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Reduced Regional Cerebral Blood Flow in Patients with Heart Failure

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Abstract

Aim—Heart failure (HF) patients show significant lateralized neural injury, accompanied by autonomic, mood, and cognitive deficits. Both gray and white matter damage appears, and likely develops from altered cerebral blood flow (CBF), a consequence of impaired cardiac output. However, the distribution of regional CBF changes in HF patients is unknown, but is an issue in determining mechanisms of neural injury. Our aim was to examine regional CBF changes in HF over control subjects using non-invasive pseudo-continuous arterial spin labeling (pCASL) procedures.

Methods and results—We collected pCASL data from 19 HF (age, 55.5±9.1 years; body-mass-index, 27.7±5.3 kg/m^2; 13 male) and 29 control subjects (51.4±5.3 years; 25.7±3.6 kg/m^2; 18 male), using a 3.0-Tesla-MRI scanner. Whole-brain CBF maps were calculated, normalized to a common space, smoothed, and compared between groups using ANCOVA (covariates; age, gender, and gray matter volume). Reduced CBF appeared in multiple sites in HF over controls,

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DECLARATION OF CONFLICTING INTERESTS

All the authors declare that they have no conflict of interest.

with principally-lateralized lower flow in temporal, parietal, and occipital regions. Areas with decreased CBF included the bilateral pre-frontal, frontal, temporal and occipital cortex, thalamus, cerebellum, corona radiate, corpus callosum, hippocampus, and amygdala.

Conclusion—HF subjects showed lower, and largely lateralized, CBF in multiple autonomic, mood, and cognitive regulatory sites. The reduced CBF likely contributes to the lateralized brain injury, leading to autonomic and neuropsychological deficits found in the condition.

Keywords

Arterial spin labelling; Brain Imaging; Cerebral blood flow; Cognition; MRI; Cerebral blood flow measurement

INTRODUCTION

A significant concern in heart failure (HF) is the development of neural injury, exemplified by both gray and white matter damage, which appears in brain areas that mediate autonomic, neuropsychologic, and cognitive regulation, resulting in serious impairments of those functions.[1–3] The neural damage appears on evaluation by several magnetic resonance imaging (MRI) procedures, and is reflected as regional loss of tissue or injury, as measured by manual assessment,[2] voxel-based-morphometry,[1] quantitative T2-relaxometry[3] and diffusion tensor imaging[4] procedures. The injury is preferentially unilateral, and principally on the right side, although left-side damage also appears. Since the injury can result in impaired physiological functions, such as autonomic dysregulation, the potential for damage to further exacerbate the HF condition is a significant concern. However, the underlying processes inducing brain tissue injury in these areas are unclear; low cardiac output and intermittent hypoxia from disturbed breathing in the condition may contribute, but distorted hemodynamic characteristics likely advance damage as well.

Brain sites that show tissue injury in HF subjects include cingulate, insular, hypothalamic, hippocampal, amygdala, brainstem, and cerebellar areas;[1,3,4] thus, if injury stems from altered cerebrovascular regulation, the impaired modulation should be reflected in abnormal cerebral blood flow (CBF) near those areas. Cerebrovascular autoregulation, a central autonomic control mechanism by which CBF remains constant despite changes in systemic blood pressure or body position,[5] is abnormal in HF subjects, establishing a potential for injury if activated tissue is inadequately perfused.[6,7] Although localized injury likely develops from altered hemodynamic patterns in the vasculature near affected tissue, little information on such regional CBF is available in HF subjects.

Magnetic resonance imaging (MRI) procedures that can assess CBF across the brain include arterial spin labeling (ASL) and dynamic contrast-based perfusion imaging. Arterial spin labeling-based perfusion MRI is a non-invasive approach, and does not use radiation or contrast agents to assess regional brain perfusion changes. Instead, the procedure uses magnetically-labeled arterial blood water as an endogenous tracer. The noninvasive nature of ASL is appealingly safe, as opposed to adverse effects from contrast use, and is especially suitable for patients with poor intravenous access and renal dysfunction, both of which are common in HF subjects. Arterial spin labeling-based CBF measurements have been

validated using ^{15}O-water positron emission tomography, and are reproducible over short and long periods, making it favorable for disease identification, tracking disease progression, and treatment effects. The procedures have been used effectively in various disease conditions, including ischemia,[8] Alzheimer disease,[9] brain tumors,[10] traumatic brain injury,[11] and Huntington's disease,[12] and may facilitate regional evaluation of brain perfusion non-invasively in HF subjects.

Our aim was to assess regional CBF changes in HF over control subjects using non-invasive ASL procedures. We hypothesized that HF patients would show reduced CBF in various brain sites that earlier showed injury, and which help regulate functions deficient in the condition.

