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The Association of Sleep-Disordered Breathing and White Matter Hyperintensities in Heart Failure Patients

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Abstract

Heart failure patients often manifest white matter hyperintensities on brain magnetic resonance imaging (MRI). White matter hyperintensities have also been linked with cognitive problems in patients with heart failure. Sleep disordered breathing may contribute to structural brain changes in heart failure. The purpose of this study was to test the extent to which the apnea hypopnea index is associated with global and regional white matter hyperintensities, and is a moderating factor in the relationship between age and white matter hyperintensities. A total of 28 HF patients [mean age (SD) = 67.89 (5.8)] underwent T1-weighted and T2FLAIR MRI and a home sleep monitoring study. The apnea hypopnea index cut off of 10 was used to compare between higher and lower risks of sleep disordered breathing. Regression analysis was used to test the association between apnea hypopnea index and both global and regional white matter hyperintensities. The interaction term was entered to identify the moderation effect. Apnea hypopnea index was associated with higher regional white matter hyperintensities but not global white matter hyperintensities. There was a significant interaction between the apnea hypopnea index and age, such that older participants with the apnea hypopnea index ≥ 10 showed greater regional white matter hyperintensities than those with the apnea hypopnea index <10 . The results of this preliminary study indicate that a higher apnea hypopnea index is associated with more white matter hyperintensities. The age-related white matter hyperintensities appear to be exacerbated by apnea

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hypopnea index in our individuals with heart failure. Future studies are needed to further investigate the underlying mechanisms.

Keywords

Sleep apnea syndrome; Heart failure; White matter hyperintensities; Structural MRI

Introduction

Heart failure (HF) is a leading cause of re-hospitalization rates among older adults.¹ Approximately 50% of HF patients manifest cognitive impairment in the domains of attention, memory and executive function.^{2,3} Cognitive impairment in HF has been associated with poor outcomes including diminished self-management skills and increased re-hospitalization.^{4–6} Cognitive impairment in HF is related to structural brain changes including changes in the prefrontal cortex, medial temporal lobe, and hippocampus compared to people without HF.^{7–10}

White matter hyperintensities (WMH) of presumed vascular origin are commonly observed in T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI in older individuals with ischemic injury. As people age, there is an increase in WMH as well.^{11,12} In people without HF, the prevalence of WMH varies from 11–21% among people around age 64 to 94% around among people age 82, but is more common in patients with cardiovascular risk factors.^{13,14} WMH have been linked with cognitive impairment and an increased risk for stroke, dementia, and death^{15,16}. WMH have also been linked with cognitive problems in patients with HF.^{8,17} However, limited research is available on the etiology of WMH in HF patients.

Sleep-disordered breathing (SDB) is a common condition in patients with HF, typically afflicting 25% to 75% of study samples.¹⁸ The increased prevalence of SDB in this population is likely due to the pathology of HF and shared risk factors such as age, obesity, and hypertension. Animal and human MRI studies indicate that SDB is associated with changes to the corpus callosum, hippocampus, thalamus, brain stem, frontal cortex, and cerebellum.^{19–22} Animal studies indicate that hypoxia is associated with increased cell death and hippocampal atrophy consistent with the idea that SDB contributes to oxidative stress and activation of inflammatory pathways resulting in neurodegeneration.^{22,23} In patients with HF, SDB may increase the risk for ischemic injury through an increased incidence of intermittent hypoxia along with reduced cerebral blood flow due to poor cardiac output.^{7,9,10}

SDB is related to WMH and cerebrovascular disease.^{24–26} Kim et al. (2013) found that moderate to severe SDB was significantly associated with WMH adjusting for demographic and clinical factor covariates compared to a non-SDB group of 503 healthy adults. They also found a higher prevalence of WMH in a group of healthy adults with moderate to severe SDB as compared to individuals with mild SDB or no SDB.²⁴ Furthermore, subclinical cerebrovascular disease has been found in patients with moderate to severe SDB.^{25,26} However, limited research has examined the causal relationship between SDB and WMH.

