Increased Global and Regional Brain Mean Diffusivity in Patients with Heart Failure

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Introduction:

Heart failure (HF) patients show gray matter and axonal deficits in multiple autonomic, cognitive, and emotional regulatory brain areas (1, 2). The processes underlying the structural deficits are unclear, but may result from compromised perfusion from low cardiac output, abnormally distributed cerebral blood flow, or from hypoxia induced by sleep-disturbed breathing in the condition, which can induce acute or chronic tissue changes. It is unknown whether the detected structural injury is acute or chronic, but that determination is essential to develop therapeutic and management strategies. Diffusion tensor imaging (DTI)-based mean diffusivity (MD) procedures measure average water diffusion within tissue, and show decreased MD values in acute conditions and increased MD values with chronic injury, and therefore may allow examination of pathological state of brain tissue in HF. Our aim was to determine whether the structural changes we found in HF resulted from transient alterations, i.e., acute tissue changes, or whether the damage indicated long-term effects. We thus examined global and regional brain MD in HF patients compared to healthy controls, and hypothesized, based on the severity and duration of autonomic changes exhibited by these patients, that both global and regional MD values would be increased in HF, reflecting chronic changes.

Materials and methods:

Sixteen hemodynamically-optimized HF (age, 55.1±7.8 years; 12 male; left-ventricular-ejection-fraction, 28.0±7.0) and 26 control (49.7±10.8 years; 17 male) subjects were studied. All HF subjects were diagnosed based on national HF diagnostic criteria, showed dilated cardiomyopathy and systolic dysfunction, and were classified as New York Heart Association Functional Class II. Heart failure subjects were without any previous history of stroke or carotid vascular disease, and were treated with angiotension-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, and beta blockers titrated to specific hemodynamic goals (3). All control subjects were healthy, had no history of cardiovascular, cerebrovascular, respiratory, or neurological disorders, and were without any cardiac or psychotropic medications. All subjects gave written and informed consent before the study, and the study protocol was approved by the IRB. Brain imaging of HF and control subjects was performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens) with an 8-channel phased-array head coil. High-resolution T1-weighted images were acquired using an MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion-time = 900 ms; flip-angle = 9°; matrix-size = 256×256; FOV = 230×230 mm; slice-thickness = 1.0 mm). Diffusion tensor imaging was performed using single-shot echo-planar imaging with twice-refocused spin-echo pulse sequence (TR = 10,000 ms; TE = 87 ms; FA = 90°; BW = 1346 Hz/ pixel; matrix size = 128×128; FOV = 230×230 mm; thickness = 2.0 mm, no interslice-gap, b = 0 and 700 s/mm^2; diffusion gradient directions = 12; separate series = 4). Using diffusion- and non-diffusion-weighted images, diffusion tensors were calculated and principal eigenvalues ($\lambda1$, $\lambda2$, and $\lambda3$) were derived by diagonalizing the diffusion tensor matrices. Using principal eigenvalues, MD maps [MD = ($\lambda1+\lambda2+\lambda3$)/3] were derived from each DTI series. Mean diffusivity maps, determined from each DTI series, were realigned, averaged, normalized to Montreal Neurological Institute (MNI) space, and smoothed (Gaussian filter, 10 mm). Gray and white matter probability maps, derived from b0 images of HF and control subjects, were also normalized to MNI space, corresponding maps averaged, and a global brain mask calculated. We also normalized high-resolution T1-weighted images of HF and control subjects to MNI space, and averaged normalized images to derive background images. We used the global brain mask and normalized MD maps to calculate global brain MD values from individual HF and control subjects, and compared these values between groups (ANCOVA; covariate, age; SPSS v20.0 software). We also compared the normalized and smoothed MD maps between the groups using ANCOVA (covariate, age; SPM8, uncorrected threshold, $p < 0.005$). Brain sites with significant clusters showing group differences between HF and controls were overlaid onto background images for structural identification.

Results:

Heart failure subjects did not differ significantly in age, gender, or body mass index from control subjects. Mean global brain MD values were significantly increased in HF compared to controls (HF vs controls; $1.09\pm0.06 \times 10^{-3}$ vs $1.05\pm0.06 \times 10^{-3}$ mm^2/s; $p = 0.038$). Multiple brain sites in HF showed significantly increased MD over control subjects (Fig. 1, warm colors). Significantly increased MD values in HF appeared in bilateral structures, including the parietal cortices, frontal white matter, caudate nuclei, internal capsules, anterior and posterior thalamus, ventral hippocampus, hypothalamus, anterior insula, cerebellar vermis and cortices, and unilateral sites in the right mid cingulate cortex, extending to corpus callosum, right posterior cingulate and corpus callosum, left mid insular cortex, right ventral temporal white matter and cortical area, right occipital cortex, left anterior putamen, and right middle cerebellar peduncle compared to control subjects. Other sites with increased MD values in HF included the midbrain, cerebellar deep nuclei, and raphe, extending to nucleus of the solitary tract over controls.

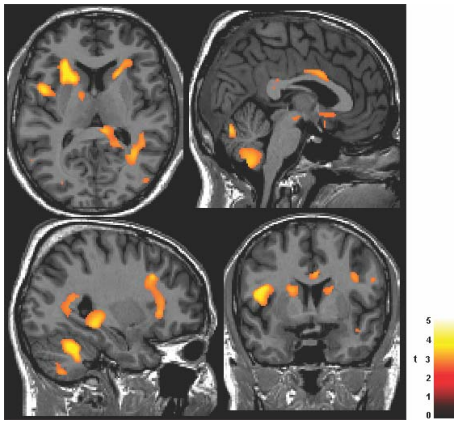

Fig. 1: Selected brain areas with increased MD values in HF (n = 16) over control subjects (n = 26).

Discussion:

Mean diffusivity measures showed increased values in multiple brain areas in HF compared to control subjects, indicating chronic tissue changes in those sites. These areas included limbic, basal ganglia, thalamic, hypothalamic, and cerebellar regions that control autonomic, cognitive, and mood functions. The pathological mechanisms contributing to chronic tissue changes in HF may result from a combination of ischemic and hypoxic processes accompanying the syndrome.

References:

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