MATERIALS AND METHODS

Subjects

Nineteen HF patients and 29 control subjects were included in this study. The demographics and other variables of all subjects are tabulated in Table 1. All HF patients were diagnosed based on national diagnostic criteria, showed systolic dysfunction and dilated cardiomyopathy, and were recruited from the Ahmanson-University of California at Los Angeles (UCLA) Cardiomyopathy Center. Of 19 HF subjects, 9 subjects were with ischemic and 10 with non-ischemic etiologies. Among 19 HF subjects, 12 subjects were hypertensive, 4 subjects with atrial fibrillation, and 5 subjects had a history of Type 2 diabetes. All HF subjects had reduced ejection fraction and were classified as the New York Heart Association Functional Class II (80%) and III (20%). HF subjects with the NYHA Functional Class IV were excluded, since subjects with such classifications cannot lay supine in the MRI scanner for sustained periods. Heart failure subjects used stable guideline-directed doses (titrated to reach targeted hemodynamic goals) of angiotensin receptor blockers (n = 6) or angiotension-converting enzyme inhibitors (n = 15), beta blockers (n = 17), and diuretics (n = 16), and excess fluid volume status was alleviated for at-least six months before collecting MRI data. None of the HF patients had evidence or history of alcohol-induced cardiomyopathy or diastolic failure, valvular congenital heart defects, drug abuse, stroke or carotid vascular disease, or head injury. Control subjects were recruited through advertisements at the UCLA hospital system and Los Angeles area. Control subjects were healthy, without any clinical history of cardiovascular disease, stroke, respiratory deficits, renal dysfunction, drug abuse, neurological or psychiatric conditions, and use of cardiac or psychotropic medications that may introduce brain injury. Since control subjects were not taking any cardiac medications and showed no signs of cardiovascular issues, subjects were not examined with echocardiography. All control and HF subjects with claustrophobia, inability to lay supine, carrying non-removable metal, embolic coils, pacemakers/implantable cardioverter-defibrillators, or stents, were excluded. Control and HF subjects provided written and informed consent before the study, and the study protocol was approved by the Institutional Review Board at UCLA.

Sleep quality and daytime sleepiness examination

Sleep quality for all subjects was assessed with the Pittsburgh sleep quality (PSQI), and daytime sleepiness with the Epworth sleepiness scale (ESS).[13, 14] The PSQI and ESS tests are self-administered questionnaires, and were performed either immediately before or after the MRI study for evaluation of sleep quality and daytime sleepiness.[13, 14]

Assessment of depression and anxiety

All HF and control subjects were assessed for depression and anxiety using the Beck depression inventory (BDI-II) and the Beck anxiety inventory (BAI), respectively.[15, 16] The BDI-II and BAI inventories are self-administered questionnaires (21 questions; each score 0–3), which were introduced either immediately before or after MRI examination, with total scores ranging from 0–63 based on symptom severity.[15, 16]

Cognitive examination

All HF and control subjects underwent the Montreal Cognitive Assessment (MoCA) test,[17] for rapid evaluation of cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A global MoCA score ≥26 is considered normal.[17]

Magnetic Resonance Imaging

All brain studies were performed in a 3.0-Tesla MRI scanner (Siemens, Magnetom Tim-Trio, Erlangen, Germany), using a receive-only eight-channel phased-array coil, and body coil as a transmitter coil. Subjects lay supine inside the scanner, and foam pads were used on both sides of the head to minimize head motion during data acquisition. Two high-resolution T1-weighted images were collected using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence [repetition-time (TR) = 2200 ms; echo-time (TE) = 2.34 ms; inversion time = 900 ms; flip-angle (FA) = 9°; matrix size = 320×320; field-of-view (FOV) = 230×230 mm^2; slice-thickness = 0.9 mm). Proton density (PD) and T2-weighted imaging (TR = 10,000 ms; TE1,2 = 12, 123 ms; FA = 130°; matrix size = 256×256; FOV = 230×230 mm^2; slice-thickness = 3.5 mm) were performed, covering the entire brain in the axial plane using a dual-echo turbo spin-echo pulse sequence. Arterial spin labeling scans were collected using a pseudo-continuous ASL (pCASL) pulse sequence in the axial plane (TR = 4000 ms; TE = 11 ms; FA = 90º; bandwidth = 3004 Hz/pixel; label-offset = 90 mm; label-delay = 1200 ms; matrix size = 64×64; FOV = 230×230 mm^2; slice thickness = 3.5 mm; distance factor = 20%; slices = 38; repeats = 40).

Data Processing and Analyses

We used the statistical parametric mapping package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/), MRIcroN, and MATLAB-based (The MathWorks Inc., Natick, MA) custom software for data processing and analyses.

We visually examined high-resolution T1-, PD-, and T2-weighted images of all subjects for any serious brain pathology, such as tumors, cysts, or major brain infarcts. Arterial spin labeling images were also examined for any potential head motion-related or other imaging

artifacts. None of the subjects included in this study showed any such brain pathology or imaging artifacts, which may affect regional CBF values.

Calculation of CBF maps—Labeled and non-labeled ASL brain volumes were realigned to remove any potential head motion-related variations. Using labeled and non-labeled echo-planar-imaging (EPI) scans, perfusion images were calculated with simple subtractions from non-labeled to labeled images. Perfusion images were used to calculate whole-brain CBF maps, as described elsewhere.[18]

Normalization and smoothing of CBF maps—The mean EPI images of each individual subject, were segmented into gray, white, and cerebrospinal fluid tissue types, and a 4D file that contained warping parameters (3D file for each direction) was generated using the modified unified segmentation approach implemented in SPM12.[19] Mean CBF, gray and white matter probability maps of the corresponding subject were transformed to Montreal Neurological Institute (MNI) space using the normalization parameters obtained earlier. The normalized CBF maps were smoothed using a Gaussian filter (kernel, 8mm).

