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
MoCA	Montreal Cognitive Assessment
MORE	myocardial oxygenation reserve
MRI	magnetic resonance imaging
OS-CMR	oxygenation-sensitive CMR

left ventricular function and tissue characteristics.[13–15] Oxygenation-sensitive magnetic resonance imaging (MRI) has the unique ability to noninvasively monitor changes in tissue oxygenation. Such changes as induced by a vasoactive maneuver can be visualized and measured through the associated change of relative concentrations of deoxyhemoglobin and its paramagnetic properties, called blood oxygen level–dependent effect.[16–18] A strong endothelial-dependent vascular response can be achieved by a standardized breathing maneuver consisting of a period of paced hyperventilation that induces vasoconstriction followed by a vasodilatory breath-hold.[19] In diseased states with impaired vascular endothelial function, this response is reduced, resulting in smaller or absent change of the oxygenation-dependent signal intensity, or even a paradoxical increase in deoxyhemoglobin, reflected by a signal intensity decrease.

Oxygenation-sensitive MRI with vasoactive breathing maneuvers offers a unique, noninvasive, needle-free methodology to quasisimultaneously investigate microvascular (endothelial) dysfunction in both the heart and brain of patients with HF.[20] It has been utilized in studies of macrovascular coronary artery disease[21] and microvascular dysfunction, in obstructive sleep apnea,[22] women with ischemia and no obstructive coronary artery disease,[23] postcardiac transplantation,[24] and in heart failure with preserved ejection fraction.[25]

This study aims to assess the myocardial and cerebral oxygenation status in patients with HF and to correlate these findings to the cardiac and cognitive functional status.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. This study was approved by the local research ethics board at the research institute of the McGill University Health Center. All subjects provided written informed consent before study enrollment.

Study participation took place in 1 session consisting of an MRI of both the heart and the brain and the completion of a cognitive assessment test. Twenty patients and 23 healthy controls were included in the study.

Participants

The inclusion criteria for patients were an age older than 50 years, 1 presenting symptom of HF at clinical presentation, hospitalization for HF, regular follow-ups in our HF clinic, and New York Heart Association functional class II or III at time of study enrollment. Patients were excluded if there was a history of neurological (ie, stroke) or severe pulmonary disease, unstable hemodynamic conditions, recent (<90 days) myocardial infarction, or general MRI contraindications (including pregnancy, foreign metallic objects, or pacemakers). Consecutive patients were screened from a HF clinic, echocardiography studies, and patients scheduled for a clinical MRI. Healthy volunteers were recruited through public poster advertisements and included if they were over 50 years of age with no history of cardiovascular, neurological, or pulmonary diseases. Healthy controls were excluded if they had general MRI contraindications, regular nicotine consumption within the last 6 months, or unstable hemodynamic conditions. Patients and healthy controls were excluded from analysis if MR imaging of the heart and the brain was not completed in the same scanning session, or if they were unable to perform the breathing maneuvers. All participants self-reported their sex (not gender) at the time of inclusion into the study.

Cognitive Assessment

Cognitive screening was performed using the Montreal Cognitive Assessment (MoCA) with a score of <26 indicating cognitive impairment.[26] We performed the MoCA test in all participants within 2 weeks of the MRI scan. The MoCA

test has previously been used as a cognitive screening tool in patients with HF, with a high sensitivity to detect mild cognitive impairment.[27]

Magnetic Resonance Imaging

MRI imaging of the heart and the brain was performed using a clinical 3 Tesla MRI system (MAGNETOM Skyra; Siemens Healthineers, Erlangen, Germany). All study subjects underwent the same MRI scanning protocol. Participants were asked to refrain from consuming caffeine or taking β-blockers for 12 hours before the exam.

Heart MRI

All patients were in sinus rhythm at the time of the MRI scan. An 18-channel body array coil was used for the CMR exam. The CMR included cine acquisition for ventricular morphology and function, and oxygenation-sensitive MRI during breathing maneuvers (25). Cine images were acquired using an ECG-gated balanced Steady-State Free Precession in 3 short-axis slices and in a 2- and 4-chamber long-axis image using a standard ECG-gated balanced Steady-State Free Precession sequence. For tissue characterization, we obtained maps of native T1 Modified Look-Locker Inversion (5[3]3, repetition time 265.5 ms, echo time 1.03 ms, slice thickness 8 mm, flip angle 35°) and T2 Fast Low Angle Shot (repetition time 209.5 ms, echo time 1.35 ms, slice thickness 8 mm, flip angle 12°) in a basal and mid-ventricular short-axis view. Oxygenation-sensitive CMR (OS-CMR) images were acquired in a basal and mid-ventricular short-axis slice using a modified balanced steady-state free precession sequence as previously described.[21,28] The OS-CMR imaging protocol involved a baseline OS-CMR acquisition, followed by 60s of hyperventilation (metronome-paced at 30 breaths/min), and then by a voluntary maximal breath-hold, during which OS-CMR images were acquired continuously. The participants were continuously monitored for any adverse effects.

