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Brain Structural Changes Associated with Aberrant Functional Responses to the Valsalva Maneuver in Heart Failure

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Abstract

Heart failure (HF) patients show inability to regulate autonomic functions in response to autonomic challenges. The autonomic deficits may stem from brain tissue injury in central autonomic regulatory areas, resulting from ischemic and hypoxic processes accompanying the condition. However, the direct evaluation of correlations between brain structural injury and functional timing and magnitude of neural signal patterns within affected areas, which may lead to impaired autonomic outflow, is unclear. In this study, we evaluate neural responses to the Valsalva maneuver with blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) in 29 HF patients and 35 control subjects and brain structural changes using diffusion tensor imaging (DTI)-based mean diffusivity (MD) in a subsample of 19 HF and 24 control subjects. HF showed decreased neural activation in multiple autonomic and motor control areas, including cerebellum cortices, vermis, left insular, left putamen, and bilateral postcentral gyrus. Structural brain changes emerged in similar autonomic, as well as cognitive and mood regulation areas. Functional MRI responses in cerebellum and insula in HF subjects are delayed or decreased

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: XS, GF, MW, RK; Methodology: XS, BR, GF, RK; Investigation: XS, BR, GF, MW, RK; Formal analysis: XS, BR; Writing – Original Draft: XS, RK; Writing – Review and Editing: BR, GF, WM, RK.

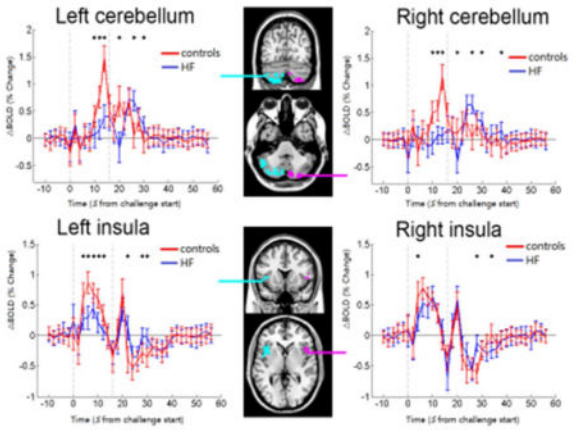
DATA ACCESSIBILITY

Additional data and documents could be requested through: rkumar@mednet.ucla.edu.

in magnitude to the challenge. The impaired functional responses of insular and cerebellar sites are correlated with the severity of tissue changes. These results indicate that the functions of insular and cerebellar regions, sites that are involved in autonomic regulation, are compromised, and that autonomic deficits in these areas have brain structural basis for impaired functions. Our study enhanced our understanding of brain structural and functional alterations underlying impaired autonomic regulations in HF subjects.

Graphical abstract text

Neural responses in cerebellum and insula in HF subjects are delayed or decreased in magnitude to Valsalva maneuver. The impaired functional responses of insular and cerebellar sites are correlated with the severity of tissue changes. These results indicate that the functions of insular and cerebellar regions, sites that are involved in autonomic regulation, are compromised, and that autonomic deficits in these areas have brain structural basis for impaired functions.



Keywords

Functional magnetic resonance imaging; Mean diffusivity; Cerebellum; Insula

INTRODUCTION

Both parasympathetic and sympathetic branches of the autonomic nervous system (ANS) are affected in patients with heart failure (HF). At rest, the sympathetic ANS outflow in HF patients is often exaggerated, the parasympathetic activity is lessened, and the interaction between these two systems is altered (Frenneaux, 2004). In addition, HF patients also exhibit a range of autonomic issues that fail to adequately regulate sympathetic and parasympathetic output in response to body position, motor, or respiratory challenges, which require input from the ANS (Floras, 2002; Floras et al., 2001; Notarius, Atchison, & Floras, 2001). Such malfunction consequences are reflected as severely altered arterial pressure, cerebral blood flow, heart rate, and abnormal sweating (Floras et al., 2001; Gruhn et al., 2001), suggesting that central mechanisms controlling both rapid and sustained responses to behaviors requiring cardiovascular adjustment are altered in HF. Although the clinical outcomes

pertaining to cardiovascular impairments are substantial, the structural and functional brain changes underlying the neural influences on autonomic regulation in HF are unknown.

The Valsalva maneuver is a noninvasive and non-pharmacologic procedure for examining both sympathetic and parasympathetic actions of the ANS (Elisberg, 1963). The autonomic challenge consists of a voluntary forced expiratory effort against a closed upper airway, which raises intrathoracic pressure and results in a sequence of hemodynamic changes and compensatory cardiovascular regulatory reflex activation. During the challenge periods, healthy subjects show appropriate increases of heart rate (i.e., sympathetic phase), which return quickly to baseline following expiratory pressure release (i.e., parasympathetic phase) (Elisberg, 1963). However, HF patients usually fail to demonstrate the normal increase in heart rate during the Valsalva maneuver (Ogren et al., 2012; Woo et al., 2007). Previous studies report nearly absent the initial transient rise and slower rate of increase in heart rate in HF subjects. In addition, following the challenge, control heart rates drop quickly, but HF patients show a slow and gradual decline (Ogren et al., 2012; Woo et al., 2007). Although delayed heart rate changes, HF patients also show inappropriate amplitude or time-distorted blood pressure changes to autonomic challenges (Paton & Spyer, 1990). Since previous HF studies suggest that disturbed outflows from forebrain structures to medullary autonomic nuclei may contribute to such autonomic deficits (Ogren et al., 2012; Paton & Spyer, 1990; Woo et al., 2007), we hypothesized that blunted or delayed neural responses induced by structural brain changes in the areas mediating autonomic regulation are the underlying cause of the abnormal physiological response to the Valsalva challenge.

