Regional brain gray matter loss in heart failure

Mary A. Woo, Paul M. Macey, Gregg C. Fonarow, Michele A. Hamilton, and Ronald M. Harper. Regional brain gray matter loss in heart failure. J Appl Physiol 95: 677–684, 2003. First published April 25, 2003; 10.1152/japplphysiol.00101.2003.—Heart failure (HF) patients exhibit enhanced sympathetic tone, aberrant responses to blood pressure challenges, and sleep-related breathing disorders, suggesting that the syndrome is accompanied by central neural deficits. We assessed regional gray matter volumes over the entire brain in nine HF patients (51 ± 10 yr; left ventricular ejection fraction 0.27 ± 0.06; six men) and 27 healthy controls (46 ± 12 yr; 22 men) using T1-weighted magnetic resonance imaging to evaluate potential neural damage. Regional volumes were evaluated by using voxel-based morphometry while controlling for age, gender, and handedness. HF patients showed significant and largely lateralized gray matter loss in autonomic and respiratory-related areas as well as regions not classically associated with such control, including the insula and basal ganglia, right cingulate gyrus, parahippocampal/fusiform gyrus, dorsal midbrain extending to the posterior and medial thalamus, ventral and superior lateral frontal cortex, bilateral cerebellar quadrangular lobules and right fastigial and neighboring nuclei, and bilateral deep parietal and lateral parietal-occipital cortex. Areas of gray matter loss may contribute to inappropriate cognitive, autonomic, and breathing regulation in HF.

autonomic; apnea; magnetic resonance imaging; Cheyne-Stokes; sleep

HEART FAILURE (HF) patients exhibit a variety of abnormal physiological and cognitive characteristics, including high levels of sympathetic tone and diminished levels of parasympathetic tone, high proportions of sleep-disordered breathing, and multiple cognitive deficits, including attention and memory issues (1, 8).

High sympathetic and decreased parasympathetic activity are characteristic of HF and are manifested as blunted baroreceptor activity (39), diminished parasympathetic effects on the sinoatrial node (14), increased norepinephrine (15), decreased heart rate variability (14, 52), and diminished responsiveness and number of β1-receptors (13). These characteristics may result from peripheral or central aberrations. The parasympathetic alterations may derive from reduced cardiac muscarinic receptors (33); however, they also may result from central nervous system (CNS) dysfunction (19).

The cognitive deficits also suggest CNS dysfunction, possibly developing from ischemic damage as a consequence of HF. The principal neurological deficit of HF patients appears to be delayed recall (42). This memory dysfunction suggests specific neural damage related to the hippocampus or frontal lobe or associated circuitry, rather than generalized deficits over the entire brain (7).

Approximately one-half of chronic HF patients exhibit obstructive sleep apnea (OSA) or Cheyne-Stokes breathing during sleep (24). OSA cases show significant gray matter loss in cerebellar, insular, and cortical areas, which may contribute to aberrant autonomic, cognitive, or breathing characteristics (31). Cheyne-Stokes breathing is sensitive to CO2 administration (28), suggesting deficient chemoreceptor integrative mechanisms in HF and specifically implicating cerebellar structures, which partially mediate such chemoreception (54). The continued presence of sleep-disordered breathing, despite optimal HF therapy and typical absence of gross anatomic features classically associated with OSA, such as obesity, micrognathia, or reduced upper airway dimensions (35), indicates a CNS component in the disturbed breathing in HF.

The collective evidence of disordered breathing during sleep, altered autonomic activity, and presence of cognitive deficits, with all characteristics occurring without obvious motor or primary sensory symptoms, suggests neural damage in sites serving specific roles in memory, CO2 regulation, and sympathetic and parasympathetic control. The objective of this study was to evaluate whether neural areas underlying control of these characteristics are affected in advanced HF patients.