Brain MRI

Using a 64-channel head coil, brain images were acquired using a high-resolution T1-weighted magnetization-prepared rapid gradient-echo sequence (repetition time/echo time/inversion time) 2200.0/2.48/900 ms, flip angle 8, voxel size 0.9×0.9×1.00 mm, field of view 230 mm, bandwidth 250 Hz/Px, acquisition time 4:01 minutes. Oxygenation-sensitive MRI was performed continuously during 3 consecutive series of breathing maneuvers (60 s hyperventilation, 60 s breath-hold, followed by 90s of normal breathing) using a blood oxygen level–dependent sequence (repetition time/echo time 3100/30 ms, flip angle 70, bandwidth 2232 Hz/Px, voxel size 3.0×3.0×3.0 mm, field of view 144×220 mm, and acquisition time 13:48 min). Instructions for the breathing maneuvers were visually communicated to the participant through an iPad placed in the line of sight of the head-coil mirror, playing a timed video with color-coded breathing commands (green: normal breathing, blue/white flashing at a rate of 30/min: hyperventilation, red: breath-hold).

Image Analysis

Deidentified images were evaluated by readers blinded to any other results. Left ventricular function was analyzed in biplanar long-axis views using certified software (cvi42; Circle Cardiovascular Imaging, Calgary, AB, Canada). The myocardial oxygenation reserve (MORE) was reported as relative OS-CMR signal intensity percent change (Δ%MORE) from the first image obtained after hyperventilation to the image acquired 30 s into the following breath-hold.[21] Oxygenation-sensitive brain images were analyzed in Neurolens2 (Neuroimaging Tools & Resources Collaboratory, obtained from www.nitrc.org) where they were converted into the subtraction image, reflecting the % change from hyperventilation to breath-hold. The high-resolution magnetization-prepared rapid gradient-echo structural images were segmented into grey matter, white matter, and cerebrospinal fluid using the Brain Extraction Tool in FSL (Functional Magnetic Imaging of the Brain's software library, www.fmrib.ox.ac.uk/fsl). Image coregistration of the % change and the grey matter images into standard Montreal Neurological Institute space was performed, measuring voxel-wise % change of blood oxygen level–dependent signal intensity of grey matter. Cerebral oxygenation reserve (CORE) was reported as a mean % signal intensity change (Δ%CORE) between hyperventilation and breath-hold across the 3 breathing maneuvers.

Statistical Analysis

Continuous data were reported as mean±SD, whereas categorical data are reported as frequency (percentage). All continuous data was assessed for normality, and nonparametric tests were used where appropriate. Binary values were compared using Fisher exact tests. $P<0.05$ were used to indicate statistical significance. Demographic data, ventricular function measurements, and global myocardial values were compared between the 2 groups using the independent Student *t* test and Welch correction, where appropriate. Correlation was assessed using Pearson correlation coefficient. Multivariable linear regression modeling was performed using a bidirectional stepwise algorithm. Tests were performed with GraphPad Prism (version 9.0, GraphPad Software, La Jolla California) and R (R version 4.0.4, platform x86_64-apple-darwin17.0).

Linear Regression Analysis and Model Development

Associations between participant demographic (sex and age), physical characteristics (body mass index and body surface area), cardiovascular parameters (Table 1), comorbidities (current smoking, hypertension, dyslipidemia, diabetes), use of medications (ace inhibitors, angiotensin receptor blockers, β-blockers, diuretics, calcium channel blocker, and aspirin), and CORE and MORE were assessed using univariate linear regression analysis.

Stepwise multivariable linear regression modeling was performed to assess the variables that best predict the change in CORE and MORE in patients with HF. We considered all variables assessed in the univariate analyses, except for participant use of β-blockers due to collinearity with the participant group factor. The Bayesian Information Criterion was used to select the best model.

RESULTS

Participants

All patients were able to perform the breathing maneuvers adequately. Two healthy control subjects were excluded due to claustrophobia onset on hyperventilation.