We also normalized high-resolution T1-weighted images of a control subject to MNI space and removed cerebrospinal fluid and other non-brain regions. The resulting images were used as background images for structural identification.

Gray Matter Volume Calculation—Both high-resolution T1-weighted images from each subject were aligned, averaged, and partitioned to gray matter, white matter, and CSF tissue types. Gray matter probability maps were used to calculate global gray matter volumes from each subject using MATLAB-based custom-written software.

Global Brain Mask—The normalized white matter probability maps from HF and control subjects were averaged, and similarly, the normalized gray matter probability maps from all subjects were averaged. The averaged gray and white matter probability maps were thresholded (white matter probability > 0.3, gray matter probability > 0.3), and combined to create a global brain mask.

Statistical Analysis

Demographics and other variables—The Statistical Package for the Social Sciences (SPSS, v20.0, New York, NY) software was used for assessment of demographic, biophysical, physiological, mood, sleep, and cognitive variables between groups using Chi-square and independent samples t-tests. A p value of less than 0.05 was considered statistically significant.

Regional CBF changes—The smoothed CBF maps were compared voxel-by-voxel between HF and control subjects using analysis of covariance (ANCOVA; SPM12; covariates, age, gender, and global gray matter volume; uncorrected threshold, $P < 0.005$). The global brain mask was used to limit the analysis to brain regions only. Brain clusters with significant differences between groups were overlaid onto background images for structural identification.

Regional CBF values—Binary masks of each individual brain regions, which showed significant differences between groups based on whole-brain voxel-based analyses, were created, and regional CBF values were calculated using the normalized and smoothed CBF maps with MATLAB-based custom-written software. Regional CBF values were compared between groups using ANCOVA, with age, sex, and global gray matter volume included as covariates to examine significant differences and effect sizes between groups on those sites. A value of $P < 0.05$ was chosen to establish statistical significance.

RESULTS

Demographics and Other Variables

Demographic, biophysical, physiological, mood, sleep, and cognitive data of HF and control subjects are summarized in Table 1. No significant differences in age, gender, body mass index (BMI), or heart rate emerged between HF and control subjects (age, $p = 0.09$; gender, $p = 0.65$; BMI, $p= 0.12$; heart rate, $p = 0.85$). However, both systolic ($p = 0.005$) and diastolic ($p = 0.02$) blood pressure values were significantly lower in HF over control subjects. PSQI scores were significantly higher in HF ($p = 0.02$) over controls; however, ESS scores showed no significant differences. HF subjects had significantly higher BDI-II ($p = 0.004$) scores as compared to controls. Global MoCA scores were significantly lower in HF compared to controls ($p = 0.02$), with significant differences in delayed recall scores ($p = 0.003$). Also, global gray matter volume significantly differed between HF and control subjects ($p = 0.01$).

Regional CBF Changes

Multiple brain areas showed reduced regional CBF in HF compared to control subjects, with principally-lateralized lower flow in occipital, temporal, frontal, and parietal regions (Fig 1). Sites with lower CBF values in HF subjects emerged in the bilateral prefrontal cortex, extending through frontal white matter and the left anterior corpus callosum. Bilateral anterior thalamus, dorsal hippocampus, amygdala, and occipital cortex showed lower CBF values in HF patients. The reduced flow was remarkable for the dorsal temporal and occipital white matter regions, along with principally right-sided appearance in corona radiate, superior parietal, mid-temporal, and mid-occipital cortices; bilateral cerebellar vermis and anterior cerebellar cortex, extending to left posterior cerebellar cortex (Fig 2, 3). A few sites with limited clusters, including the bilateral inferior frontal white matter, showed increased CBF values in HF over control subjects.

Regional CBF values

Regional CBF values of HF and control subjects are summarized in Table 2. All brain sites showed significant reductions in HF over control subjects (Table 2).

DISCUSSION

Regional CBF reduction in HF patients appeared in multiple brain sites, and those regions included vascular beds over the frontal, parietal, and occipital cortices, hippocampus, thalamus, and cerebellar areas; the majority of these brain sites also show brain tissue injury,

based on previous studies.[1,3] A remarkable aspect is laterality of the CBF reduction, with the principal decline on the right side, appearing in cortical, and diencephalic areas; other areas showed bilateral CBF reductions, especially in the cerebellum and corona radiate. The decreased regional CBF may contribute to tissue injury in affected areas, and participate in the autonomic, neuropsychologic, and cognitive regulatory deficits found in the condition.