METHODS

Subjects

Nine advanced HF patients (mean age = 51 ± 10 yr; six men) and 27 healthy controls (mean age = 46 ± 12 yr; 22 men) participated in this study. The mean body mass index of HF patients was 26 ± 5 kg/m², and the body mass index for the controls was 26 ± 4 kg/m². The HF patients met national HF diagnostic criteria (22a). All HF patients exhibited sys-
tolic dysfunction and were in New York Heart Association Functional Class III–IV. Three HF cases had coronary artery disease, and six were classified as idiopathic for the underlying etiology of their disease. Left ventricular ejection fraction for the HF patients was 0.27 ± 0.06. All HF patients were treated with optimal medical therapy [medications included angiotensin-converting enzyme inhibitors and diuretics titrated to specific hemodynamic goals (47)] and maintained stable weights (i.e., not in acute HF exacerbation and showing normal \(O_2\) saturations during waking). Four of the HF patients were taking aspirin, and four were taking warfarin. One of the HF patients had a history of stroke, which impacted his short-term memory, but did not leave residual motor dysfunction. The remaining eight HF patients did not have a clinical history of stroke, transient ischemic attack, or systolic embolization. Eight of the HF patients were in sinus rhythm, and one was in atrial fibrillation. The healthy controls were not on cardiac medications and had no history of cardiovascular disease.

All HF cases underwent a complete overnight polysomnographic recording at the University of California at Los Angeles Sleep Laboratory, an accredited facility, before the study. Sleep-disturbed breathing was considered present if the respiratory distress index (RDI) was >5 or if more than 30 apneic events per night occurred. Twenty-four of the 27 control subjects were monitored in the scanner facility until quiet sleep was established.

This study was approved by the Human Subjects Institutional Review Board at the University of California at Los Angeles. Written, informed consent for these studies was obtained from each subject.

**Structural MRI Acquisition and Analysis**

Anatomic T1-weighted image volumes were collected on a General Electric 1.5-T MRI scanner, with each consisting of 124 sagittal slices of 256 × 256 pixels, with a field of view of 30 × 30 cm, a slice thickness of ~1.2 mm, with no interslice gap. The Spoiled Gradient Recalled Acquisition in the steady-state sequence was used (repetition time = 24 ms, echo time = 9 ms, flip angle = 22°), and no MRI contrast media were administered.

The structural brain MRI data were analyzed by using SPM99 (16) and Matlab 6.5 (Mathworks, Natick, MA). Voxel-based morphometry (VBM), a method for detecting regional gray matter volume changes in magnetic resonance images, was used. The technique allows whole brain analysis of large samples, as opposed to manual definition of regions on a subject-by-subject basis (3). Whole brain volumes were initially spatially registered to a template based on the Montreal Neurological Institute MRI Brain Atlas (32). Volumes then were segmented into gray and white matter based on voxel intensity, with a correction for intensity differences due to MRI field inhomogeneities and a priori knowledge of likely distribution. The segmented images were corrected for volumetric changes resulting from the registration process. A “brain” mask, based on the segmented gray and white matter and removal of outlying unrelated clusters, was applied to the segmented volumes, removing regions outside the brain from gray matter volumes. The total volume of gray matter was calculated from these volume-adjusted, segmented, and masked images.

For regional comparisons, the volume-adjusted, segmented, and masked images were smoothed by using a Gaussian filter (12-mm full width at half-maximum). Smoothed images were analyzed for regional volumetric differences by using VBM. Statistical analysis consisted of population-level \(t\)-tests, resulting in statistical parametric maps (16) of the \(t\)-statistic for all voxels in the brain and indicating statistical level of volume differences. The effects of group membership were modeled while controlling for age, gender, and handedness. Significance level for the \(t\)-tests was set at \(P < 0.005\), with minimum cluster size of 200 voxels. Details of the VBM procedure, including issues of appropriate sampling and resolution, are described elsewhere (3).

**RESULTS**

Sleep-disordered breathing of either an obstructive or Cheyne-Stokes nature (or both) was found in seven of nine HF cases. None of the 24 control cases showed indications of either type of sleep-disordered respiration during monitoring. None of the remaining three controls reported any signs of impaired breathing during sleep. The extent of breathing impairment in the HF group was substantial (RDI median = 14, range = 3–74). Of the seven cases with RDIs >5, four showed both Cheyne-Stokes and obstructed breathing, and three showed only obstructed events. One patient showed \(O_2\) desaturation to 70% during apneic events; the remaining cases did not desaturate <90%.