Table 1. Baseline Characteristics for Heart Failure Patients and Healthy Controls

Clinical characteristics	Healthy controls (n=21)	Patients (n=20)	*P* value
Age, y	55.0±5.1	64.4±8.3	<0.001*
Male sex (n)	8 (38.1%)	10 (50.0%)	0.46
Body mass index, kg/m^2	25.2±2.6	29.7±6.6	0.006*
Body surface area, m^2	1.80±0.24	1.97±0.26	0.043*
Heart rate, bpm	65±9	68±13	0.38
Systolic blood pressure, mm Hg	120±15	117±14	0.46
Diastolic blood pressure, mm Hg	77±10	74±10	0.38
Comorbidities			
Current smoking	0 (0%)	0 (0%)	1.00
Hypertension	0 (0%)	10 (50%)	<0.001*
Dyslipidemia	0 (0%)	9 (45%)	<0.001*
Diabetes	0 (0%)	7 (35%)	0.003*
Current medications			
ACE inhibitor	0 (0%)	4 (20%)	0.031*
Angiotensin receptor blocker	0 (0%)	5 (25%)	0.014*
β-Blocker	0 (0%)	19 (98%)	<0.001*
Diuretic	0 (0%)	11 (55%)	<0.001*
Calcium channel blocker	0 (0%)	1 (5%)	0.30
Aspirin	0 (0%)	9 (45%)	<0.001*

Statistical analysis of continuous and binary variables are presented as mean±SD, and binary variables are presented as number (%). ACE indicates angiotensin-converting enzyme.

*P<0.05 were used to indicate statistical significance.

Demographic Data

Twenty patients with HF (mean age, 64.4±8.3 years; 50% female sex) and 21 healthy controls (mean age, 55.0±5.1 years; 62% female sex) were included in the analysis. Clinical characteristics and concomitant medications are presented in Table 1.

Of the patients with HF, 10 had a reduced ejection fraction, 2 had a mid-range ejection fraction, and 8 had a preserved ejection fraction. Two patients with heart failure had a previous diagnosis of coronary artery disease with 1 of those having had a myocardial infarction and subsequent coronary artery bypass graft 2 years before participation in this study. Additionally, 4 patients had an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2, and none had an estimated glomerular filtration rate of <30 mL/min per 1.73 m^2. The average hemoglobin for patients with HF was 140±17; all results were within normal reference ranges.

On average, patients were older than healthy controls and had higher body mass indices. No significant differences were found for sex, baseline heart rate, systolic blood pressure, or diastolic blood pressure between patients, and healthy controls. As per exclusion criteria, none of the healthy control subjects had cardiovascular comorbidities, such as hypertension, dyslipidemia, or diabetes. No participant was a current smoker.

Functional MRI Parameters

MRI baseline functional characteristics in patients and healthy controls are presented in Table 2. Patients with HF had a lower left ventricular ejection fraction (HF, 47±18%; healthy, 70±6%; P<0.001) and MoCA score (HF, 23.8±3.7; healthy, 27.8±1.5; P<0.001) when compared with healthy volunteers. Patients had a larger end-diastolic volume (HF, 180±65; healthy, 121±23; P<0.001), and end-systolic volume (HF, 101±58; healthy 37±12; P<0.001) when compared with healthy participants. In patients with HF, reduced left ventricular ejection fraction was moderately correlated with an increased end-diastolic volume (r=–0.49, P=0.023).

Tissue Characterization

patients with HF had higher myocardial T1 and myocardial T2 values than healthy volunteers. Local site myocardial T1 and T2 normal values are 1220±32 and 38.2±2.5 ms, respectively.

Tissue Oxygenation Response

On average, CORE and MORE were lower in patients with HF when compared with healthy controls (MORE: –0.1±3.3 versus 5.0±4.2; P<0.001, CORE 0.43±0.47 versus 1.21±0.60; P<0.001; Figure 1A and 1B). Moderate correlations between CORE and MORE (r=0.47; P=0.036; Figure 1C) and between CORE and systolic blood pressure (r=–0.45, P=0.049) were found in

Table 2. MRI and Functional Hemodynamic Measures

	Healthy controls (n=21)	Patients (n=20)	*P* value
MoCA score	27.8±1.5	23.9±3.7	<0.001*
End-diastolic volume, mL	121±23	180±65	<0.001*
End-systolic volume, mL	37±12	101±58	<0.001*
Left atrial volume index, mL	32±14	35±24	0.69
Stroke volume, mL	84±17	79±29	0.54
Cardiac output, L/min	5.5±1.4	5.2±1.6	0.53
Left ventricular ejection fraction, %	70±6	47±18	<0.001*
Cardiac index, L/min per m^2	3.01±0.55	2.61±0.74	0.057
Myocardial T1 (basal)	1225±28	1304±64	<0.001*
Myocardial T1 (mid)	1226±31	1303±70	<0.001*
Myocardial T2 (basal)	37.7±2.2	39.6±1.8	0.009*
Myocardial T2 (mid)	38.0±2.3	39.7±1.8	0.021*
MORE	5.0±4.2	-0.1±3.3	<0.001*
CORE	1.22±0.60	0.43±0.47	<0.001*

Statistical analysis of continuous variables are presented as mean±SD. ACE indicates angiotensin-converting enzyme; CORE, cerebral oxygenation reserve; MoCA, Montreal Cognitive Assessment; MORE, myocardial oxygenation reserve; and MRI, magnetic resonance imaging.