Structural brain injury in both gray and white matter sites appears in HF subjects, providing a structural basis for disturbed autonomic functions in the condition (Kumar, Nguyen, et al., 2011; Kumar, Woo, et al., 2011; Kumar et al., 2015; Woo, Kumar, Macey, Fonarow, & Harper, 2009; Woo et al., 2015). Structural brain changes in several sites, including cerebellar and limbic regions, are of major concern. Both cerebellar fastigial nuclei and cerebellar cortices, which dampen extremes of hypo or hypertension, are involved in modulating vestibulo-cardiovascular responses, with deep nuclei or vermis injury in animals leading to fatal outcomes with hypotension or attenuated heart rate increase (Holmes, Cotter, Arendt, Cass, & Yates, 2002; Lutherer, Lutherer, Dormer, Janssen, & Barnes, 1983). In addition, damage to limbic areas, such as stroke in left insular cortex, resulting in exaggerated sympathetic tone, with an accompanying higher incidence in myocardial infarction and heart failure (Laowattana et al., 2006; S. M. Oppenheimer, Kedem, & Martin, 1996). Such data from structural changes in areas outside classic medullary autonomic regulatory sites emphasize the widespread central influences on autonomic regulation. However, no study has directly linked brain structural changes to aberrant neural functional responses to autonomic challenges, or evaluated the correlations and overlap between sites with structural and functional deficits in HF.

In this study, we used blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to evaluate neural responses to the Valsalva maneuver, and diffusion tensor imaging (DTI)-based mean diffusivity (MD) procedures to assess regional brain structural changes in HF over control subjects. Using fMRI, specific behaviors or stimuli induced hemodynamic activities within brain areas can be visualized, and the timings and patterns of

central neural responses to autonomic challenges can be determined (Woo et al., 2007). Mean diffusivity, which measures average water diffusion within tissue and indicates changes in tissue integrity, affected by extracellular/intracellular water content and tissue barriers, including cellular and axonal membranes and macromolecules (Le Bihan et al., 2001), shows decreased values in acute and increased values in chronic pathological conditions (Ahlhelm, Schneider, Backens, Reith, & Hagen, 2002). We hypothesized that brain areas with chronic structural changes will overlap areas with aberrant fMRI responses (i.e., lesser or delayed neural activity) to the Valsalva challenge, and the brain structural severity will correlate with the level of aberrant fMRI responses to ANS stimuli in HF subjects.

MATERIALS AND METHODS

Subjects

We included 29 hemodynamically-optimized (i.e. drug dosages were titrated to reach targeted hemodynamic goals) HF subjects and 35 age- and sex-comparable healthy controls. Demographic, clinical, and physiologic data of HF and control subjects are summarized in Table 1. All HF patients were recruited from the Ahmanson-University of California at Los Angeles (UCLA) Cardiomyopathy Center. The diagnosis of HF was based on national diagnostic criteria (Jessup et al., 2009), and all subjects included in this study were with New York Heart Association Functional Class II at the time of MRI (Radford et al., 2005). All HF patients were without any history of valvular congenital heart defects, pregnancy induced cardiomyopathy, drug abuse, or previous history of stroke, carotid vascular disease, head injury, or any diagnosed psychiatric condition. HF patients were treated with guideline-directed medical therapy, including angiotensin receptor blockers (n = 11) or angiotensin-converting enzyme inhibitors (n = 19), beta blockers (n = 27), and diuretics (n = 26), and were stabilized for hemodynamics and body-weight for at least six months prior to the participation in MRI studies.

Control subjects were recruited through advertisements at the UCLA campus and West Los Angeles area. All control subjects were in good health, without any clinical history of cardiovascular, stroke, respiratory, neurological, or psychiatric disorders that may introduce brain changes. HF and control subjects were excluded from the study if they were claustrophobic, carrying non-removable metal, such as embolic coils, pacemakers/implantable cardioverter defibrillators, stents, or body weight more than 125 kg (scanner limitation). Two HF subjects weighed more than 125kg and were excluded from the study. All participants gave written informed consent before MRI scanning or other data collection, and the study protocol was approved by the Institutional Review Board at UCLA.

Valsalva Maneuver

The Valsalva maneuver was performed in a sequence of four 16-s vigorous and forceful exhalations into a mouthpiece, spaced 120 seconds apart, to a target expiratory pressure of 30 mmHg. There was a 160 seconds baseline before the first period of the challenge. The mouthpiece was connected to a pressure gauge, which allowed continuous assessment of exhalation pressure. The pressure signal was calibrated before each experiment. The closed

exhalation circuit allowed a slow air leak, guaranteeing an open glottis, which ensured that intra-thoracic pressure could be raised. Following each 16-s challenge period, the closed exhalation circuit was removed and the subject breathed normally for 120 seconds. A light signal was used to indicate onset of the challenge for the Valsalva effort to the subject. Subjects were instructed to, upon seeing the light signal, take a breath and exhale against a resistance, maintaining a target pressure. A second light was illuminated when the subject achieved this 30 mmHg target pressure. Subjects practiced the Valsalva maneuver prior to scanning, and the research team observed each challenge to ensure the target pressure was achieved and maintained for each of the four expiratory periods.

Magnetic Resonance Imaging

Twenty-nine HF and 35 controls underwent brain structural and functional imaging in a 3.0-Tesla MRI scanner (Siemens, Erlangen, Germany). We used foam pads on either side of the head to minimize head motion during scanning. BOLD-fMRI data were collected with an echo planar imaging (EPI)-based pulse sequence in the axial plane [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field-of-view (FOV) = 230×230 mm^2; matrix size = 64×64; slice thickness = 4.2 mm; volumes = 352]. During the fMRI scanning, all subjects were instructed to rest with their eyes open for 3 minutes before the first Valsalva maneuver started, without focusing on any specific thoughts. Each of the four Valsalva maneuver trials lasted for 16-s and were followed by a 120-s rest period. High-resolution T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence (TR = 2200 ms; TE =2.34, 2.41ms; FA = 9°; FOV = 230×230 mm^2; matrix size = 320×320; voxel size = 0.72×0.72×0.9 mm^3). Proton density (PD) and T2-weighted images were also obtained, using a dual-echo turbo spin-echo pulse sequence (TR = 10,000 ms; TE1, 2 = 17, 134 ms; FA = 130°; matrix size = 256×256; FOV = 230×230 mm^2; slice thickness = 4.0 mm) in the axial plane. DTI data were acquired from a sub-sample of 19 HF and 24 controls, and were collected using a single-shot echo-planar imaging with twice-refocused spin-echo pulse sequence (TR = 12,200 ms; TE = 87 ms; FA = 90°; bandwidth = 1,345 Hz/pixel; matrix size = 128×128; FOV = 230×230 mm^2; slice thickness = 1.7 mm, no interslice gap, diffusion values = 0 and 800 sec/mm^2; diffusion gradient directions = 30; series = 2).