**Total Gray Matter Volume Differences**

Whereas there was a tendency for increased overall gray matter in control subjects over HF cases, after correction for age and gender, that tendency was not statistically significant. With the exception of one HF subject (one of nine), no brain infarction sites in our sample were noted. The infarcted site of the one subject did not overlay any of the regional areas with reduced gray matter volume.

**Regional Gray Matter Volume Differences**

After the effects of age, gender, and handedness were controlled for, HF patients showed substantial gray matter loss in cortical, subcortical, and cerebellar regions. Losses were frequently lateralized, with the most prominent deficits found on the right side. No areas emerged with increased gray matter in HF subjects.

**Insular cortex and basal ganglia.** Significant gray matter loss occurred in both the left and right insular cortex. The loss was substantially larger on the right side, covered the entire insular region, and extended dorsally to the inferior border of the overlying frontal cortex (Fig. 1, A, B, and D). The right side loss extended medially to the ventral putamen and globus pallidus of the basal ganglia (Fig. 1B). A localized area of loss in the anterior-dorsal portion of the left insula (Fig. 1, B–D) emerged. The smaller area on the left side was also continuous, with a region of loss in the left dorsal putamen and globus pallidus, largely sparing the caudate (Fig. 1, B and D).

**Deep and inferior temporal cortex-parahippocampal gyrus.** An inferior temporal lobe cortical area bordering the hippocampus, extending forward within the depth of the collateral sulcus between the parahippocampal and fusiform gyri, showed gray matter loss (Fig. 2).
Cingulate gyrus, dorsal midbrain, and thalamus.
The right cingulate cortex showed significant loss over portions of the entire extent of the structure. The deficits clustered in four regions of loss within the gyrus (Fig. 3A). The left cingulate gyrus showed virtually no loss.

The right dorsal midbrain, extending to the posterior thalamus and also to the right medial thalamus, showed loss (Fig. 3A and C).

Cerebellum. Both cerebellar cortex and deep cerebellar nuclei were affected. Gray matter loss was found in a site overlapping the fastigial and globose nuclei and extended laterally to the dentate nucleus (Fig. 4, A–C). Significant loss was apparent bilaterally in the caudal quadrangular lobule of the cerebellar cortex (Fig. 4, D–F).

Ventral frontal, deep anterior parietal, superior lateral frontal, posterior parietal/occipital, and superior temporal cortex. The gray matter loss found in the right cingulate gyrus was adjacent to deep anterior parietal cortex loss (Fig. 5, A and B, and Fig. 6, B and C). The anterior parietal cortex areas of loss did not reach the surface and were bilateral and extensive.

The right caudal orbital frontal cortex showed an area of loss extending in a band from near the midline...
laterally to the lateral sulcus (Fig. 5, C and D, and Fig. 6, A and C). The band of loss was sited at the rostral-caudal level immediately forward to the optic chiasm and extended deep to the surface.

The right occipital cortex, overlapping the posterior parietal cortex, showed significant loss (Fig. 5, E and F, and Fig. 6, A, C, and D). The loss was principally on the right side. A small area of loss emerged on the left occipital cortex (Fig. 6D).

A region encompassing an area of the right-side superior surface of the temporal lobe and bordering the parietal cortex superiorly showed gray matter loss. This area lay in cortical sites external to the insula (Fig. 6C).

**DISCUSSION**

Significant gray matter loss was found in specific brain regions of HF patients and included structures that serve demonstrated roles in cognitive functions (parahippocampal gyrus, frontal cortex), autonomic control (insula), as well as areas (cerebellum, frontal cortex) not classically associated with cardiovascular or respiratory control, but that have recently been shown to play essential roles in cardiovascular action and breathing (10, 12, 29, 30, 41, 53). Some areas of gray matter loss overlapped regions found in OSA cases, which also show similar loss (31) or exhibit aberrant normal functional MRI (fMRI) signals to a Valsalva or cold pressor challenge (21, 22). These sites of comparable loss may have resulted from obstructed
breathing found in a proportion of these HF cases. Other areas were unique to HF patients and included the parahippocampal gyrus (not the hippocampus, as was the case in OSA), bilateral deep parietal cortex, and extensive portions of the insula and basal ganglia. Lateralization of tissue loss in HF cases was remarkable, just as was earlier found in OSA cases.