*P<0.05 were used to indicate statistical significance.

patients with HF. These correlations were not present in healthy participants.

Cognitive Dysfunction

The MoCA score in patients with HF was moderately correlated with body mass index (r=0.62, P=0.003), body surface area (r=0.65, P=0.002), stroke volume (r=0.59, P=0.006), cardiac output (r=0.55, P=0.011), and MORE (r=0.46, P=0.040; Figure 2). In the 10 patients with heart failure with reduced ejection fraction, there was a high, positive correlation between MORE and the MoCA score (r=0.81, P=0.008), stroke volume (r=0.80, P=0.010), and cardiac index (r=0.85, P=0.003) but not left ventricular ejection fraction (r=0.14, P=0.72).

Factors Contributing to the Cerebral and Myocardial Oxygenation Reserve

Associations between participants' characteristics (including age, sex, body mass index, etc), medical history, and CORE were investigated and summarized in Table 3. Disease status (HF versus control), the use of β-blockers, end-diastolic volume, and cardiac output were associated with CORE in the univariate analysis. When using the Bayesian Information Criterion for model selection, the presence of HF and cardiac output were the best predictors for CORE (Table 3). When controlling for cardiac output, patients with HF had a Δ%CORE that was 0.41 (95% CI, −0.71 to −0.11; P=0.011) lower than that of healthy controls.

The associations of participant characteristics and medical history with MORE are summarized in Table 4. MORE was reduced in the presence of HF, systemic hypertension, the use of angiotensin II receptor blockers, β-blockers, and antiplatelet therapy, as well as ejection fraction. Model selection using the Bayesian Information Criterion identified the presence of HF and end-diastolic volume as the best predictors for MORE (Table 4). When controlling for end-diastolic volume, Δ%MORE was 7.37 (95% CI, −10.03 to −4.71; P<0.001) lower than that of healthy controls.

DISCUSSION

To our knowledge, this is the first study to perform a quasi-simultaneous assessment of cerebral and myocardial