Data Processing

We first examined anatomical scans for any serious brain pathology using high-resolution T1-weighted, PD-, and T2-weighted images of all subjects. We also assessed fMRI and DTI data for imaging or head motion-related artifacts before data preprocessing. None of the subjects included here showed any serious brain injury, or head motion-related or other imaging artifacts.

Prior to first-level analysis, fMRI data were preprocessed using DPARSFA (Chao-Gan & Yu-Feng, 2010) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm) software: the initial ten brain volumes were discarded to avoid signal saturation issues; the remaining 342 volumes were realigned to eliminate potential head-motion, and co-registered to T1-weighted images. Since the Valsalva maneuver requires the movement of mouth and forceful exhalations, head motion is inevitable. In order to eliminate signal contamination from head motion, the

effects of six rigid-body motion parameters, their first and second derivatives were regressed out as covariates from the time series of each voxel. In addition, challenge-induced linear trend and global brain signal changes were also regressed out from the time series of each voxel. BOLD images were then spatially normalized to Montreal Neurological Institute (MNI) common space using nonlinear transformation procedures and spatially-smoothed with a 4-mm full-width at half-maximum Gaussian kernel. Averaged cortical maps, derived from high-resolution T1-weighted images of HF and controls, and averaged whole-brain T1-weighted images, calculated from normalized T1-weighted images of all HF and controls, were used for anatomical identifications.

For first-level analysis, the Valsalva maneuver was modeled to an “on-off” pattern as a stimulus function. The expected BOLD response was produced by convolving this stimulus function with the canonical hemodynamic response function. An activation map for each subject was generated by fitting the time series from each voxel to the expected BOLD response using the general linear model approach in SPM12. Individual activation maps were then subjected to second-level, random-effects analysis to generate group-level statistical maps.

For DTI images, the average background noise level from outside the brain was derived by using non diffusion- and diffusion-weighted images; this noise threshold was used in all subjects to suppress noise outside the brain parenchyma during MD calculations. Using diffusion-weighted ($b = 800$ sec/mm^2) and non-diffusion-weighted ($b = 0$ sec/mm^2) images, diffusion tensors were calculated in DTI Studio software (H. Jiang, van Zijl, Kim, Pearlson, & Mori, 2006), and principal eigenvalues ($\lambda 1$, $\lambda 2$, and $\lambda 3$) were derived by diagonalizing the diffusion tensor matrices. Using principal eigenvalues, MD maps ($MD = [\lambda 1 + \lambda 2 + \lambda 3]/3$) were derived from each DTI series; both maps were realigned to remove any potential motion and averaged. The averaged MD maps of all HF and control subjects were normalized to the standard MNI space. An isotropic Gaussian filter (10-mm kernel) was used to smooth the normalized MD maps.

We also normalized high-resolution T1-weighted images of HF and control subjects to MNI space and averaged to create a background image as a reference for the selection of regions of interest (ROI) on functional data. A standard single-subject T1-weighted MNI template background image was used to overlay for structural identification.

Statistical Analyses

Demographic and physiologic data were examined by the Chi-square (categorical values) and independent samples *t*-tests (numerical values). We performed one-sample *t*-tests on the activation contrast maps to examine brain areas that were activated during the Valsalva maneuver in HF and control subjects. We applied false discovery rate corrections for multiple comparisons (FDR) at $P<0.050$. We compared the activation contrast maps between HF and control subjects using analysis of covariance [(ANCOVA); covariates, age and sex; FDR, $P<0.050$]. In addition, we compared the normalized and smoothed MD maps between HF and control subjects using ANCOVA (covariates, age and sex; FDR, $P<0.050$).

To determine the time course responses in specific brain structures, region of interest (ROI) analyses were performed. Six sites that showed altered MD and/or BOLD activations were selected as ROIs, including the left and right cerebellar cortices, left and right anterior insular cortices, cerebellar vermis, and right ventral medial prefrontal cortex (vMPFC). The time course of each ROI for an individual subject was standardized by subtracting and dividing its own baseline mean value (mean value of the 140s BOLD intensity before the onset of the first Valsalva challenge period).

The group-mean BOLD responses of each ROI were calculated by averaging the standardized ROI time courses across HF subjects and controls over the 4 repeated Valsalva challenges. Repeated measures ANOVA (RMANOVA) was used to identify time points of significant response differences ($P<0.050$) between HF and controls during the Valsalva and subsequent recovery periods.

The averaged and normalized MD maps were resliced to match the resolution of BOLD maps. The resliced MD and BOLD contrast maps were in the standard MNI space and had the same spatial resolution. We further examined cross-subject partial correlations between the resliced MD maps and BOLD activation contrast maps in HF subjects (covariates: age and sex; Alphasim corrections for multiple comparisons, corrected $P<0.050$, with voxel-level $p<0.005$, cluster size > 25 voxels).

RESULTS

Demographic and physiological variables

No significant differences in age, sex, or education appeared between groups (Tables 1 and 2). HF patients did not differ in BMI (p = 0.163) or heart rate (p = 0.395) compared to controls. However, HF subjects had lower systolic (p = 0.038) and diastolic (p = 0.002) blood pressure compared with the controls (Tables 1 and 2).

BOLD signal responses during the Valsalva maneuver in HF

The Valsalva maneuver significantly contributed to BOLD signal increase in bilateral cerebellum, temporal poles, insular, brainstem, lateral prefrontal cortices, middle occipital gyrus, postcentral gyrus, and right inferior parietal lobule in control subjects (Fig. 1A). Similar brain areas showed signal increase in HF, however less extensively, including bilateral cerebellum, temporal poles, brainstem, lateral prefrontal cortices, middle occipital gyrus, postcentral gyrus, and right insula (Fig. 1B).

Compared to healthy controls, HF subjects showed decreased neural responses to the Valsalva maneuver in bilateral posterior cerebellar cortices, vermis, brainstem, left anterior insula, left putamen, bilateral postcentral gyrus, precuneus, and paracentral lobule (Fig. 1C). No significant increased neural responses were observed in HF over control subjects.

