Voxel-based T2 Relaxometry Detects Brain Injury in Autonomic and Cognitive Regulatory Areas in Patients with Heart Failure

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Summary:

Heart failure (HF) patients often show severe autonomic, emotional, and cognitive deficits which could only result from brain alterations; yet, there are few reports describing brain injury in this group. We assessed neural injury in HF and controls using voxel-based T2 relaxometry. Higher T2 relaxation values in HF, indicating areas of injury, emerged in hypothalamus, solitary tract nucleus, hippocampus, cerebellum, caudate, thalamus, anterior fornix, corpus callosum, cingulate, and insula. The affected structures are essential to maintain autonomic, mood and cognitive functions. The mechanisms underlying damage are unclear, but may result from ischemic or hypoxic processes.

Introduction:

Autonomic, cognitive, and emotional deficits are common in heart failure (HF) and are linked to increased morbidity and mortality. These deficits are associated with brain injury in other populations, but the linkage has not been examined in HF. Isolated white matter infracts appear in HF, and gray matter volumetric procedures show gray matter deficits in cerebellar, limbic and cortical regions (1). Areas with gray matter loss overlapped sites of altered functional MR signals to Valsalva maneuver and cold pressor challenges (2, 3), and may contribute to the physiological and behavioral deficits found in the syndrome. However, gray matter volumetric procedures are restricted to gray matter assessment, and do not show the extent of injury in the entire brain, especially of fiber systems which interconnect different brain structures. Magnetic resonance T2 relaxometry assesses free water content in tissue, a measure that increases with cellular injury. Our aim was to determine, with T2 relaxometry procedures, regional brain injury which could underlie the autonomic, cognitive, and emotional deficits in HF.

Materials and methods:

Thirteen hemodynamically optimized HF patients (age range = 40 - 64 years; mean age ± SD = 54.6 ± 8.3 years; 9 male) and 49 control subjects (39 - 64 years; 50.6 ± 7.3 years; 29 male) were studied. All HF patients were diagnosed based on national HF diagnostic criteria, and showed systolic dysfunction with New York Heart Association functional class I-II. Left ventricular ejection fraction for all HF subjects was < 40%. All control subjects were without history of cardiovascular, respiratory, or neurological disorder.

Brain images were collected using a 3.0 Tesla MRI scanner (Magnetom Tim-Trio, Siemens). Proton-density (PD) and T2-weighted images (TR = 10,000 ms; TE1, TE2 = 17, 134 ms; FA = 130°; turbo factor = 5; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 4.0 mm) were collected using a dual-echo turbo spin-echo sequence in the axial plane. T1-weighted images were also collected using a MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; TI = 900 ms; FA = 9°; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 1.0 mm; number of slices = 176) for evaluation of anatomical defects and structural identification. Data were analyzed with SPM5 and Matlab-based custom software. Using PD and T2-weighted images, voxel-by-voxel T2 relaxation time values were calculated and T2 maps were constructed. T2 maps were normalized to the standard Montreal Neurological Institute space, and smoothed. The normalized and smoothed T2 maps of HF and control subjects were compared at each voxel using analysis of covariance, with age and gender as covariates ($p < 0.005$, uncorrected). The brain areas with T2 value differences between HF and control groups were overlaid onto mean anatomical image for structural identification.

Results:

Multiple brain sites in HF subjects showed significantly higher T2 values compared to control subjects, indicating brain tissue injury. No brain regions emerged with higher T2 values in control subjects compared to HF subjects. Brain areas with significantly increased T2 values in HF subjects appeared in genu, and rostral portions of the corpus callosum, genu, mid and posterior cingulate cortices, left posterior and right anterior insular cortices, ventral medial prefrontal cortex, anterior fornix and basal forebrain, posterior hypothalamus, anterior thalamus, bilateral caudate nuclei, cingulum bundle bordering to parahippocampal gyrus, hippocampus, and then posterior limb of internal capsule. Significantly prolonged T2 values also appeared in solitary tract nucleus extending to dorsal pons, dorsal superior and dorsolateral surface of the temporal cortices, bilateral superior and left medial prefrontal, occipital, and parietal cortices. Abnormal clusters also emerged in the cerebellar vermis, bilateral caudal and left ventral cerebellar cortices, and cerebellar deep nuclei.

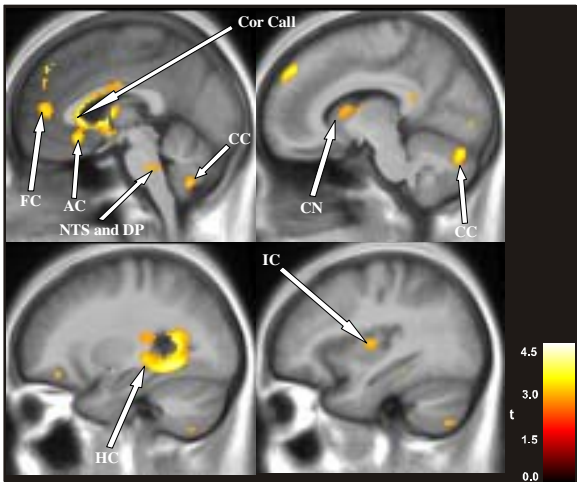

Figure 1: Brain regions with significantly increased T2 values in HF vs controls. FC = Frontal cortex, AC = Anterior cingulate, NTS and DP = Solitary tract nucleus extending through the dorsal pons, CC = Cerebellar cortex, Cor Call = Corpus callosum, CN = Caudate nuclei, HC = Hippocampus, IC = Insular cortex.

Discussion:

Several brain sites in HF patients show prolonged T2 values, suggesting damage in those areas. Brain injury emerged in the cerebellum, insula, solitary tract, cingulate, ventral prefrontal cortex, anterior thalamus, basal forebrain and posterior hypothalamus; these sites are essential for maintaining autonomic control, which is severely affected in HF. Brain structures, including the insular and cingulate cortices, have been implicated in mediating depression and anxiety symptoms in addition to autonomic control; both depression and anxiety are common in HF. Other abnormal brain regions included the caudate nuclei, corpus callosum, thalamus, anterior fornix, hippocampus, frontal, parietal, and occipital cortices. Several of these regions, including the hippocampus and its projecting fibers in the fornix, play significant roles in short term memory; the caudate nuclei and prefrontal cortex play additional roles in cognitive function, which is frequently disturbed in HF subjects. The mechanisms underlying the damage are unclear, but may include ischemic or hypoxic processes.

References:

1. Woo MA et al., *J Appl Physiol* 95: 677-684, 2003.
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