Reduced CBF in Autonomic Regulatory Sites

Autonomic nervous system abnormalities, including exaggerated sympathetic tone, excessive catecholamine outflow, impaired dynamic responses to cardiovascular challenges, and altered fluid regulation, are hallmarks of HF, and are present in nearly all persons with this condition.[20–23] Multiple brain autonomic regulatory sites showed reduced CBF in HF subjects, and include the hippocampus, thalamus, corona radiate and cerebellar sites. The affected structures also show abnormal functional MRI signal responses to autonomic and cardiovascular challenges in HF.[24] Structural injury has been identified in these brain sites by various MRI procedures, and the overlap of regional CBF reduction and injury suggests significant relationships between perfusion changes and brain tissue integrity. The cerebellar cortex, although usually implicated in movement control, is now recognized as playing major roles in blood pressure regulation, especially in coordinating blood pressure changes with motion or dampening extremes of blood pressure.[25–27] Cerebellar Purkinje cells primarily inhibit neurons of the fastigial nuclei, which project to brainstem and rostral brain sites that regulate sympathetic nervous outflow. The cerebellum coordinates motor patterning for smooth execution of voluntary movements and acquisition of motor behaviors along with coordination of breathing,[28] and respiratory timing interactions with momentary blood pressure changes, and integration of essential cardiovascular control processes, including the baroreflex and chemoreflexes.[29] Thus, reduced CBF in cerebellar sites has the potential to significantly influence autonomic patterning and contribute substantially to cardiovascular control deficits in HF.

Altered CBF values in Mood Regulatory Sites

HF patients exhibit high levels of mood symptoms,[30] which can impede self-care and lead to deterioration of quality of life. In this study, both depression and anxiety symptoms were significantly increased in HF subjects. Brain sites associated with mood regulation include the prefrontal cortex, cingulate, insula, hippocampus, amygdala, and cerebellar areas.[3] These brain sites have been associated with injury in subjects with depression only;[31] however, the majority of these areas also showed reduced CBF here in HF subjects. The amygdala is also involved in anxiety regulation, and the bilateral amygdalae showed reduced CBF here. Reduced CBF in these regions likely contribute to tissue changes, and thus, have the potential to modify levels of depressive and anxiety symptoms in HF subjects.

Altered CBF in Cognitive Regulatory Regions

Brain sites that regulate short-term memory and decision-making executive functions, including the hippocampus and prefrontal cortex, showed CBF changes in HF subjects. The affected areas include large collections of nerve fibers; the corpus callosum serves verbal memory functions, among other actions, and the corona radiate are associated with intellectual, social, and emotional functioning. The hippocampus sends information to the

mammillary bodies through the fornix fibers, and the mammillary bodies project to the anterior thalamus, from which information is distributed to cortical and other sites;[32] the CBF reduction is particularly shown in Figures 2 and 3. Although altered CBF appeared only on hippocampal regions and the thalamus, structural injury emerged on the majority of these sites as noted on previous studies,[33,34] and tissue injury in this memory circuitry can affect memory processing issues accompanying the condition. Our previous studies showed hippocampal volume loss in HF, predominantly in the CA1 subregion and hippocampal-mammillary body circuitry, leading to impaired anterograde and spatial memory functions.[34]

Short-term memory loss is one of the most common cognitive issues in HF, with an incidence ranging from 23–80% in the condition.[35] Subjects with short-term memory loss show impaired ability to learn and carry out essential self-management strategies, such as accurately and appropriately following dietary and medication regimens, recognizing symptoms associated with deteriorating health, and communicating clearly with a health care provider.[35,36] The loss of memory and learning abilities to self-manage HF increases the risk for HF exacerbations and associated morbidity and mortality in this condition.

CBF reductions appeared in the prefrontal cortex, a structure which plays critical roles in cognitive actions, including executive decision-making. The region sends and receives information from cortical sensory, sub-cortical, and motor areas, including the caudate nuclei and putamen; changes in this site may contribute to altered decision making functions in the condition.

Executive decision-making includes initiating, maintaining, and ceasing actions to organize behaviors toward a specific target with abstract and conceptual thinking. These functions are impaired in HF, and can afflict 19–50% of these patients.[37] The pre-frontal cortex is the most common brain region associated with impaired executive decision-making,[38] and damage shows a form of “psychological inertia” (inability to stop or change a behavior), which can impede important self-care behaviors, deficient in HF.

Reduced CBF in vision, language and speech regulation sites

HF patients often suffer from abnormal visual, language, and speech functions.[35,39–42] Multiple brain areas, including the superior parietal, mid-temporal and mid-occipital cortices, which help regulate these deficient functions,[43–45] showed reduced CBF in HF patients. Temporal cortical areas that play significant roles in speech control,[43] and tissue under the superior parietal regions that regulate language[44] show reduced CBF in HF patients. Other cortical sites that control visual domains include mid-occipital, lingual, precuneus, and superior parietal cortex.[45] Altered CBF in these visual and language regulatory areas may contribute to impaired functionality.

Reduced CBF in various White Matter regions

Reduced CBF in white matter regions are associated with poorer cognitive function, may put individuals at risk for development of dementia, and are more prevalent among certain psychiatric disorders.[9] Further, an inverse association exists between cardiac output and white matter hyperintensities, suggesting that systemic hypoperfusion may increase the risk

for development of hyperintensities,[46] and might lead to lower CBF on those white matter regions.[47]