Given that SDB is a common comorbidity of HF and both HF and SDB impact cerebral perfusion, we hypothesized that severity of SDB is associated with elevated WMH in HF patients. Using an at home sleep apnea testing, we calculated apnea hypopnea index (AHI).²⁷ We hypothesized that increases in AHI is associated with elevated WMH in HF patients. First, we examined the how increases in AHI was associated with changes in WMH. Second, we explored whether SDB moderates the relationship between age and WMH in individuals with HF, given that age is a major known contributing factor to WMH. Determining the role of SDB in WMH formation is important, particularly given that it may be a modifiable factor contributing to further brain injuries in HF patients.

Methods

Participants

A total of 28 community-dwelling, stable HF patients with New York Heart Association Class (NYHA) I-III were included in this analysis. We included both systolic and diastolic HF patients to increase variability across different left ventricular ejection fraction. They were all from a larger parent study centered on evaluating cognitive and brain changes in HF. The parent study used convenience sampling. From the 39 participants in the parent study,²⁸ we excluded 11 participants who identified to have treatments for SDB, such as positive airway pressure or oxygen to control for unclear treatment adherence. The eligibility criteria are described in Table 1. Table 2 provides the demographic information for this sample. The University of Wisconsin Health Sciences Institutional Review Board approved all study procedures and each participant provided signed consent before participation.

Sleep-disordered breathing (SDB)

The ApneaLink Plus (ResMed Corp, San Diego, California), an in-home multichannel portable sleep monitoring device was used to evaluate SDB.²⁹ This device yields measures of nasal airflow, respiratory effort, and oxygen saturation. ApneaLink Plus software was used to calculate the apnea hypopnea index (AHI), providing a measure of the severity of SDB using the number of apnea and hypopnea events in an hour from nasal airflow and respiratory effort. The data were autoscored. A board-certified clinician reviewed the data to ensure the quality (CM). The AHI measured by ApneaLink Plus has been shown to have a high correlation with the values measured by polysomnography ($r = 0.98$ and $r = 0.88$).^{30,31} The sensitivity and specificity was shown to 95% and 90% in adults using an AHI cutoff of 10.³² Also, the device was used successfully in HF samples.^{33,34} Consistent with previous research, we used an AHI cutoff of 10 to compare higher AHI and lower AHI groups for descriptive purposes and to calculate the effect size.³⁵

Brain imaging acquisition

Participants in this study underwent MRI on a General Electric 3.0 T Discovery MR750 (Waukesha, WI) system with an 8-channel head coil. T1-weighted images were acquired in the axial plane with a 3D fast spoiled gradient-echo sequence using the following parameters: inversion time (TI) = 450 ms; repetition time (TR) = 8.1 ms; echo time (TE) 3.2 ms; flip angle = 12°; acquisition matrix = 256 × 256 mm, field of view (FOV) = 256 mm; slice thickness = 1.0mm. The 3D T2 FLAIR scans were acquired in the sagittal plane using

the following parameters: T1 = 1867 ms; TR = 6000 ms; TE 123 ms; flip angle = 90°; acquisition matrix = 256 × 256, FOV = 256 mm; slice thickness = 2.0 mm, no gap, yielding a voxel resolution of 1 mm × 1 mm × 2 mm.

White matter hyperintensity calculation

The Lesion Segmentation Tool version 1.2.3 implemented in Statistical Parametric Mapping (SPM) 8 (<http://www.fil.ion.ucl.ac.uk/spm>) was used to calculate the total volume of WMH.³⁶ Lesions are seeded based on spatial intensity probabilities from T1 images and hyperintense outliers on T2 FLAIR images. We first set the initial threshold at 0.30 to create a binary conservative belief map from the gray and white matter lesion belief maps, which is consistent with previous research.^{36,37} Second, the conservative lesion belief map toward a probabilistic liberal lesion belief map from gray matter, white matter, and cerebrospinal fluid belief maps allowed us to produce a growth algorithm. Finally, to remove any voxels that had a low probability of being lesions, a threshold of 1.00 was used on the resulting lesion belief map. All final segmentation maps were inspected by experts (CM and KM) to ensure quality.

To analyze the differences in global WMH volume, the total volume of WMH was divided by the intracranial volume (ICV) and was multiplied by 100 to give a white matter hyperintensity percent (WMHp). This allowed us to analyze the total lesion volume adjusted for intracranial volume.