Sites with Increased MD values in HF

Compared to healthy controls, HF subjects showed increased MD values in the right posterior cerebellar lobe, bilateral anterior and posterior insular cortices, ventral medial prefrontal cortex (vMPFC), bilateral dorsal lateral prefrontal gyrus, left ventrolateral

prefrontal gyrus, bilateral middle occipital gyrus, lingual gyrus, calcarine, cuneus, precuneus, angular gyrus, inferior parietal lobule, and right postcentral gyrus (Fig. 2A). No significant decreased MD values were observed in HF over control subjects. Brain sites with significantly increased MD values overlapped with brain regions that exhibited decreased neural responses to the Valsalva maneuver in left posterior cerebellar lobe, left anterior insula, precuneus, and bilateral postcentral gyrus (Fig. 2B).

Functional time course responses - ROI analyses

Six ROIs showed distinct neural response patterns to the Valsalva challenge in HF over control subjects (Fig. 3). RMANOVA showed that bilateral cerebellar regions were significantly activated 10-s after the onset of Valsalva maneuver, reaching peak at 14-s, and decreased rapidly afterward until the end of the challenge; the signal in left cerebellum remained elevated for another 10-s after the cessation of the challenge in control subjects. The bilateral cerebellar regions in HF showed significantly lower activation during the challenge, but a significantly delayed activation emerged at 8-s after the end of Valsalva maneuver. The bilateral insular regions were activated immediately (4-s) after onset of the challenge in controls, reaching peak at 6-s, and gradually-declined to below baseline until the end of challenge. A sharp increase of the signal 4-s after the challenge and a following undershoot were observed. Although the insula in HF did not show any delayed response, the activation level was significantly lower in the left insula in HF over controls during the Valsalva maneuver, and the signal decrease at 10-s after the Valsalva maneuver was less in amplitude than controls. The vermis sites were activated 8-s after the onset of challenge in both control and HF subjects; however, the control responses were significantly stronger. While the vermis showed an undershoot signal response 10-s after the challenge in controls, HF showed a delayed activation 8-s after the challenge instead of returning to baseline. The vMPFC region in control subjects demonstrated a sharp activation 4-s after the onset of the challenge, and then deactivated until 8-s after the challenge, and then returned to baseline gradually. The vMPFC site in HF showed similar patterns, however without any significant activation during the challenge. See supplementary table 1 for the numeric outputs of RMANOVA post-hoc tests on the effect of group differences at each time point.

Correlations between MD values and BOLD neural responses in HF

Partial correlation analysis showed that higher MD values are significantly correlated with lower activation levels in the bilateral cerebellum cortices, insular cortices, and left putamen in HF (Fig. 4). In addition, MD values are also positively correlated with activation levels in the bilateral ventral lateral thalamus in HF subjects.

DISCUSSION

Overview

Heart failure patients showed decreased neural activation in multiple autonomic control areas over control subjects. Brain fMRI responses to the Valsalva maneuver in HF are either delayed or decreased indicating that neural regions responsible for maintaining magnitude and timing of heart rate responses to blood pressure challenges are compromised. The impaired brain responses in HF may underlie the classic abnormal heart rate response to the

Valsalva maneuver, failing to increase rate quickly during the challenge period, and not showing the normal rapid decline below baseline during the recovery period. Structural brain injury in HF subjects occurs in autonomic and motor control areas, as well as cognitive and mood regulatory regions that may contribute to deficient autonomic, emotion regulation, and cognitive functions in HF. The impaired neural responses in insular and cerebellar sites are significantly correlated with increased MD values, indicating that chronic neural changes in these regions are the structural basis for impaired autonomic regulatory function in the condition.

Impaired functional responses to the Valsalva challenge

The Valsalva maneuver challenge involves an interaction between sensorimotor components, as well as autonomic regulatory aspects. Active forced expiration, which is the motoric component, induced significant neural responses in motor control areas in healthy controls, including the bilateral motor cortices, supplementary motor area, cerebellar, and striatum (Fig. 1A); however, these areas showed less activation in HF subjects (Figs. 1B and C), indicating less involvement in motor control. The disruption of the striatal-cortical-cerebellar circuit will result in ataxia, difficulties in smooth pursuit of action, and other movement disorders (Hu, Song, Li, et al., 2015; X. Song et al., 2015). HF patients show multiple motoric impairments, such as dysfunctions in complex planning, spatial attention, motor speed, grip strength, and gait (Davies, Greig, Jordan, Grieve, & Lipkin, 1992; Notarius et al., 2001). Reduced neural responses in the primary motor cortices and supplementary motor areas to the Valsalva challenge in HF subjects may directly underlie these motor disorders. As important parts of the striatal-cortical-cerebellar circuit, the putamen and globus pallidus play a significant role in motor planning, motivation, emotional regulation, and memory function (Hu, Song, Yuan, et al., 2015; Kumar, Nguyen, et al., 2011), and these sites show structural injury in HF, as determined by voxel-based T2-relaxometry, diffusion tensor imaging, and manual gray matter volume assessment (Kumar, Nguyen, et al., 2011; Kumar et al., 2015; Woo et al., 2009). In this study, we found reduced neural responses to breathing challenge in the putamen, providing basis for motor patterning coordination dysfunction in HF.

Since the Valsalva maneuver involves both sensorimotor and autonomic regulation networks, impaired cerebellar and insular neural responses would have implications for both sensorimotor and cardiovascular dysregulation in HF. Among damaged brain areas, cerebellar sites, including the cortices and deep nuclei, are key for timely coordination of sympathetic and parasympathetic attributes, and for dampening extremes of hypotension and hypertension induced by other injured regions, including the hypothalamic and limbic areas (Lutherer et al., 1983; Ogren et al., 2012). Functional cerebellar impairments in HF subjects would not only lead to deficits in motor coordination, but also to sympathetic deficits, and thus, blood pressure regulations. The insular cortices serve interoceptive awareness and autonomic regulatory functions via projections to visceral, thalamic, brainstem, and limbic areas (Cerliani et al., 2012), and have been identified as the “central command” center that ensures heart rate and blood pressure increase at body movement (Nowak, Holm, Biering-Sorensen, Secher, & Friberg, 2005). The insular cortices also receive input from multiple cortical areas that are involved in sensorimotor functions, many of those can trigger

sympathetic and parasympathetic actions (Goswami, Frances, & Shoemaker, 2011), and may contribute to motoric activity, including hand and eye movement, swallowing, and gastric motility (Fink, Frackowiak, Pietrzyk, & Passingham, 1997). In addition, the insular sites are also involved in motor learning and have been identified as playing roles in motor recovery from stroke (Weiller, Ramsay, Wise, Friston, & Frackowiak, 1993). The decreased insular responses found here in HF subjects indicate impaired motor control and interoceptive awareness of body states during autonomic challenge and might contribute to dysregulation of heart rate and blood pressure.