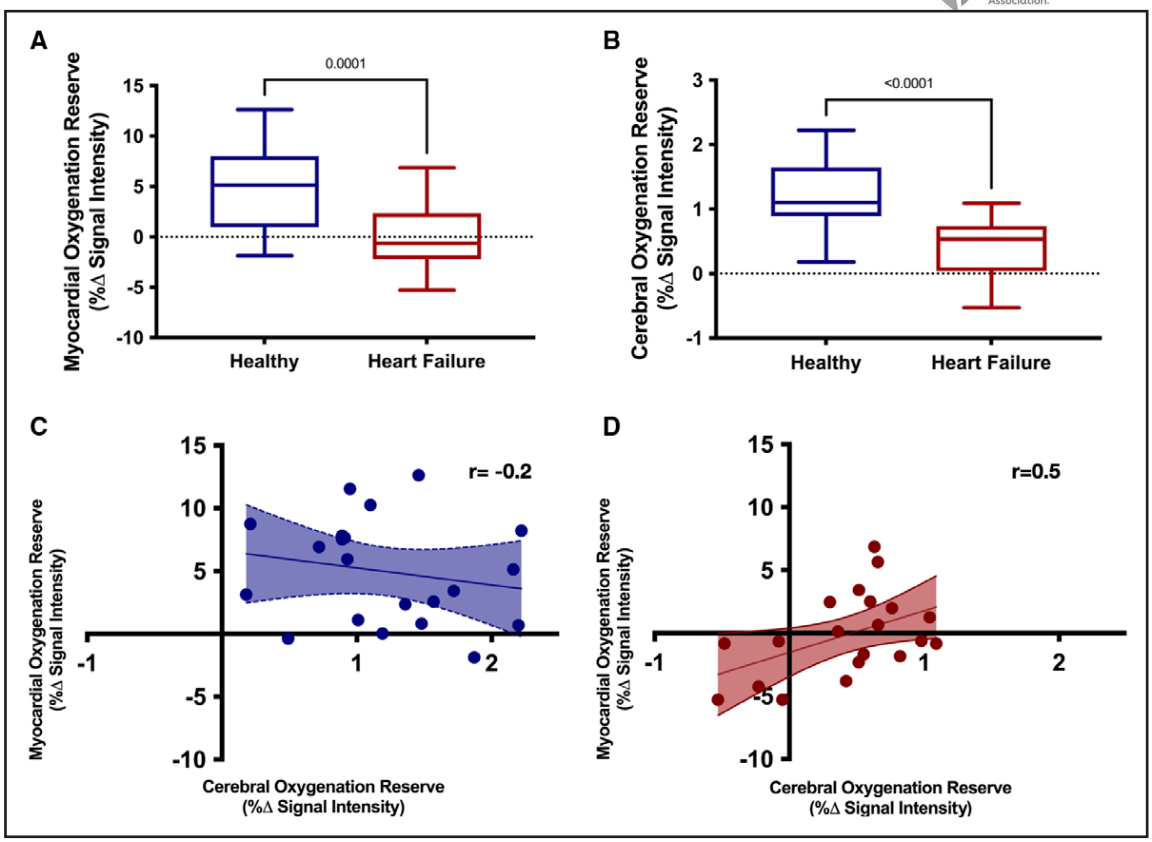

Figure 1. Myocardial oxygenation reserve, cerebral oxygenation reserve, and their correlation in healthy volunteers and heart failure patients.

The comparison of myocardial (MORE) and cerebral oxygenation reserve (CORE) after vasoactive breathing maneuvers in heart failure patients and healthy controls. **A**, The MORE and (**B**) CORE were both significantly reduced in heart failure patients when compared with healthy subjects. **C**, There is no significant correlation between degree of myocardial and cerebral oxygenation reserve in healthy volunteers. **D**, There is a moderate correlation between degree of myocardial and cerebral oxygenation reserve impairment in patients with heart failure.

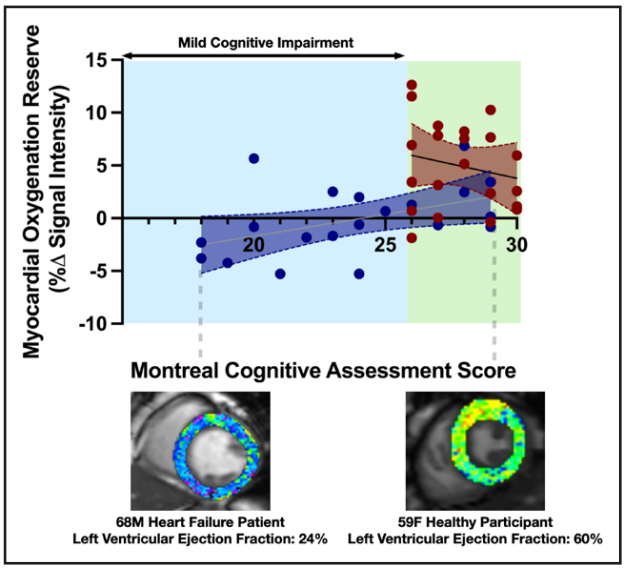

Figure 2. Tissue oxygenation status and cognitive dysfunction.
The correlation between Montreal Cognitive Assessment (MoCA) score and global myocardial oxygenation reserve (MORE) in patients with heart failure (blue) and healthy volunteers (red). The image on the **right** demonstrates the preserved oxygenation reserve (MORE=3.42Δ% signal intensity) of a 59-y-old female patient with heart failure who received a score of 29 on the MoCA test. The image on the **left** displays impaired oxygenation reserve (MORE=−2.31Δ% signal intensity) in a 68-y-old male patient with heart failure who received a score of 18 on the MoCA test. A MoCA score of <26 represents mild cognitive impairment.

oxygenation changes during vasoactive interventions. In the present study, we observed a reduced oxygenation reserve in both myocardial and cerebral vascular beds of patients with HF, that was not related to left ventricular ejection fraction but to cardiac output. A reduced oxygenation reserve was also observed in the brain, where it was associated with a reduced cognitive function. Furthermore, an impaired myocardial oxygenation reserve was also moderately associated with reduced cognitive assessment scores in patients with HFrEF. Our data, therefore, indicate that in patients with heart failure, an impaired cardiac output, but not left ventricular ejection fraction, is associated with vascular dysfunction and cognitive impairment (Figure 3).

A growing body of evidence has provided links between cardiovascular risk factors and disease and their potential negative effects on brain health. The presence of cognitive impairment in 65% of our HF patient population is consistent with previously published data using the MoCA.[6] A reduction in cerebral oxygenation was previously demonstrated in patients with HF with chronic obstructive pulmonary disease using near-infrared spectroscopy.[29] In patients with known or suspected coronary artery disease, abnormal cardiac function and perfusion was associated with increased resting metabolic activity in the amygdala, providing further evidence of a link between the brain and cardiovascular disease.[30] Cardiovascular risk factor burden has also been associated with a disruption of white matter network organization and subsequent cognitive decline.[31] The present study demonstrated lower cognitive assessment scores in patients with HF, and an association between cognitive impairment and myocardial oxygenation deficits, highlighting a possible association of microvascular dysfunction in the heart and brain with cognitive function.