In addition to the global WMH, we evaluated the regional WMH maps to explore the specific regions of the brain that are related to AHI using a voxel-wise analysis. WMH probability maps produced from the Lesion Segmentation Tool were normalized to Montreal Neurological Institute space and smoothed with a 12mm Gaussian kernel. We restricted analysis to white matter in the probability maps using an explicit mask, which was created by a thresholding the ICBM tissue probabilistic atlas white map at 0.30. The results were considered at thresholds of $p < 0.001$ and $p < 0.005$, uncorrected for multiple comparisons. To increase the anatomic plausibility of the results, clusters were included using a threshold of > 20 voxels.

Intracranial volume (ICV)

We calculated ICV using a “reverse brain masking” method to adjust for inter-person differences in brain size in the analyses³⁸. First, we summed the grey, white, and CSF probability maps from the International Consortium for Brain Mapping (ICBM) for each image, created with an ICV probability map. Then, the inverse deformation field was applied to the ICV probability map to produce an ICV mask in the native space. A threshold of 90% was applied to this subject-specific ICV probability map and the total volume was extracted.

Demographic and clinical variables

Demographic (age and sex) and clinical data (presence of hypertension (yes/ no), NYHA class (I, II, III, and IV), LVEF (%), and type of HF (systolic or diastolic) were gathered through medical records review.

Statistical analysis

We compared the demographic and clinical variables and WMHp by the AHI status (AHI ≥ 10 and AHI <10) using independent t-test or chi-square statistics where appropriate. We used Microsoft Excel to calculate Hedge's g for effect sizes regarding the continuous variable. To test the association between AHI and WMHp, we used AHI as an independent variable and WMHp as a dependent variable. The covariates included in the model were age, sex, the presence of hypertension, and LVEF.^{7,8,17,39} To test the interaction between AHI and age, we entered the interaction term into the model. The interaction term was created by multiplying AHI and age. All of the above analyses were done using SPSS version 22 (Chicago, IL, USA). The type I error rate was set at $p < 0.05$ for the above analysis.

To examine the association between AHI and lesion probability of WMH on a regional, or voxel-wise basis, we used a multiple linear regression models implemented in SPM8. The independent variable was AHI and the dependent variable was lesion probability of WMH. Age, sex, ICV, the presence of hypertension, LVEF were entered as covariates; these have been associated independently with WMH.^{7,8,17,39} To test whether AHI moderated the relationship between age and the lesion probability of WMH, we again used a multiple linear regression models on a voxel-wise based regression model in SPM8. Age, sex ICV, the presence of hypertension, LVEF, AHI, and the interaction term between AHI and age were entered into the model. The voxel-level intensity threshold of $p < 0.001$ (uncorrected for multiple comparison) was used to determine significance.

Results

Comparison by AHI status

Table 2 presents a comparison of demographic information between AHI ≥ 10 and AHI <10 group. There were no differences between these two groups on most of the demographic factors except for sex and AHI ($p < 0.05$). LVEF (means = 45.53 (AHI ≥ 10) and 47.08 (AHI <10)) was similar in both groups. Higher numbers of obstructive sleep apnea and central sleep apnea events were observed in the AHI ≥ 10 group than the AHI <10 group ($p < 0.05$). Of the 15 people with AHI ≥ 10 , only 1 person (6%) had predominantly central sleep apnea (central events $\geq 50\%$). There were also no significant differences between the two groups in WMHp.

Effect size

We estimated the effect size of a relationship between SDB status and WMH; WMH was WMHp was $g = 0.43$ (CI = -0.32 to 1.19).

Main effect of AHI on WMH

None of the covariates were significant predictors of global WMHp, including AHI and LVEF (Table 3). The regional voxel-wise regional analysis indicated that higher AHI was associated with WMH in right anterior corona radiata, right inferior frontal gyrus, left orbital gyrus, right superior corona radiata, and left post central gyrus, left precentral gyrus, and right superior parietal lobule ($p < 0.005$, uncorrected, Table 4). Table 4 summarizes the MNI coordinates of the peaks and voxel sizes of significant clusters. Figure 1-A shows significant

clusters of the brain that were significant at $p < 0.001$ and $p < 0.005$. Figure 1-B shows the plot of extracted WMH probability values from different regions of the brain identified from the corresponding regional analysis adjusted for age and sex.