Structural brain changes in HF

Multiple autonomic, motor, cognitive, and mood regulatory sites in HF subjects showed increased MD values, indicating chronic tissue injury (Fig. 2A). Since the Valsalva maneuver challenge mainly activates autonomic and motor control areas, the overlapped areas between increased MD and decreased fMRI responses to the Valsalva challenge were mainly found in autonomic and motor control regions, including the left anterior insular, left cerebellum cortex, posterior cingulate cortex, and bilateral postcentral gyrus (Fig. 2B), and suggest such basis for functional deficits.

Insular cortices have autonomic control roles, along with sensory integration and pain-regulatory functions (Cerliani et al., 2012; Nowak et al., 2005). The cerebellum plays autonomic and chemoreceptor regulatory roles, as well as respiratory motor control (Holmes et al., 2002). Our MD data here showed extensive insular and cerebellar structural brain injury in HF subjects, and fMRI data indicated compromised, including diminished in magnitude and distorted insular, cerebellar cortex and deep nuclei responses in HF compared to control subjects. Other brain areas, as major contributors to autonomic regulation and visceral sensory information processing, including the middle and posterior cingulate cortices (Critchley et al., 2003), as well as the ventral medial prefrontal cortices (King, Menon, Hachinski, & Cechetto, 1999), also showed structural changes in HF subjects. HF patients show both persistent increased sympathetic and altered parasympathetic tones, and chronic tissue changes in the insular, cerebellum, and cingulate cortices found here would have greatly contributed to those altered autonomic responses.

Beside the autonomic and motor control areas, regions that regulate cognitive, executive, attentional, and emotional functions including the ventral medial prefrontal, bilateral orbital frontal, dorsal lateral prefrontal, inferior parietal, cuneus, precuneus, posterior cingulate, and middle occipital cortices, also showed tissue changes in HF subjects. HF patients show a variety of cognitive and mood regulation issues, in addition to autonomic dysfunctions in the condition. Attention deficits, difficulty with complex reasoning, and inability to absorb and retain information have been reported in up to 80% of HF patients (Zuccala et al., 2005). Previous studies showed that bilateral orbital frontal and dorsal lateral prefrontal areas play important roles in attention and affect reaction time to external stimuli when performing cognitive tasks (Song et al., 2017). In addition, brain lesion studies also showed that damage in the frontal-parietal network can result in significant visuospatial attention and executive functional deficits (Han et al., 2004). The comorbid cognitive and attention issues in HF may stem from damage appearing in frontal-parietal areas. Another common comorbid

characteristic of HF is high incidence of depression or depressive symptoms (40–60%) (W. Jiang et al., 2007). Several brain regions, including the middle and posterior cingulate cortices, ventral medial prefrontal cortex, and parietal areas, are damaged in subjects with depression (Hu, Song, Li, et al., 2015; Xiaopeng Song et al., 2015). Brain tissue changes in these sites would exert prominent emotional and behavioral effects on HF subjects as reported in the condition (Zhenghua Hou, Xiaopeng Song, et al., 2016a, 2016b; Hou, Sui, Song, & Yuan, 2016; Z. Hou et al., 2016). Other sites, including the angular gyrus, posterior cingulate, and medial frontal cortices all showed damage here, which may affect mood in the condition. The cuneus, calcarine gyrus, middle occipital gyrus, and superior parietal areas, sites that are comprised in the primary and secondary visual regions, and high order dorsal visual stream, also showed increased MD which may contribute to visuospatial dysfunctions, as another comorbid condition frequently reported in elderly HF (Elliott, McGwin, Kline, & Owsley, 2015).

Distorted temporal patterns of fMRI response to the Valsalva challenge

Cerebellum—Both left and right cerebellar cortices and vermis neural responses emerged immediately to the challenge in controls, but such responses are significantly delayed in HF. Neural response timing from forebrain structures to medullary autonomic nuclei, including coordination of input from multiple peripheral and central brain sources, is frequently neglected as a source of autonomic, and especially cardiovascular dysfunction. Delayed cerebellar responses to somatosensory information may result in distorted autonomic changes. The most common demonstration is postural change-induced syncope resulting from late cerebellar coordination of afferent vestibular information to trigger appropriate increased sympathetic outflow from the rostral ventrolateral medulla, which in turn leads to a tardy increase in blood pressure (Holmes et al., 2002; Paton & Spyer, 1990). Other illustrations derive from late or absent blood pressure responses to enhanced respiratory efforts, resulting in reduced heart rate variation.

The delayed neural activity might have developed from alterations in response coordination between the cerebellar cortex and deep nuclei, which also showed decreased response to the Valsalva maneuver. Cerebellar cortices and deep nuclei interact with each other, playing important roles in blood pressure control with a significant contribution to limiting the extremes, as well as breathe-to-breathe blood pressure changes (Harper et al., 1998; Rector, Richard, & Harper, 2006). The cerebellar cortices and deep nuclei also receive projections from the ventral respiratory nuclei group, serving significant chemoreceptor, heart rate regulation, and respiratory timing roles (Xu & Frazier, 1997). Thus, the delayed and magnitude-reduced cerebellar responses during the challenge have the potential to exert significant influences on blood pressure, heart rate variations, and respiratory patterning in HF subjects.

The cerebellar cortices integrate afferent activity from the upper body and visceral structures through vagal pathways (Hennemann & Rubia, 1978). The sensory information here likely included input from thoracic wall afferents used for elevating expiratory thoracic pressure, as well as negative pressure information from the lungs conveyed by vagal afferents projecting to the cerebellum (Hennemann & Rubia, 1978). Such information relaying would be

severely affected by cerebellar injury, which is revealed by our MD procedures, and lead to a delayed cerebellar responses to the challenge. In addition, the putamen, globus pallidus, supplementary motor area, and primary motor cortices serve time-coordination aspects in sensory and motor information processing. Structural brain changes and decreased responses to the Valsalva challenge may also contribute to the delayed and muted cerebellar responses here.