Cerebellum

Cerebellar structures classically have been associated with roles in motor coordination; however, regulation of autonomic and respiratory patterning also is a major function for these structures (30, 33, 55), as manifested in developmental breathing disorders from cerebellar damage (11, 50), triggering of inspiration after apnea (30), compensatory responses for hypotension, and roles in CO₂ regulation (29, 54). Increased exposure to CO₂ will normalize Cheyne-Stokes breathing (28), as will the pronounced swings in blood pressure and cardiac rate associated with that breathing pattern (27). The cerebellar fastigial nucleus participates in CO₂ regulation (54), suggesting that the gray matter loss found in that nucleus may lessen sensitivity to CO₂ and enhance the potential for appearance of Cheyne-Stokes breathing patterns in HF.

The anatomic arrangement of climbing fibers from the inferior olive to cerebellar neurons leads to an extraordinary sensitivity to excitotoxic processes from ischemia or toxins (34, 51). Exposure to repetitive intermittent hypoxia of sleep-disordered breathing or ischemia from hypotensive episodes related to the disease process may have resulted in the cerebellar damage found here.

Insular Cortex

HF patients exhibit chronically elevated sympathetic tone and inappropriate heart rate and blood pressure responses to blood pressure challenges (14, 39). The insular cortex receives nociceptive and viscerosensory input and exerts significant influences on sympathetic and parasympathetic nervous system activity (10, 38, 43, 45, 56). A series of animal and human studies indicates that the left insula is predominantly associated with parasympathetic effects, and the right side is implicated in sympathetic roles (10, 36, 37). Both the left and right insula showed gray matter loss here, with the right side showing much more extensive loss. It would be difficult to partition the net neural effect of such bilateral damage, because both sides apparently interact (56); however, the bilateral damage likely contributes to alterations in autonomic control characteristic of the syndrome. Insular fMRI signals are disturbed to Valsalva and cold pressor challenges in OSA patients (21, 22), a patient group also showing increased sympathetic tone and higher heart rates (46).
A frequent complaint of HF patients is that of dyspnea, or feeling of breathlessness, to even moderate exertion (39). Respiratory tasks that induce dyspnea recruit the right anterior insula (6, 41) and cingulate cortex (41); both areas showed damage in the HF subjects.

**Basal Ganglia**

Damage in insular areas extended to the putamen and globus pallidus. Both structures are somatomotor control areas and have major projections to the deep cerebellar nuclei. The putamen participates in mediating severe load breathing tasks that result in dyspnea (41). The basal ganglia deficits may contribute to motoric aspects of the breathing difficulties observed in HF.

**Midbrain and Thalamus**

The dorsal midbrain, including the right colliculi and periaqueductal gray extending to the dorsal and medial thalamus, was affected in HF cases. Projections among the colliculi, periaqueductal gray, medial frontal cortex, and insular areas have been demonstrated in animals (26), and insular areas project to mediodorsal, ventroposteriormedial, centromedial, and paracentral nuclei of the thalamus (43). The dorsal midbrain integrates defensive and visual behavior (5, 25); the superior colliculus may relate to the occipital cortex losses found here. The superior colliculus and periaqueductal gray, on electrical stimulation, show cardiovascular responses (25). Portions of the superior colliculi project to the midline thalamus in rats (26), a projection that may mediate arousal components of cardiovascular responses.

**Cortical Regions**

The cortical regions showing gray matter loss included areas with extensive projections to limbic regions [caudal orbital frontal, left superior frontal, and right superior temporal cortex (9, 40)], sites with demonstrated roles in perception of dyspnea and vocalization [cingulate cortex (17, 41, 49)], and somatosensory integration (parietal cortex). In addition, the right parahippocampal gyrus that receives projections from the cingulate cortex (23) and communicates with the hippocampus proper, a structure with short-term memory and cognitive roles (2), was affected. Both cognitive and memory deficits are characteristic of HF patients (1), feelings of dyspnea are common (1, 39), and anecdotal reports of speech problems in HF exist.