Recently, hypoperfusion of the brain leading to hypoxia and nerve cell damage has been hypothesized as a potential pathway to explain the role of HF in the cause of cognitive impairment, dementia, and Alzheimer disease.[9,10,32,33] In the present study, cognitive impairment

Table 3. Univariate and Multivariate Associations Between Risk Factors and Cerebral Oxygenation Reserve

	Change in CORE (95% CI)	*P* value
Univariate		
Presence of heart failure	−0.39 (−0.71 to −0.07)	0.023*
Age, y	−0.00 (−0.03 to 0.02)	0.72
Sex (male)	−0.24 (−0.57 to 0.10)	0.17
Body mass index, kg/m²	−0.02 (−0.05 to 0.02)	0.34
Body surface area, m²	−0.43 (−1.09 to 0.23)	0.21
Resting heart rate, bpm	−0.01 (−0.02 to 0.01)	0.59
Resting systolic blood pressure, mm Hg	−0.00 (−0.02 to 0.01)	0.60
Resting diastolic blood pressure, mm Hg	0.01 (−0.00 to 0.03)	0.10
Systemic hypertension	−0.35 (−0.74 to 0.04)	0.091
Dyslipidemia	−0.23 (−0.65 to 0.19)	0.30
Diabetes	−0.33 (−0.79 to 0.14)	0.18
ACE inhibitors	−0.20 (−0.77 to 0.36)	0.49
Angiotensin II receptor blockers	−0.15 (−0.72 to 0.41)	0.60
β-Blockers	−0.40 (−0.72 to −0.08)	0.020*
Diuretics	−0.34 (−0.71 to 0.04)	0.092
Calcium channel blocker	−0.33 (−1.42 to 0.75)	0.55
Antiplatelet (aspirin)	0.04 (−0.44 to 0.52)	0.87
End-diastolic volume (per 10 mL)	−0.03 (−0.06 to −0.00)	0.033*
End-systolic volume (per 10 mL)	−0.03 (−0.06 to 0.01)	0.10
Stroke volume (per 10 mL)	−0.05 (−0.13 to 0.02)	0.18
Ejection fraction, %	0.01 (−0.00 to 0.02)	0.23
Myocardial oxygenation reserve	0.03 (−0.00 to 0.07)	0.093
Cardiac index, L/min per m²	−0.20 (−0.45 to 0.06)	0.14
Cardiac output, L/min	−0.12 (−0.23 to −0.01)	0.040*
Multivariate		
Presence of heart failure	−0.41 (−0.71 to −0.11)	0.011*
Cardiac output, L/min	−0.13 (−0.23 to −0.03)	0.019*

Univariate linear regression analysis was used to demonstrate associations between participant characteristics and participant-measured CORE. Multivariable linear regression analysis using Bayesian Information Criteria–based best-fit model for CORE. ACE indicates angiotensin-converting enzyme; and CORE, cerebral oxygenation reserve.

*P<0.05 were used to indicate statistical significance.

Table 4. Univariate and Multivariate Association Between Risk Factors and Myocardial Oxygenation Reserve

	Change in MORE (95% CI)	*P* value
Univariate		
Presence of heart failure	−5.27 (−7.63 to −2.90)	<0.001*
Age, y	−0.16 (−0.34 to 0.03)	0.10
Sex (male)	0.80 (−2.10 to 3.70)	0.59
Body mass index, kg/m²	−0.21 (−0.48 to 0.05)	0.12
Body surface area, m²	−0.32 (−5.99 to 5.35)	0.91
Resting heart rate, bpm	−0.13 (−0.28 to 0.01)	0.086
Resting systolic blood pressure, mm Hg	−0.03 (−0.13 to 0.07)	0.54
Resting diastolic blood pressure, mm Hg	0.02 (−0.12 to 0.17)	0.76
Systemic hypertension	−3.64 (−6.88 to −0.40)	0.034*
Dyslipidemia	−3.02 (−6.48 to 0.44)	0.095
Diabetes	−3.58 (−7.43 to 0.27)	0.077
ACE inhibitors	−4.16 (−8.75 to 0.43)	0.084
Angiotensin II receptor blockers	−4.92 (−9.43 to −0.41)	0.039
β-Blockers	−4.51 (−7.05 to −1.97)	0.001*
Diuretics	−3.22 (−6.38 to −0.06)	0.053
Calcium channel blocker	−2.46 (-11.61 to 6.69)	0.60
Antiplatelets (eg, aspirin)	−4.41 (−8.17 to −0.64)	0.027*
End-diastolic volume (per 10 mL)	−0.05 (−0.31 to 0.21)	0.73
End-systolic volume (per 10 mL)	−0.15 (−0.44 to 0.13)	0.30
Stroke volume (per 10 mL)	0.46 (−0.18 to 1.09)	0.17
Ejection fraction, %	0.09 (0.00 to 0.17)	0.050*
Cerebral oxygenation reserve	2.30 (−0.31 to 4.91)	0.09
Cardiac index, L/min per m²	1.47 (−0.66 to 3.61)	0.18
Cardiac output, L/min	0.50 (−0.46 to 1.46)	0.32
Multivariate		
Presence of heart failure	−7.37 (−10.03 to −4.71)	<0.001*
End-diastolic volume (per 10 mL)	0.33 (0.09 to 0.57)	0.010*