Potential Mechanisms for Reduced Regional CBF

Precise mechanisms that may contribute to decreased regional CBF in HF are unknown, but may include low cardiac output, endothelial dysfunction, ischemic changes and disruption of cerebral autoregulation. Low cardiac output is characteristic of HF, leading to ischemia, which affects both tissue and vasculature, altering endothelial function. Altered endothelial function can contribute to abnormal cerebral autoregulation, reflected as decreased CBF in HF subjects. Cerebral autoregulation is affected by exaggerated sympathetic activity[48] and the renin-angiotensin system, which is a central neurohormonal response to maintain cardiac output and systemic hemodynamics.[49] Endothelin concentration, a vasoconstrictive peptide might increase from disturbed neurohormonal activity and consequently increases vascular resistance of cerebral vascular bed and reduces CBF.[50,51] Exacerbated neurohormonal system releases β-type natriuretic peptide, a marker of HF severity, as a response to increase ventricular wall stretch and may cause distortion of autoregulation and reduced CBF.[52] Both endothelin[53] and β-type natriuretic peptide[54] neurohormones play an important role in endothelial dysfunction. Cerebral autoregulation maintains a stable CBF over a wide range of mean arterial pressure; however, HF-induced activation of neurohormonal systems may play a crucial role in distorting autoregulation.[55] All our HF subjects had reduced systolic left ventricular function, which decreases perfusion pressure, and thus, can potentially reduce CBF.[56] Cardiomyopathic rabbits show CBF reduction following chronic low cardiac output.[49] HF is accompanied by reduced end-respiratory CO_2 concentrations that reduce the partial pressure of blood CO_2. Lower CO_2 contributes to reduced cerebral arteriolar dilation, which leads to reduced CBF.[48,55] Though 80% of our HF subjects were on angiotension-converting enzyme inhibitors, which maintain or increase CBF in HF,[57–59] reduced CBF levels indicate that additional mechanisms are operating. Local CBF loss can lead to focal cerebral ischemia, contributing to further brain tissue injury. The accumulation of such brain injury can directly contribute to pathogenesis of autonomic and other dysfunctions in HF.[60,61] Mild non-ischemic HF subjects showed significant changes in basilar inflow volume, cerebral autoregulation and vasomotor reactivity, although the small sample size precluded CBF to reach significant levels.[62]

Limitations

Several limitations of this study should be acknowledged. Some brain sites, including the cerebellar regions, temporal white matter, and corona radiate showed significant dispersion in CBF values in a few HF subjects. However, other sites showed minimal dispersion, which encouraged us to include these subjects in the analyses. Also, HF subjects showed significant low blood pressure as compared to controls. Those differences in blood pressure may contribute to compromised CBF; further studies are needed to explore the influence of this issue.

CONCLUSIONS

HF patients show decreased regional CBF values in several brain regions, compared to control subjects. The reduced CBF in HF patients appeared over prefrontal, parietal, and occipital cortices, corpus callosum, temporal regions, thalamus, hippocampus, amygdala and cerebellar regions that control autonomic, cognitive, and mood functions. The pathological processes that contribute to decreased regional CBF in HF are unknown, but may include reduced cardiac outflow commonly found in the condition, as well as increased sympathetic influences on the local cerebral vascular from the overall exaggerated sympathetic tone.

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ABBREVIATIONS

ASL	Arterial Spin Labeling
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
CBF	Cerebral Blood Flow
EPI	Echo Planar Imaging
ESS	Epworth Sleepiness Scale
FA	Flip Angle
FOV	Field Of View
HF	Heart Failure
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
pCASL	Pseudo-Continuous Arterial Spin Labeling
PD	Proton Density
PSQI	Pittsburgh Sleep Quality Index
SPM	Statistical Parametric Mapping

TR	Repetition Time
TE	Echo Time

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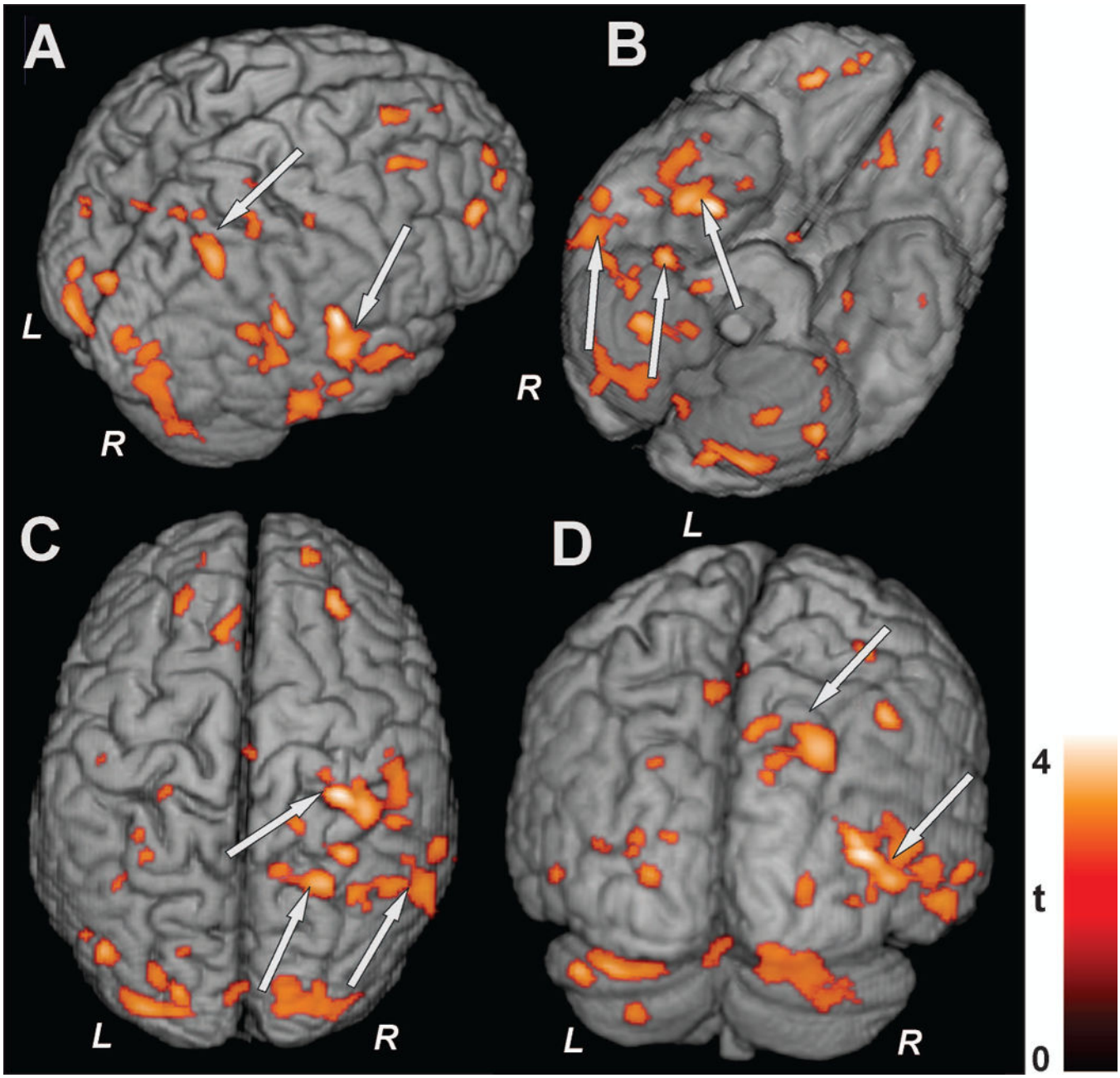