The vermis also plays crucial roles in autonomic and chemoreceptor regulation, as well as in respiratory motor regulation (Holmes et al., 2002). The vermis injury is typically accompanied by breathing disorders, which is common in HF (Triposkiadis & Skoularigis, 2012). The site is activated immediately on resumption of breathing after apnea and induce compensatory actions to dampen extreme blood pressure changes (Lutherer & Williams, 1986). Blood pressure regulation is impaired both during the challenge and recovery periods of the Valsalva maneuver in HF (Shamsham & Mitchell, 2000), and structural deficit in vermis may directly result in dysregulation of blood pressure. A previous study showed that weak vermis stimulation was enough to induce marked hypotension (Rector et al., 2006), and we observed here a slight signal reduction in the control subjects at the beginning of the challenge which might accompany the rise of blood pressure at the onset of the autonomic challenge. However, such vermis signal decline was absent in HF subjects. As the breathing challenge goes on, the vermis signal increase significantly in the control subjects, but not in the HF, indicating a less sufficient control of hypertension. During the recovery phase of the challenge, HF patients typically show little or no rise in blood pressure (Shamsham & Mitchell, 2000), the activity of vermis returns to baseline level in control subjects, but HF group shows a prolonged activation, likely reflecting a delayed return to baseline blood pressure levels.

Insula—The left insula showed significantly decreased neural response to the Valsalva maneuver, while the right insula showed less functional impairment in HF subjects. Earlier studies showed preferential unilateral brain structural injury in gray matter in HF, including the insula and mesial temporal lobe (Kumar, Nguyen, et al., 2011). Lateralized functional impairments can exert profound influences on autonomic outcomes. Autonomic regulation is thought to be heavily lateralized; the right insula primarily serves sympathetic regulation, and the left principally underlies parasympathetic action (S. M. Oppenheimer et al., 1996), and part of the normal interactions between sympathetic and parasympathetic systems result from inhibitory or excitatory projections from the right side to the left, and vice versa (S. M. Oppenheimer et al., 1996).

The insula appears to be involved in human heart rate regulation and damage may encourage a pro-arrhythmic state (S. Oppenheimer, 1993). Damage to the left insula could shift cardiovascular balance towards increased basal sympathetic tone, a pro-arrhythmic condition, and may contribute to the higher risk of cardiac mortality following stroke (S. M. Oppenheimer et al., 1996). Previous studies reported that acute left insular stroke increased basal cardiac sympathetic tone and was associated with a decrease in randomness of heart rate variability (S. Oppenheimer, 1993; S. M. Oppenheimer et al., 1996). In addition, phase relationships between heart rate and blood pressure were disturbed, implying a disruption of oscillators involved in cardiovascular control (S. M. Oppenheimer et al., 1996). The left

insular stroke is also associated with an increased risk of adverse cardiac outcome, such as angina, myocardial infarction, heart failure, and cardiac death, as well as decreased cardiac wall motion compared to strokes in other brain locations (Laowattana et al., 2006), but the right insular stroke was not associated with adverse cardiac outcomes (Laowattana et al., 2006).

Our findings indicate that the primarily unilateral functional deficits have resulted in loss of the normal suppressive or excitatory action of one side on the other, which likely contributes to the exaggerated sympathetic tone in HF, gated by the insula.

vMPFC—Different from the cerebellar and insular areas, the vMPFC is involved in autonomic regulation in an indirect way. The vMPFC showed an initial increase in response to the challenge and deactivated rapidly during the challenge in control subjects. The overall negative response patterns are similar in HF, but with a less significant initial increase of signals. The physiological stress response induced by the Valsalva maneuver engages autonomic and high-order executive systems to mobilize energy needed to meet the challenge at hand. Accordingly, these responses are both tightly regulated throughout the brain and adaptable to the energetic needs of the individual (McKlveen, Myers, & Herman, 2015). The vMPFC, as a coordinator of behavioral and physiological stress responses, also plays an important role in the coordination of anticipatory responses to upcoming challenges (McKlveen et al., 2015). The initial increase of neural activities in the vMPFC indicated a process of modulating physiological energetic systems to mobilize or limit as needed to ultimately promote behavioral adaptation to the challenge (McKlveen et al., 2015), and this process is impaired in HF. In addition, the vMPFC is also a key node of the default mode network which is involved in self-referential thoughts and emotion regulation (Song et al., 2017), and is usually active during the resting-state and deactivated during the task (Song et al., 2017). Decreased signal in the vMPFC during the challenge indicated reallocation of energy and executive resources from internal mood and cognitive processing areas to autonomic control sites.

Correlations between functional deficits and structural changes

HF patients showed widespread brain structural changes, indicated by increased MD values, in autonomic, respiratory, motor, mood, and cognitive control sites. Among these sites, the autonomic, respiratory, and motor control regions also showed decreased neural responses to the Valsalva maneuver. Since the Valsalva maneuver is a breathing challenge, it mainly triggered autonomic, respiratory, and motor control processes, and the areas of overlap between increased MD and decreased neural responses in HF are also mainly located in these sites. Also, further correlation analyses confirmed close relationships between structural changes and functional deficits in the bilateral insular and cerebellar cortices.

Pathological processes contributing to structural and functional deficits

Although the precise pathological processes underlying the associated structural and functional impairments are unclear, several possibilities exist. HF patients show compromised cerebral perfusion resulting from low cardiac output, and insular and cerebellar structural changes may have developed from ischemia or inadequate perfusion

accompanying the syndrome (Ng & Freedman, 2009). Cerebellar, insular, and limbic structures are especially vulnerable to hypoxia/ischemia, and even short-term exposure to intermittent hypoxia can cause severe injury (Almendros, Wang, & Gozal, 2014; Veasey et al., 2004). Acute tissue changes show reduced MD values, and chronic brain changes show increased MD values. Since HF subjects showed only increased MD values here, the processes may include chronic pathological mechanisms. We believe that a portion of deficient neural responses to the Valsalva maneuver may derive from impaired neurons within the structures and axons affecting the neural pathways connecting the insula and cerebellum to other brain sites. However, initial injury to autonomic control sites, including the insular and cerebellar areas, may compromise vascular activity and heart rate regulation, which may lead to altered perfusion, introducing secondary brain injury in limbic and other rostral brain areas (Roy et al., 2017). The tight correlations between increased MD values and decreased neural responses in cerebellum and insula provide the structural basis for brain functional impairments in HF.