Univariate linear regression analysis was used to estimate associations between participant characteristics and MORE. Multivariable linear regression analysis using Bayesian Information Criteria–based best-fit model for MORE. ACE indicates angiotensin-converting enzyme; and MORE, myocardial oxygenation reserve.

*$P<0.05$ were used to indicate statistical significance.

was found to be positively correlated with reduced overall ventricular function (stroke volume and cardiac output), suggesting a potential role of chronic hypoperfusion in the development of cognitive impairment in patients with HF. Cerebral oxygenation reserve was best predicted by cardiac output and the presence of HF.

The presence of HF was associated with a reduced CORE, even when controlling for cardiac output, suggesting that the presence of HF alone was the most significant predictor of cerebrovascular dysfunction. In contrast to previous results in patients with heart failure and preserved ejection fraction,[25] there was no clinically meaningful increase in myocardial T2 as a marker of myocardial edema in our study, suggesting that severe congestion was not present at the time of investigation.

Impaired myocardial oxygenation reserve was best predicted by end-diastolic volume and the presence of HF. The role of the end-diastolic volume as a strong predictor may related to an increased intraventricular pressure and its impact on microvascular function which is consistent with our findings of an association between impaired heart function (stroke volume, cardiac index) and reduction in MORE. An association with MORE and systemic hypertension was also demonstrated, a finding that is consistent with the proposed implications of elevated blood pressure on endothelial and microvascular dysfunction.[7,34,35] Pharmacological therapy consisting of angiotensin II receptor blockers, β-blockers, and anti-platelet agents (aspirin), all standard-of-care therapeutics in patients with HF, were also associated with a reduction in MORE.

The observed positive correlation between cerebral and myocardial oxygenation reserve indicates a possible parallel pathophysiology of microvascular dysfunction in both vascular beds. This may be explained by systemic factors, such as hypertension and associated therapies as confounders, or chronic hypoperfusion caused by reduced overall ventricular function.[36,37]

Limitations

The small sample size and cross-sectional design of the study represent important limitations in the broad applicability of this study. However, the findings are consistent with previous studies and serve as a proof-of-concept with quasisimultaneous data in 2 vascular beds. Our strict inclusion criteria for patients with HF, with the exclusion of recent myocardial infarction and any history of past transient ischemic attacks in the brain limit the applicability of our findings in a more general HF population. However, the strict inclusion criteria and no observed evidence for regional injury allow for the assumption that the observed cognitive disturbance is not caused by macrovascular ischemic events. Further research including healthy participants with cardiovascular risk factors (including systemic hypertension) may further contextualize and inform our results in the broader population. The cross-sectional design of the study does not provide information on the longitudinal course of oxygenation response deficits or their role in the development of cognitive impairment. Longitudinal follow-up studies with a larger sample size and broader inclusion criteria are needed to investigate these long-term changes. Additionally, although there was no statistically significant difference between age and sex of healthy volunteers and heart failure groups in this study, the observed differences in the 2 groups may have affected our results. Sex differences may play a role in the identification of the contribution of end-diastolic volume to a reduced myocardial oxygenation reserve as men with