Figure 1.

Lateralized CBF changes in HF subjects. 3D views (A–D) of brain with decreased regional CBF in HF compared to control subjects, with arrows pointing to widespread sites suggesting lateralized CBF changes. Clusters are overlaid onto a 3D whole-brain cortical surface for structural identification (*L = Left; R = Right*). Color bar indicates t-statistic values.

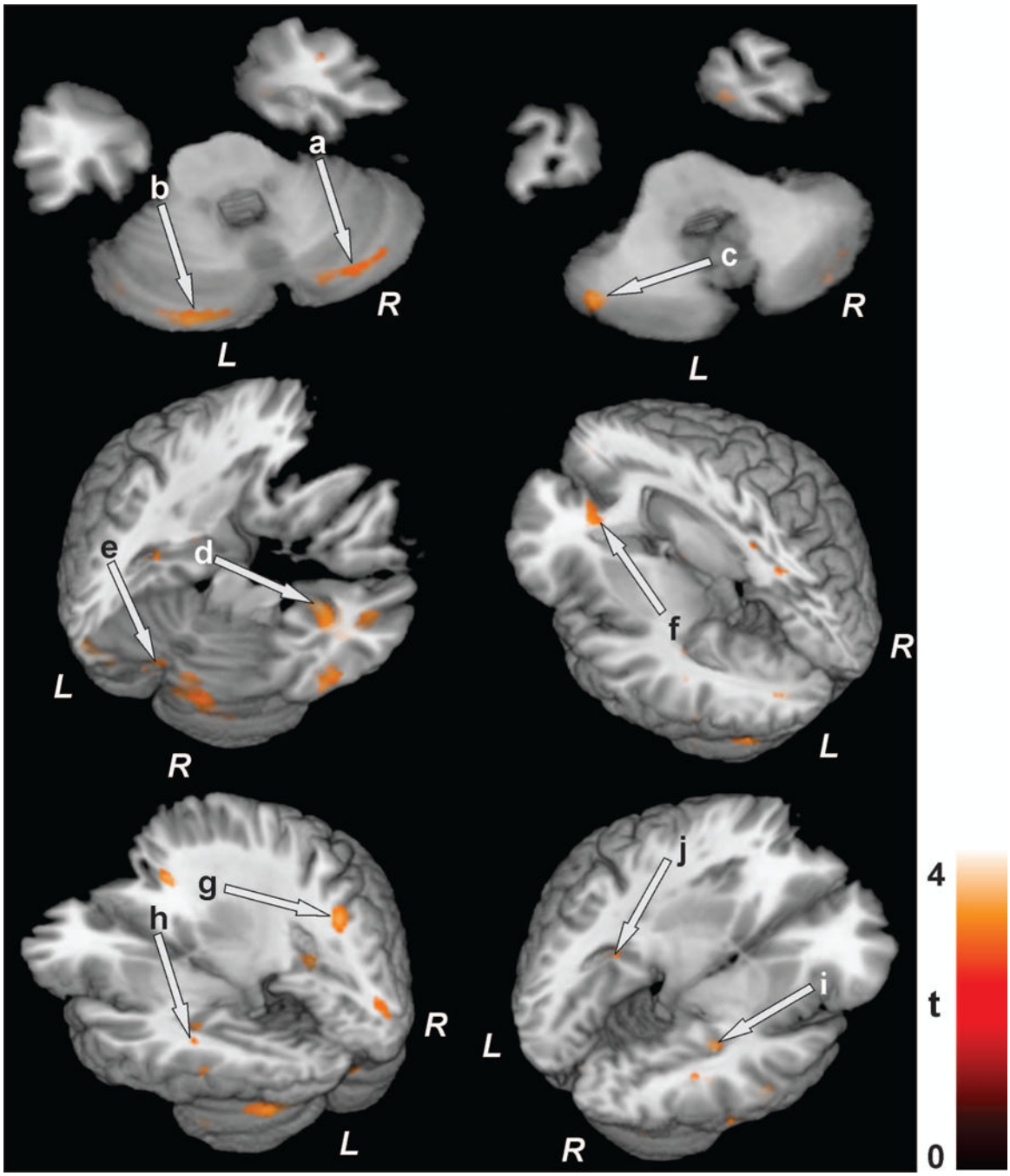

Figure 2.