**Relationship to Gray Matter Loss in OSA Cases**

Both OSA and a proportion of HF cases share sleep-disordered breathing and aberrant blood pressure control characteristics. Although more extensive gray matter loss occurred in HF cases, cerebellar, cingulate, and frontal cortex structures were affected in both groups (31). Insular and frontal cortex areas also show deficient fMRI signals to Valsalva and cold pressor challenges in OSA patients (21, 22, 31). The failure to show insular anatomic deficits in OSA cases may relate to severity of the syndrome or resolution of the procedure.

A subset of HF cases showed central apnea, others showed obstructive events, a proportion showed both characteristics, and others breathed normally during sleep. Partitioning the role of each type of respiratory disturbance or normal breathing pattern in HF would require a much larger number of subjects than that used here and should also include controls for correction of impaired breathing by use of continuous positive airway pressure or other means.

**Mechanisms Underlying Gray Matter Loss**

The underlying mechanism(s) that induced these changes in regional brain gray matter is unclear. The compromised tissue volume, and particularly the cerebellar cortex loss, most likely resulted from ischemia associated with perfusion deficits accompanying HF. HF is frequently associated with periods of hypotension secondary to the disease process or to pharmacological interventions. HF diminishes the effectiveness of neural circulation autoregulation, and cerebral blood flow is lower in the syndrome (18). Autoregulatory dysfunction and high risk for hypotension in HF pose a risk for global cerebral ischemia and atrophy. However, we found selective gray matter loss at particular brain sites, rather than global deficits.

The regional gray matter loss described here should be differentiated from cerebral infarctions. Such infarctions are common (20%) in neurologically asymptomatic HF patients (44); our sample showed a similar incidence (one of nine). However, we used T1 procedures for assessment, not the T2 protocols normally employed for infarct detection.

Damage was preferentially on the right side of the brain. The midbrain, thalamic, insular, cingulate, fastigial/deep cerebellar nuclei, parahippocampal, ventral frontal, superior frontal, superior temporal, and parietal/occipital cortex losses were on, or predominantly on, the right side. Only the deep anterior parietal and cerebellar cortex damage was bilateral. Neural losses stemming from HF may be revealing the “normal” perfusion mechanisms of the brain: blood pressure manipulations normally recruit structures unilaterally (20), and those structures may be more sensitive to inadequate vascular delivery. With reduced overall perfusion, areas of highest demand may be first affected.

Because some of the gray matter loss occurred in discrete, normally well-perfused regions and was lateralized in most structures, a speculative possibility exists that genesis of the etiology of the damage results from a developmental, toxic, or other insult to select brain areas. This scenario could subsequently lead to progressive deterioration in HF through aberrant sympathetic outflow or sleep-disordered breathing, resulting from impaired neural structures. A more likely sequence, particularly for HF cases developing from a
history of associated cardiac disease, is that the initial neural damage results from consequences of aberrant perfusion, leading to CNS-mediated disturbed breathing and autonomic control dysfunction, which, in turn, result in progressive deterioration. That possibility may be especially the case for certain brain areas, such as the insula, which are particularly affected by perfusion issues (48).

Limitations

These data were derived from a small number of relatively young end-stage HF patients who were seen at a specialized HF clinic in a tertiary referral center. Subsets of patients who exhibit other physiological characteristics may reveal differently affected brain areas from those described here.

It should be emphasized that the physiological deficits found in HF may result from neural dysfunction not associated with structural loss, i.e., the gray matter loss may be partially or largely independent of alterations in sympathetic tone, breathing, and cognitive deficits. The particular structures involved make such a relationship unlikely, although that possibility exists.

Conclusions

The localization of gray matter loss in HF, appearing in regions with demonstrated roles in cardiovascular, CO2, cognitive, and motor regulation, suggests that characteristics of autonomic disturbances, memory deficits, and sleep-disordered breathing may partially derive from gray matter loss in the syndrome. The development of new therapies that protect, support, or derive from gray matter loss in the syndrome. The developmental course and mechanism of genesis of structural changes and the relationship of these changes to HF outcome would significantly enhance insights into the syndrome.

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DISCLOSURES

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