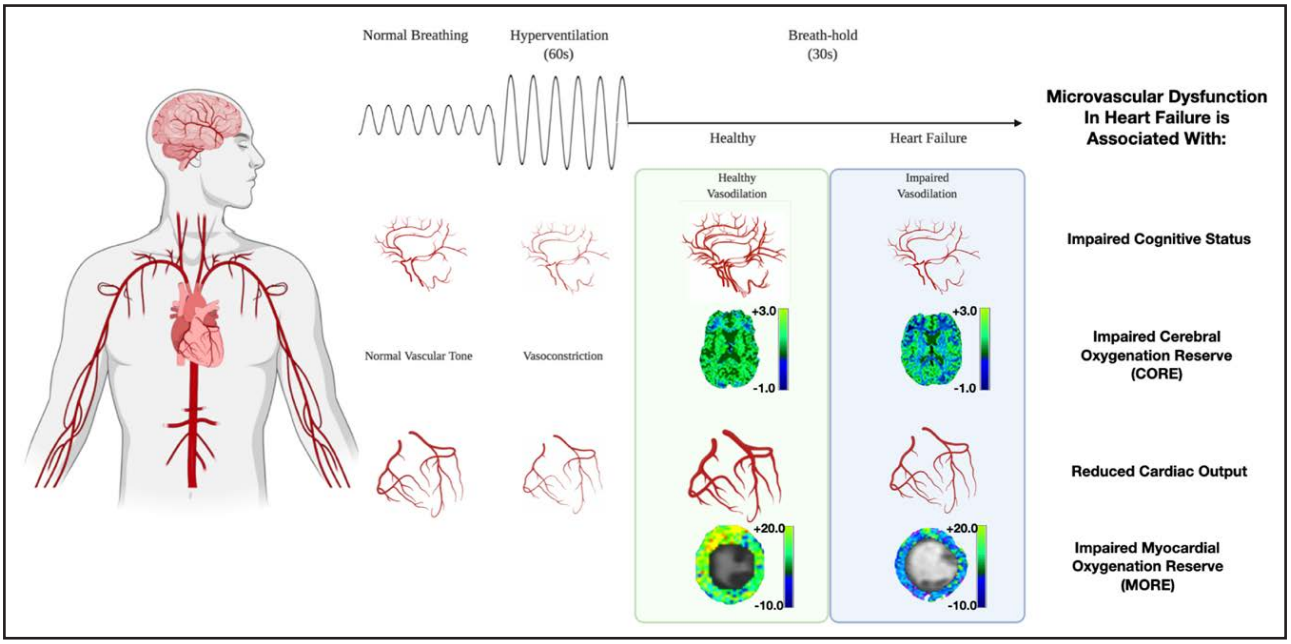

Figure 3. Microvascular dysfunction and cognitive impairment in patients with heart failure.
When performing vasoactive breathing maneuvers with oxygenation-sensitive cardiac magnetic resonance imaging, patients with heart failure have reduced vasodilation in both the heart (impaired myocardial oxygenation reserve) and brain (impaired cerebral oxygenation reserve) during apnea when compared with the vasodilatory response of healthy subjects. Microvascular dysfunction of the heart and brain may act as a link between cognitive impairment and heart failure in this patient population. CORE indicates cerebral oxygenation reserve; and MORE, myocardial oxygenation reserve.

larger volumes are more prevalent in HFrEF populations. This study did not have the sample size to further explore this relationship. However, 50% of our study population and 44% of both HF with reduced and preserved ejection fraction subgroups self-reported as female, likely limiting the risk for sex bias in this study. Finally, the potential impact of myocardial scar in patients with past myocardial infarction on the assessment of breathing-enhanced MORE has not been fully explored. However, given that only 1 patient in this study had a history of past myocardial infarction and that the breathing-enhanced MORE can still likely be applied in the presence of past infarct as it would still correctly classify an area without abnormal deoxygenation, this principle likely did not impact the results of this study. Future research about breathing-enhanced MORE in areas with known late gadolinium enhancement on CMR would clarify, how the (lack of) response in infarcted tissue differs from that in normal myocardium.

Conclusions

Our results indicate that heart failure is an independent predictor of both coronary and cerebral microvascular dysfunction as defined by a reduced response to a vasodilatory breathing maneuver. This impaired response was associated with reduced cognitive function.

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Dr Hillier was involved in the design, participant recruitment, image and statistical analysis, and development of the article. J. Covone was involved in statistical analysis, writing, and editing of the article. Dr Fischer was involved in study design and editing of the article. Dr Hafyane was involved in the analysis of brain magnetic resonance images and editing of the article. Dr Chen was involved in statistical analysis, interpretation of data, and editing of the article. Dr Friedrich was involved in study design and article editing.

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Disclosures

Dr Friedrich is shareholder and advisor of Area19 Medical Inc (Montreal, QC, Canada) and Circle Cardiovascular Imaging (CVI) Inc (Calgary, AB, Canada). Drs Fischer and Friedrich are inventors of but no longer hold the international patents to the following: US patent 14/419 877: Inducing and measuring myocardial oxygenation changes as a marker for heart disease; US patent 15/483 712: Measuring oxygenation changes in tissue as a marker for vascular function; US patent 10 653 394: Measuring oxygenation changes in tissue as a marker for vascular function–continuation; Canadian patent CA2020/051776: as of April 2018, the patent rights were transferred to Circle CVI Inc (Calgary, AB, Canada). Drs Friedrich and Hillier are listed as holders of international patent CA2020/051776: Method and apparatus for determining biomarkers of vascular function utilizing bold cardiac magnetic resonance imaging (CMR) images. The other authors report no conflicts.

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