Brain regions with reduced CBF in HF over control subjects. These sites with reduced CBF included the bilateral anterior cerebellar cortex (a, b), left posterior cerebellar cortex (c), right amygdala (d), cerebellar vermis (e), left anterior corpus callosum (f) bilateral mid-dorsal temporal white matter (g, h), and bilateral dorsal hippocampus (i, j). All images are in neurological convention (*L = Left; R = Right*). Color bar indicates t-statistic values.

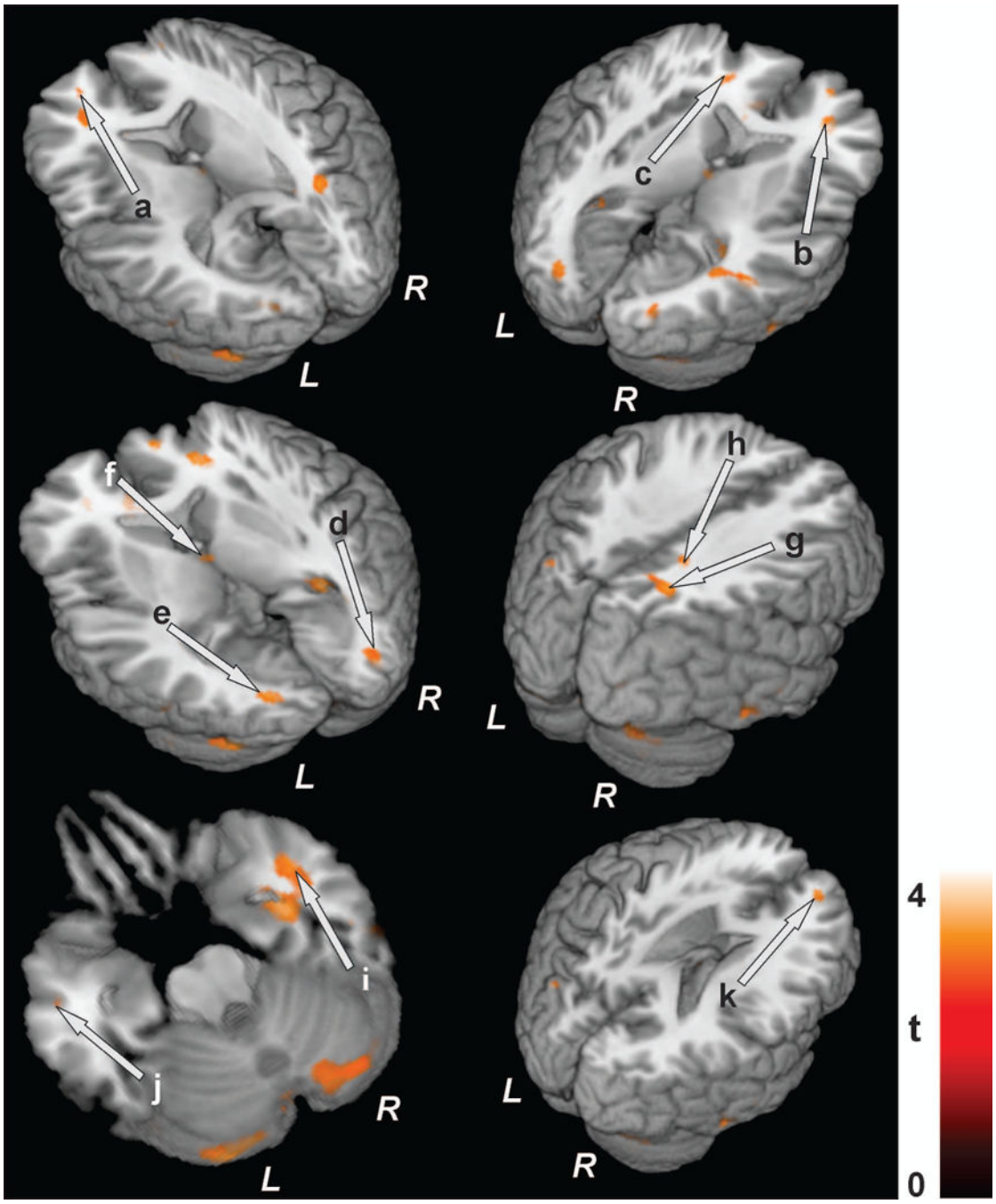

Figure 3.