Moderation effect of AHI in the relationship between age and WMH

AHI was not a moderating factor on the relationship between age and global WMH. Table 3 shows the coefficients and values correspond with the regression model. However, we found AHI modified the relationship between age and the lesion probability of WMH in the regional analysis. Specifically, AHI interacted with age in left angular gyrus, right corpus callosum, left inferior frontal gyrus, left middle frontal gyrus, right supramarginal gyrus, left precentral gyrus, right inferior fronto-occipital gyrus, left superior frontal gyrus, right precentral gyrus, and right superior occipital gyrus ($p < 0.005$, uncorrected, Table 4). Figure 2-A shows significant clusters. Figure 2-B shows the plot of extracted regional WMH probability values adjusted for sex. There was a significant interaction between AHI and age, regionally; indicating that WMH increases with age, but the degree of association was stronger in HF patients with AHI ≥ 10 than those with AHI < 10 .

Discussion

This study examined the relationship between AHI and WMH in HF patients. Although the global analyses did not reveal an association between AHI and WMH, regional analyses demonstrated that increases in AHI are associated with higher WMH and there was a moderation effect of AHI and age on WMH burden. In certain regions of the brain, we also found age-related WMH burden is amplified by AHI status; AHI ≥ 10 group showed higher age-related WMH burden than AHI < 10 group. The combined effect of increases in AHI and older age is associated with deleterious effects on brain white matter in HF patients. This study preliminarily supports that AHI is associated with WMH and age-related WMH could differ by degree of AHI in individuals with HF. Such findings suggest that SDB may affect WMH and exacerbate age-related WMH in certain regions of the brain among individuals with HF.

We found that AHI is associated with regional WMH but not global WMH among individuals with HF. The effect size was medium ($g = 0.43$). The findings indicate that increases in AHI are associated with localized areas of ischemic injury. Our results support prior findings in HF and non-HF samples indicating a correlation between SDB and WMH. Patel and colleagues (2015) found that SDB was associated with greater WMH in individuals with minor stroke and transient ischemic stroke.⁴⁰ In addition, SDB, hypoxemia and inflammation were associated with WMH in people with SDB.⁴¹ In contrast, some studies indicate a lack of association between SDB and WMH. For instance, in a study of hypertensive patients, researchers did not find that severity of SDB was associated with white matter disease based on a visual rating scale.⁴² Likewise, in rheumatic valvular disease patients, AHI was not significantly different in those with and without WMH.⁴³ Our findings suggest that SDB severity may be an important factor in predicting WMH burden, but the relationship still needs to be determined by further studies using larger and more diverse samples.

There are two potential pathways to explain how SDB and WMH are related. First, recurrent episodes of hypoxia could trigger subcortical injury by inducing oxidative stress,⁴⁴ increases in systemic inflammation,⁴⁵ hypomyelination,⁴⁶ and microglial alterations.⁴⁷ For example, intermittent hypoxia increases oxidative stress in the central nervous system, which could trigger the neurobehavioral impairments.⁴⁴ Second, impaired sleep architecture in SDB could change brain structure. In SDB, alterations in sleep architecture include sleep fragmentation, deficits in rapid eye movement sleep, and deficits in the delta power of non-rapid eye movement from intermittent arousals from hypoxic events.⁴⁸ In animal studies, sleep loss has been shown to be associated with astrocytic phagocytosis of synaptic elements. Chronic sleep loss is associated with activation of microglia and phagocytic activity, which could increase the brain's susceptibility to injury.⁴⁹ Thus, in HF, hypoxia and sleep fragmentation in conjunction with an underlying cardiovascular condition could influence ischemic lesions in the brain.