Limitations

The current study has several limitations. The current study is a cross-sectional examination, and the sample size is relatively small. Since we wanted to keep a homogenous HF group, we recruited hemodynamically-optimized HF subjects with NYHA functional class II with stable condition for at-least 6 months. We are continuing to recruit more subjects, but many subjects not meeting these criteria were not included, which resulted in a small sample size. In addition, a longitudinal study with a larger sample size would be useful in the future for examining the progression of HF with time. Sex differences can be an important variable in HF subjects. Since the current study mainly focused on examining brain structural and functional differences in HF relative to controls, we included subjects of both sexes and matched the sex of HF to control subjects, which resulted no significant differences in sex between groups. In addition, we regressed out the effect of sex as one of the covariables in ANCOVA and correlation analyses. Although sex was taken into account, further study with direct comparison between male and female HF subjects would provide insights into cardiovascular disease variations between sexes. Also, comorbid conditions and medications may affect the findings. Coexistence of conditions, including the renal insufficiency or chronic kidney disease, Type 2 diabetes, and OSA, are common in HF and may contribute to autonomic dysfunctions. The medications for management of heart failure or hypertension also mediate their effect by moderating the autonomic nervous system, and therefore may contribute to altered autonomic functions. Such conditions and medication effects should be partitioned in future studies with a large sample size.

CONCLUSIONS

Based on functional and structural MRI data, our results revealed brain structural basis for the impaired dynamic changes in autonomic outflow in HF subjects. In addition, these findings demonstrate close relationships between brain tissue changes resulting from ischemic/hypoxic processes accompanying the syndrome and the inability of autonomic regulatory structures to adequately respond in amplitude and in timely fashion to the challenge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE STATEMENT

Autonomic, motor, and cognitive impairments are common in heart failure (HF) condition. By using MRI technique, we revealed the brain structural and functional deficits underlying these symptoms. HF patients show abnormal neural responses to the Valsalva maneuver, a voluntary exhalation task, in multiple autonomic and motor control areas. Brain structural changes emerge in similar sites, as well as cognitive and mood regulatory areas, and are correlated with the level of functional impairments. The brain structural, and thus, functional deficits may result from reduced cardiac outflow commonly found in the condition.

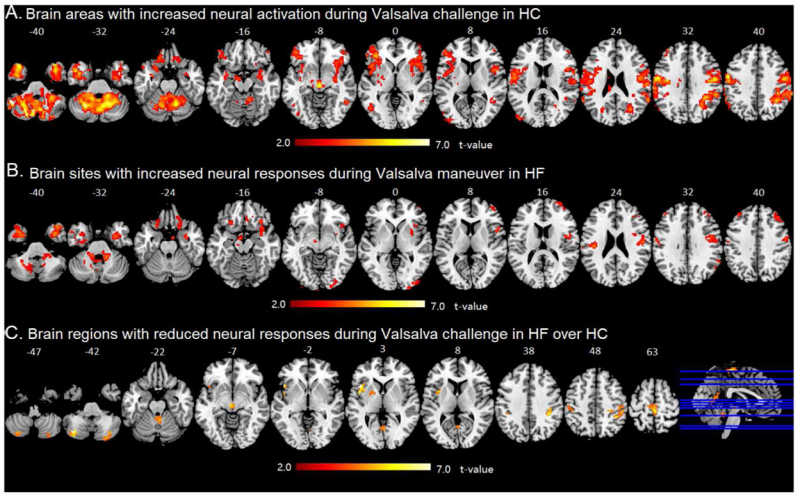

Figure 1.

Brain areas with increased neural activities during the challenge in healthy controls (A; one-sample *t*-tests, n = 35, FDR $P < 0.050$), sites with increased neural activities during the challenge in HF patients (B; one-sample *t*-tests, n = 29, FDR $P < 0.050$), and regions with lower neural activation in HF (n = 29) compared to control (n = 35) subjects (C; ANCOVA, FDR $P < 0.050$). All images are in neurologic convention, and color scales show *t*-statistic values.

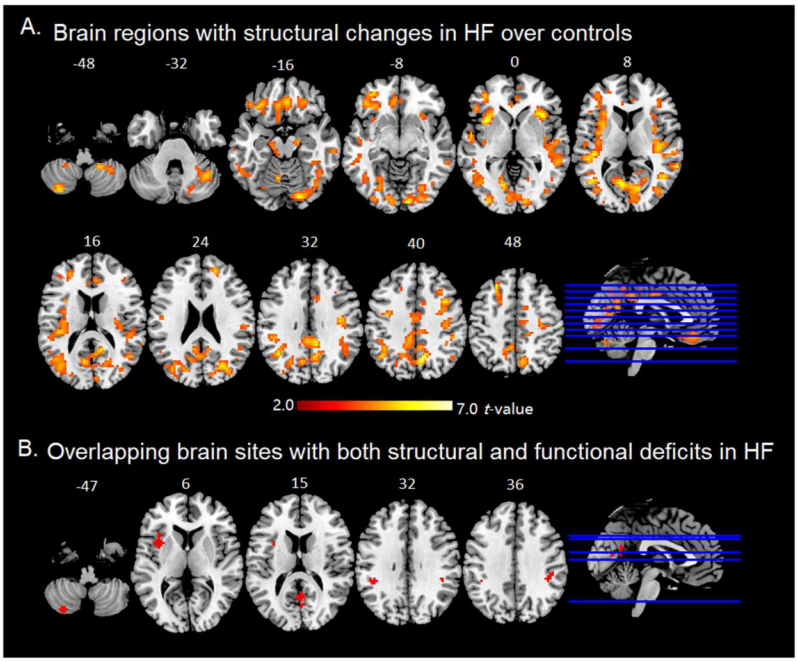

Figure 2.

Brain areas with increased MD values in HF (n = 19) over control (n = 24) subjects (A; ANCOVA, FDR $p < 0.05$). Brain sites with overlapped structural and functional deficits in HF subjects (B; areas with red color).

