Regional Reduction in Cerebral Blood Flow in Patients with Heart Failure

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Introduction:

Heart failure (HF) patients show multiple autonomic, neuropsychological, and cognitive deficits, which are related to their increased morbidity and mortality. Such aberrant symptoms are only possible from alterations in central nervous structure and function. Both gray and white matter show injury in HF, as assessed by several MRI procedures, including voxel-based morphometry (1), quantitative T2-relaxometry (2), and diffusion tensor imaging (3); the damage may develop from perfusion changes in the condition. Although gross cerebral blood flow (CBF) is distorted across the brain in HF, localized CBF changes are unknown. Arterial spin labeling (ASL)-based perfusion imaging offers a non-invasive, no-contrast means to examine regional CBF across the entire brain, using magnetically labeled arterial blood water as an endogenous tracer. The noninvasive nature of ASL is appealing for subjects with poor renal function or difficult intravenous access, such as many HF patients. ASL-based CBF measurements have been validated using 15O-water positron emission tomography, and are reproducible over hours and days, making it favorable for disease identification, tracking disease progression, and treatment effects. The stable, non-invasive nature of ASL measures offered the potential to assess regional CBF changes in HF. Our specific purpose for this study was to examine regional CBF changes in HF over control subjects. We hypothesized that localized CBF would be altered in HF in brain areas that control functions deficient in the condition.

Materials and methods:

Six hemodynamically-optimized HF (age, 52.7±11.8 years; body mass index, 31.0±2.3 kg/m^2; left ventricular ejection fraction, 32.3±9,3; 4 male) and 6 control subjects (age, 56.3±2.9 year; body mass index, 25.3±2.2 kg/m^2; 3 male) were included in this study. HF subjects were diagnosed based on national diagnostic criteria, recruited from the UCLA Cardiomyopathy Center, and body weights were stabilized for at-least 6 months prior to MRI data collection. Control subjects were healthy, without any disorder that might introduce brain injury, and were recruited through the UCLA hospital system and Los Angeles area. Control and HF subjects provided written and informed consent before the study, and the study was approved by the IRB at UCLA.

Brain studies were performed in a 3.0-Tesla MRI scanner (Magnetom Trio, Siemens, Germany). High-resolution T1-weighted images were collected using a MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion time = 900 ms; FA = 9°; matrix size = 256×256; FOV = 230×230 mm; slice-thickness = 1.0 mm). ASL scans were collected using a pseudo-continuous ASL pulse sequence in the axial plane (TR = 4000 ms; TE = 11 ms; FA = 90º; BW = 3004 Hz/pixel; label offset = 90 mm; label-delay = 1200 ms; matrix size = 64×64; FOV = 230×230 mm; slice thickness = 3.5 mm; distance factor = 20%; slices = 38; repeats = 40). Data were analyzed using the statistical parametric mapping package (SPM8), MRIcroN, and MATLAB-based custom software. Labeled and non-labeled ASL brain volumes were realigned to remove any head motion-related variation. Using labeled and non-labeled EPI scans, perfusion images were calculated with simple subtractions from non-labeled to labeled images, and whole-brain CBF maps were calculated from these images. The EPI scans and CBF maps were averaged across the series to derive a mean EPI scan and CBF map per individual. Mean CBF maps of individual HF and control subjects were normalized to the Montreal Neurological Institute (MNI) space, using unified segmentation approach (4). The normalized CBF maps were smoothed using a Gaussian filter (kernel, 10 mm), and compared between groups using ANCOVA (covariates, age and gender; uncorrected threshold, $p < 0.005$) implemented in SPM8 software. The brain clusters with significant regional differences between the groups were overlaid onto background images for structural identification.

Results:

Age ($p = 0.48$) and gender ($p = 0.34$) showed no significant differences between HF and control subjects. However, body mass index significantly differed between the groups ($p = 0.001$). Multiple brain areas in HF subjects showed regionally decreased CBF values compared to control subjects (Fig. 1; gray areas). No regions appeared with increased CBF values in HF compared to control group. Sites with decreased CBF values in HF subjects emerged in the left prefrontal and parietal cortices, anterior corpus callosum, right occipital cortices, right dorsal, mid, and ventral temporal lobe, bilateral anterior, mid, and posterior thalamus, bilateral putamen, right insula, bilateral dorsal hippocampus, midbrain and pons, bilateral caudal cerebellar cortices, left mid and inferior cerebellar peduncles, and regions within the medulla.

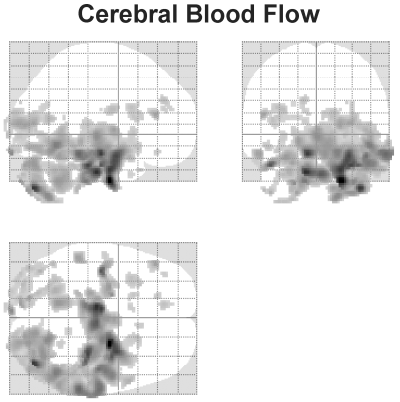

Fig. 1: Brain regions with significantly reduced CBF in HF over control subjects.

Discussion:

Declines in CBF in HF are remarkably localized to specific brain areas that contribute to the deficient neuropsychological and physiological characteristics in the condition. The memory and cognitive issues in HF may be related to the diminished flow in hippocampal, putamen, prefrontal cortex and cerebellar regions, while the blood pressure and other autonomic deficits likely stem from diminished insular and medullary flow, and language problems from the anterior corpus callosum and frontal cortex perfusion characteristics. The severe affective issues may arise from the multiple limbic and midbrain reduced flow. The pathological processes contributing to the localized decreased CBF in HF are unknown, but may cascade from initial injury to autonomic brain areas, especially raphe medullary areas, which then affect regional vascular beds.

References:

1. Woo, M.A., Macey, P.M., Fonarow, G.C., Hamilton, M.A., Harper, R.M. *J. Appl. Physiol.* 95: 677-84, 2003.
2. Woo, M.A., Kumar, R., Macey, P.M., Fonarow, G.C., Harper, R.M. *J. Card. Fail.* 15: 214-223, 2009.
3. Kumar, R., Woo, M.A., Macey, P.M., Fonarow, G.C., Hamilton, M.A., Harper, R.M. *J. Neurol. Sci.* 307: 106-13, 2011.
4. Ashburner, J., Friston, K.J. *Neuroimage* 26(3):839-51, 2005.

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