There was no main effect of LVEF on WMH in our sample (Table 3). The reduced cardiac function had been hypothesized and found to be associated with cerebral brain perfusion and, in turn, these changes are thought to contribute to structural changes in the brain within HF. LVEF is an indirect measure of ventricular function, which is equal to stroke volume divided by end-diastolic volume. With the loss of contractility in systolic dysfunction, LVEF also decreases. Decreases in cardiac output is correlated with reduced LVEF, and decreases in cardiac output and LVEF can lead to decreased brain perfusion and neurologic deterioration.⁵⁰ Bratzke-Bauer et al. (2013) suggest that the characteristics of cognitive impairment could differ by left ventricular function type in patients with HF. They examined 80 stable HF patients and found that individuals with systolic dysfunction presented lower scores on global cognition, immediate and delayed memory than those with diastolic dysfunction.⁵¹ Alosco et al. (2013) found that there is a combined effect of cardiac index and elevated systolic blood pressure is associated with WMH. The authors found that decreases in the cardiac index are associated with higher WMH burden among HF patients with elevated systolic pressure, whereas, WMH burden was only minimally changed by cardiac index in HF patients with mean systolic pressure after examining 48 HF patients. However, the presence of self-reported SDB was not associated with changes in WMH burden.⁵² Although we did not find a main effect of LVEF on WMH, future studies are needed to validate this result, using a larger sample size, greater variability in LVEF, and control group of healthy adults.

Existing literature suggests that age is a significant factor related to WMH burden in a sample without HF.³⁷ When we tested how AHI changed the relationship between age and WMH, we found that SDB was a significant moderating factor in the relationship between age and WMH in HF. Although both SDB and age were not significant factors in the regression models (Table 3), there was a synergetic effect of SDB with age, particularly on the left angular gyrus, right corpus callosum, left inferior frontal gyrus, left middle frontal gyrus, right supramarginal gyrus, left precentral gyrus, right inferior fronto-occipital gyrus, left superior frontal gyrus, right precentral gyrus, and right superior occipital gyrus after controlling for covariates. We identified WMH lesions consistent with both periventricular white matter hyperintensities and deep white matter hyperintensities. Given the likely multifactorial etiology of WMH in HF, this finding is not an unexpected finding and has

been observed in the prior studies on aging^{37,53}. As seen from the Figure 2 A and B, the significant regions are located in frontal and temporal regions bilaterally. The extracted values from the regions demonstrated that the slope of age-related WMH change is higher in those with AHI ≥ 10 than those with AHI < 10 , which is consistent with our hypothesis. Although findings related to SDB and structural brain changes are equivocal, our findings support prior studies which report that SDB is related to brain change and that age is a factor of brain alterations in non-HF samples.^{19,26,54} Given that white matter change could be directly linked to axonal change, further analysis could help understand the underlying mechanisms.

Despite the significant findings, this study has limitations that deserve mention. First, the sample size was limited, so the results need to be interpreted as preliminary. Second, the cross-sectional nature of the study precludes determining causal relationships, in this case, between the presence of SDB and the relationship with developing WMH. Third, home sleep monitoring has shown efficacy and acceptability in HF samples, but use of the device may not capture comprehensive sleep measures similar to an in-lab polysomnography.³⁴ There are several implications for future research. First, studies using a longitudinal design and larger sample would help other researchers understand the causal relationships and generalize the findings. Second, use of further MRI analysis methods are warranted to see how SDB plays a role in changing axonal changes or cerebral blood flow in HF patients, using techniques such as diffusion tensor imaging, 4-D phase contrast-isotropic-voxel radial projection imaging, or arterial spin labeling to explore changes in cerebral blood flow.⁵⁵ Third, there is a need for careful examination of other comorbidities such as atrial fibrillation, atrial function, and size in future studies to discover the complicated nature of brain injuries in HF sample. Finally, researchers who want to assess SDB should also use in-lab sleep studies in conjunction to portable sleep apnea monitoring methods to obtain more comprehensive sleep data. In terms of clinical implications, clinicians should be aware of the impact of SDB, not only on the cardiovascular system but also on neural health. If HF patients have cognitive impairment, clinicians can monitor patients with HF for neuropsychological changes and SDB status in outpatient or inpatient settings. Clinicians can also recognize early signs of cognitive impairment through both comprehensive interviews using routine evaluations and additional MRIs. Appropriate management of not only HF itself but also SDB is required for both general health and neural health.