Brain sites with lower CBF values in HF over control subjects. Decreased CBF values appeared in the bilateral pre-frontal cortex (a, k), frontal white matter (b, c), occipital cortex (d, e), anterior thalamus (f), right superior parietal cortex (g), right corona radiata (h), and bilateral mid-temporal cortex (i, j). Figure conventions are same as in Figure 2.

Table 1

Demographics and other variables of HF and control subjects.

Variables	HF (Mean ± SD) [n = 19]	Controls (Mean± SD) [n = 29]	*p* values
Age (years)	55.5 ± 9.1	51.4 ± 5.3	0.09
Gender (Male:Female)	13:6	18:11	0.65
BMI (kg/m^2)	27.7 ± 5.3	25.7 ± 3.6	0.12
Heart rate (beats/min)	73.0 ± 15.9	73.8 ± 13.6 (n= 23)	0.85
Systolic BP (mmHg)	106.6 ± 15.2	122.4 ± 18.4 (n= 23)	0.005
Diastolic BP (mmHg)	68.9 ± 10.8	78.8 ± 14.4 (n= 23)	0.02
PSQI	8.2 ± 4.7 (n= 10)	3.6 ± 2.5 (n= 22)	0.02
ESS	6.0 ± 2.7 (n= 10)	5.1 ± 4.1 (n= 22)	0.53
BDI-II	10.0 ± 6.6(n= 10)	4.1 ± 4.1(n= 22)	0.004
BAI	10.2 ± 9.6(n= 10)	3.5 ± 4.7 (n= 22)	0.06
Global MoCA scores	25.1 ± 3.6	27.4 ± 1.7 (n= 23)	0.02
MoCA: Visuospatial	3.7 ± 1.2	4.3 ± 0.8 (n= 23)	0.09
MoCA: Naming	3.0 ± 0.0	2.8 ± 0.5 (n= 23)	0.10
MoCA: Attention	5.3 ± 1.0	5.6 ± 0.7 (n= 23)	0.20
MoCA: Language	2.3 ± 0.8	2.3 ± 1.0 (n= 23)	0.85
MoCA: Abstraction	1.9 ± 0.3	2.0 ± 0.0 (n= 23)	0.16
MoCA: Delayed recall	2.9 ± 1.9	4.4 ± 0.7 (n= 23)	0.003
MoCA: Orientation	6.0 ± 0.0	6.0 ± 0.0 (n= 23)	
LVEF (%)	30.5 ± 11.5	–	–
Global GM volumes (L)	0.61 ± 0.07	0.66 ± 0.06	0.01

HF= Heart failure; SD = Standard deviation; BMI = Body-mass-index; BP= Blood pressure; PSQI= Pittsburgh Sleep Quality Index; ESS= Epworth Sleepiness Scale; BDI-II= Beck Depression Inventory II; BAI= Beck Anxiety Inventory; MoCA= Montreal Cognitive Assessment; LVEF = Left ventricular ejection fraction; GM= Gray Matter.

Table 2

Regional brain CBF values of HF and control subjects corrected for age, gender and gray matter volume.

Regions	**HF Mean CBF ± SD (mL/100 g/min)**	**Controls Mean CBF ± SD (mL/100 g/min)**	***p* values**
Left Anterior Cerebellar Cortex	22.2 ± 20.0	43.8 ± 19.6	0.001
Right Anterior Cerebellar Cortex	23.6 ± 23.5	47.6 ± 23.0	0.002
Left Posterior Cerebellar Cortex	22.1 ± 16.8	38.1± 16.4	0.003
Cerebellar Vermis	17.4 ± 17.5	35.0 ± 17.1	0.002
Left Amygdala	42.7 ± 12.3	54.3 ± 12.0	0.004
Right Amygdala	36.8 ± 14.3	53.2 ± 14.0	0.001
Left Hippocampus	30.9 ± 15.1	45.9 ± 14.8	0.002
Right Hippocampus	33.2 ± 15.4	49.8 ± 15.1	0.001
Anterior Thalamus	32.7 ± 18.7	50.1 ± 18.3	0.004
Left Dorsal-Temporal WM	7.2 ± 10.8	17.9 ± 10.5	0.002
Right Dorsal-Temporal WM	16.6 ± 13.9	31.8 ± 13.6	0.001
Left Occipital Cortex	17.8 ± 14.0	32.8 ± 13.7	0.001
Right Occipital Cortex	21.1 ± 14.3	35.6 ± 14.0	0.002
Left Pre-frontal cortex	27.1 ± 11.4	37.8 ± 11.2	0.004
Right Pre-frontal cortex	26.3 ± 12.5	39.5 ± 12.2	0.001
Left Frontal WM	16.6 ± 11.2	27.9 ± 11.0	0.002
Right Frontal WM	16.8 ± 10.2	28.3 ± 10.0	0.001
Right Superior Parietal Cortex	27.0 ± 18.5	46.6 ± 18.1	0.001
Left Anterior Corpus Callosum	24.3 ± 10.4	35.7 ± 10.2	0.001
Right Corona Radiata	15.6 ± 18.3	33.4 ± 17.9	0.003

CBF= Cerebral blood flow; HF= Heart failure; SD = Standard deviation; WM= White matter.