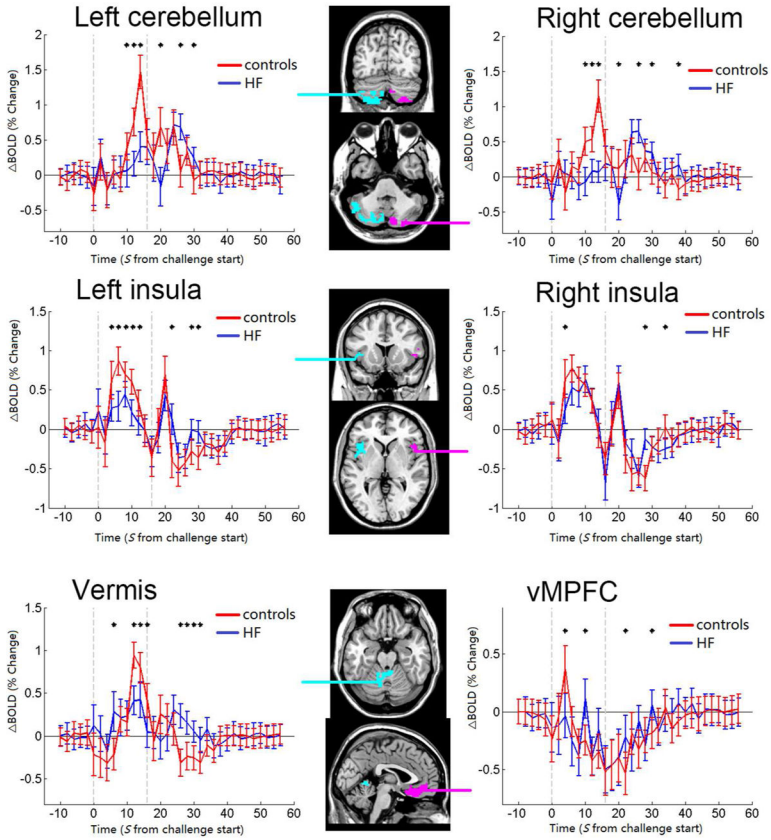

Figure 3.

Mean neural responses over 4 repeated Valsalva challenges in HF (n = 29) and controls (n = 35). Vertical bars indicate the standard error of mean. Time points of significant differences between groups are indicated above the curves with asterisks (RMANOVA, $p < 0.050$).

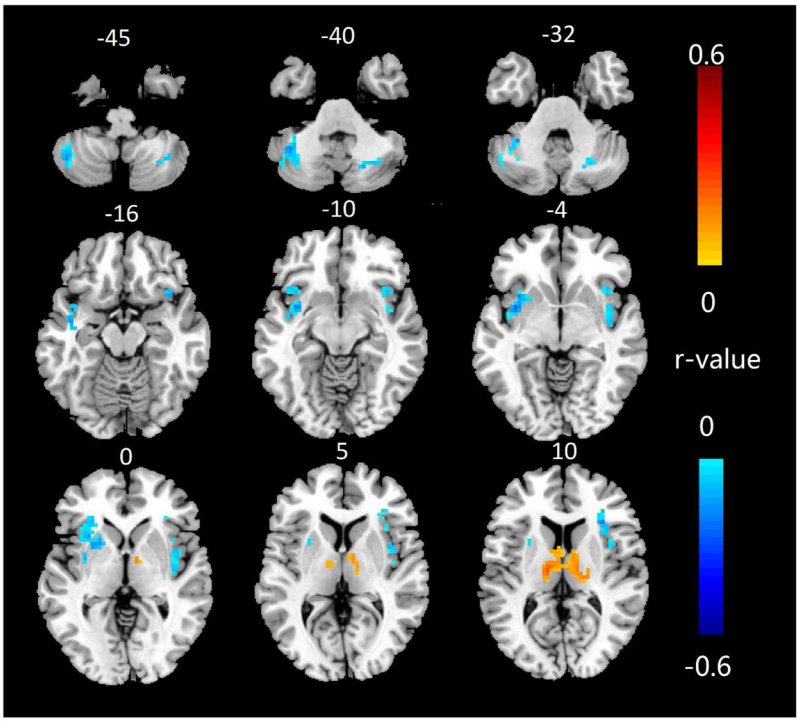

Figure 4.

Brain areas with significant correlations between MD values and neural responses in HF subjects (n = 19). Alphasim correction based on the Monte Carlo Simulation was adopted for multiple comparisons, with corrected cluster-level $P < 0.050$. Positive and negative correlations are presented in warm and cold colors, respectively.

Table 1

Demographic, biophysical, and clinical data of HF and control subjects with brain functional MRI.

Variables	HF (n = 29)	Controls (n = 35)	p values
Age range (years)	40–66	40–61	–
Mean age (years)	54.2±8.0	51.2±5.9	0.090
Sex (Male: Female)	22:7	22:13	0.169
BMI (kg/m^2)	26.8±5.1	25.4±3.0	0.163
Education (years)	15.2±3.2	16.1±2.2	0.162
Heart rate (beats/min)	72.2±11.7	69.7±11.8	0.395
Systolic BP (mm Hg)	107.9±21.0	117.8±16.8	0.038
Diastolic BP (mm Hg)	66.6±11.4	76.4±12.8	0.002
LVEF (%)	26.3±8.5	-	-

HF, Heart failure; BMI, Body mass index; BP, Blood pressure; LVEF, Left ventricle ejection fraction.

Table 2

Demographic, biophysical, and clinical data of HF and control subjects with brain structural MRI.

Variables	HF (n = 19)	Controls (n = 24)	p values
Age range (years)	40–65	40–60	–
Mean age (years)	51.9±7.6	50.3±6.4	0.462
Sex (Male: Female)	14:5	17:7	0.196
BMI (kg/m^2)	27.5±5.2	25.3±3.1	0.092
Education (years)	15.5±3.7	16.1±2.4	0.532
Heart rate (beats/min)	71.1±9.2	67.5±11.1	0.268
Systolic BP (mm Hg)	111.4±22.4	120.5±16.6	0.133
Diastolic BP (mm Hg)	67.4±12.2	77.0±12.2	0.011
LVEF (%)	26.3±6.5	-	-

HF, Heart failure; BMI, Body mass index; BP, Blood pressure; LVEF, Left ventricle ejection fraction.