Conclusion

In conclusion, this study preliminarily showed an association between SDB and WMH burden and age-related WMH burden could be more detrimental in HF patients with SDB than those without SDB. The findings suggest that clinicians should monitor and intervene in HF patients' SDB as well as cardiac status to improve patients' neurological outcomes, which, in turn, may translate to improved overall daily function and self-care management abilities. Effective management of SDB may be one way to help improve outcomes in people with HF given that cognitive impairment may affect mortality and re-hospitalization rates because of its influence on a patient's ability to engage in self-management, such as recognition of worsening symptoms of HF.

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Abbreviations

FOV	field of view
HF	heart failure
ICBM	The International Consortium for Brain Mapping
ICV	Intracranial volume
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MNI	Montreal Neurological Institute
AHI	apnea hypopnea index
SDB	sleep disordered breathing
SPM8	statistical parametric mapping 8
T2FLARE	T2 Fluid attenuation inversion recovery
TE	echo time
TI	inversion time
TR	repetition time
WMH	white matter hyperintensities
WMHp	white matter hyperintensity percent

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Figure 1.

Main effect of apnea hypopnea index (n=28) Note: A. The relationship between apnea hypopnea index (AHI) and white matter hyperintensities (WMH) probability belief maps for age, sex, intracranial volume, hypertension, and left ventricular ejection fraction in red colors ($p < 0.005$ uncorrected) and yellow ($p < 0.001$ uncorrected) colors. The colored bars indicates the magnitude of the t-value. Peak voxel coordinates, t-value, p-value, and cluster size are listed in Table 4. B. Residuals of the WMH ratio (WMHp (% of intracranial volume)) and regional WMH extractions as a function of AHI for sex adjusted fit in the

linear model AHI= Apnea hypopnea index; L = Left ; R= Right ; WMHp = White matter hyperintensity percent

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Figure 2.

Interaction between age and apnea hypopnea index ($n = 28$) Note: A. The combined relationships of age and apnea hypopnea index (AHI) on white matter hyperintensities (WMH) probability belief maps for age, sex, intracranial volume, hypertension, and left ventricular ejection fraction in red colors ($p < 0.005$ uncorrected) and yellow ($p < 0.001$ uncorrected) colors. The colored bars indicates the magnitude of the t-value. Peak voxel coordinates, t-value, p-value, and cluster size are listed in Table 4.B. Residuals of the WMH ratio (WMHp (% of intracranial volume)) and regional WMH extractions as a function of

interaction term (age and AHI) for sex adjusted fit in the linear model AHI= Apnea hypopnea index; L = Left ; R= Right ; WMHp = White matter hyperintensity percent

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Table 1.**Eligibility Criteria**

Inclusion criteria	
	Age 60
	Able to speak and write English
	On a stable guideline-based medication regimen for at least four weeks prior to enrollment.
Exclusion criteria	
	Dementia determined by a Mini-Mental Status score of less than 24
	Current diagnosis of neurological illnesses or movement disorders (e.g., Alzheimer's dementia, Parkinson's disease, epilepsy)
	History of substance abuse or treatment;
	untreated depression;
	history of stroke;
	hepatic insufficiency determined by aspartate transaminase and alanine transaminase greater than twice the normal limits;
	severe renal failure determined by serum creatinine greater than 2.5 mg/dl;
	Untreated anemia;
	Contraindications for MRI
	Left ventricular assist device
	History of unstable cardiac condition within three months of study enrollment (e.g., acute myocardial infarction, unstable angina, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or biventricular pacemaker insertion)

Table 2.

Comparison by sleep-disordered breathing status (n = 28)

	Higher AHI (AHI ≥ 10) (n=15)		Lower AHI (AHI <10) (n=13)		<i>p</i>
	Mean ± SD	n (%)	Mean ± SD	n (%)	
Age	68.40 ± 4.94		67.3 ± 6.8		0.628
Sex (male)		12 (80)		5 (39)	0.025
NYHA functional class					0.758
I		5 (33)		4 (31)	
II		9(60)		7 (54)	
III		1 (7)		2 (15)	
Heart failure type					0.662
Systolic		8 (53)		8 (62)	
Diastolic		7 (47)		5 (39)	
Hypertension		7 (47)		7 (54)	0.705
AHI	19.07 ± 9.35		4.31 ± 3.01		.000
Obstructive apnea (numbers)	33.40 ± 32.47		2.33 ± 4.74		0.001
Central Apnea (numbers)	5.13 ± 6.42		1.08 ± 2.15		0.014
LVEF	45.53 ± 12.42		47.08 ± 12.82		0.749
ICV	1540.33 ± 169.83		1477.20 ± 112.58		0.265
WMH volume (mm ³)	37.10 ± 15.85		30.75 ± 12.01		0.249
WMHp (% of ICV)	2.38 ± 0.91		2.08 ± 0.82		0.364
Mini-Mental State Examination	29.53 ± 0.516		29.00 ± 1.225		0.136

AHI = Apnea Hyperpnea Index; ICV = Intracranial volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; WMHp = White matter hyperintensity percent

Table 3.
Summary of regression analysis for variables predicting WMHp by apnea hypopnea index (n = 28)

Main effect of AHI					Moderation effect of AHI					
	B	SE (B)	β	R ²	R ² /Adjusted R ²	B	SE (B)	β	R ²	R ² /Adjusted R ²
Intercept	-0.648	2.136								0.306/0.108
Age	0.039	0.031	0.259	0.104		3.285	3.064			
Gender	0.178	0.348	0.103	0.068		-0.023	0.006	-0.152	0.104	
Hypertension	0.353	0.338	0.208	0.066		0.171	0.334	0.099	0.068	
LVEF	-0.008	0.014	-0.109	0.033		0.375	0.324	0.221	0.066	
AHI	0.016	0.017	0.189	0.032		-0.002	0.014	-0.023	0.033	
AHI X Age					0.208/0.028	-0.420	0.254	-4.991	0.028	
						0.006	0.004	5.289	0.306	

LVEF = Left ventricular ejection fraction; AHI = apnea hypopnea index; WMHp = white matter hyperintensity percent

Note: None of the independent variables had p value less than .05

*
p < .05

Table 4.

Summary of peak voxel correlations between AHI and voxel-wise lesion probabilities in the Montreal Neurological Institute coordinates

		p < 0.001				P < 0.005					
Main	Location	MNI coordinates			Cluster size	T	MNI coordinates			Cluster size	T
		x	y	z	k	t*	x	y	z	k	t*
AHI	Right anterior corona radiata	26	36	-0	205	3.98	26	36	-0	1174	3.98
	Right inferior frontal gyrus	26	30	18		3.62	26	30	18		3.62
	Left middle orbital gyrus	-14	26	-15	76	3.95	-14	26	-15	381	3.95
	Right Superior corona radiata	27	-1	34	72	3.71	27	-1	34		3.71
	Left post central gyrus	-26	-34	45	41	3.68	-26	-34	45	722	3.68
	Left post central gyrus						-14	-28	52		3.11
	Left precentral gyrus						-22	-7	48	618	3.50
	Right superior parietal lobule						18	-51	43	173	3.17
AHI X Age	Left angular gyrus	-40	-40	19	1123	4.93	-40	-40	19	2469	4.93
		-34	-58	12		4.32	-34	-58	12		4.32
		-24	-54	7		3.72	-24	-54	7		3.72
	Right Corpus Callosum	26	-52	13	897	4.49	26	-52	13	3122	4.49
		42	-55	21		4.31	42	-55	21		4.31
		27	-34	18		4.03	27	-34	18		4.03
	Left Inferior frontal gyrus	-34	35	9	157	4.05	-34	35	9	1018	4.05
	Left middle frontal gyrus	-26	-3	48	78	3.97	-26	-3	48	342	3.97
	Right supramarginal gyrus	44	-40	31	38	3.77	24	35	25	65	3.45
	Left precentral gyrus						-10	-24	60	128	3.36
	Right inferior fronto-occipital gyrus						22	20	-12	86	3.23
	Left superior frontal gyrus						-14	-10	55	41	3.22
	Right precentral gyrus						44	-9	34	118	3.11
	Right superior occipital gyrus						16	-90	7	59	3.11

AHI = apnea hypopnea index ;Montreal Neurological Institute (MNI)