Continuous positive airway pressure therapy reduces right ventricular volume in patients with obstructive sleep apnea: a cardiovascular magnetic resonance study

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Relevant conflicts of interest: none for any author

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ABSTRACT

Study Objectives. There are few data on continuous positive airway pressure (CPAP) therapy’s effects on the structural and functional characteristics of the right heart in patients with obstructive sleep apnea (OSA). We sought to leverage the advantages of cardiac magnetic resonance (CMR) imaging and hypothesized that CPAP treatment will improve right ventricular (RV) function in a group of OSA patients who are free of other co-morbid conditions.

Methods. Patients with severe (apnea-hypopnea index ≥30/h), untreated OSA were prospectively enrolled. CMR included three-dimensional measurement of biventricular size and function and rest/stress myocardial perfusion and were performed at baseline and after 3 months of CPAP therapy.

Results. Fifteen patients with mild to moderate desaturation were enrolled; two could not undergo CMR due to claustrophobia and obesity. There was significant decrease in the Epworth Sleepiness Scale score (p<0.0001), and significant decreases in right ventricular (RV) end-systolic and RV end-diastolic volumes (p<0.05) with CPAP. There was a trend toward improvement in RV ejection fraction, but did not reach statistical significance. Other measures such as left ventricular (LV) volumes, LV ejection fraction, myocardial perfusion reserve index, and thickness of the interventricular septum and ventricular free wall did not change significantly.

Conclusions. This preliminary study found that CPAP treatment decreases right ventricular volumes in OSA patients with severe disease who are otherwise healthy. CMR offers a novel technique to determine the effects of CPAP on ventricular structure and function in OSA patients. A randomized controlled study is needed to confirm the results of our study.
Key Words

obstructive sleep apnea
continuous positive airway pressure
magnetic resonance imaging
right ventricle
heart function tests
Introduction

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality. Although the exact mechanism for this effect remains unclear, abnormalities of cardiac structure and function have been reported in patients with OSA. These latter studies mainly examined the effects of OSA on left ventricular changes with both systolic and diastolic dysfunctions reported. Indeed, even in patients with established congestive heart failure, CPAP improves left ventricular systolic function.

There are few data on the structural and functional changes of the right heart in patients with OSA and the effects of CPAP therapy on right ventricular function. Most of these studies employed echocardiography and suggested significant association of the severity of OSA, assessed by the apnea-hypopnea index (AHI), to right ventricular dysfunction. One study examined the effects of CPAP treatment on the right heart and these authors reported improvements in right ventricular tissue Doppler systolic velocity after 6 months of therapy. However, the inherent challenges of echocardiography-based imaging of the right ventricle, further compounded by the frequently poor acoustic window in obese OSA patients, may limit the reproducibility of these findings.

The volumetric nature of cardiac magnetic resonance imaging (CMR), which is not affected by body habitus, has made this modality the current gold standard for quantifying ventricular size and function and the preferred modality for precise measurements in clinical trials. CMR provides an accurate and reproducible measurement of ventricular structure and function by assessment of volumes, ejection fraction and mass and is particularly useful in evaluation of the right heart. Compared to other modalities, the improved precision reduces the
sample size required in clinical studies. Furthermore, the superior spatial resolution of CMR affords recognition of subtle subendocardial perfusion abnormalities, not feasible with any other noninvasive modality. This is of particular interest since subclinical atherosclerotic heart disease has been reported in patients with OSA. We sought to leverage these advantages of CMR in implementing a comprehensive evaluation of cardiac structure, function and myocardial perfusion reserve in OSA patients. Specifically, we hypothesized that CPAP treatment will improve right ventricular function even in a group of OSA patients who are free of other comorbid conditions.

**Methods and Materials**

**Patient Population**

Patients referred for suspicion of OSA were initially evaluated by a sleep disorders specialist (UJM) and included in the study if they met the following inclusion criteria: AHI > 30 by overnight polysomnography (PSG) and Epworth Sleepiness scale score > 10. The PSG methods and definition of respiratory events are described below. These characteristics identify a group of OSA patients with severe disease who likely would be compliant with CPAP treatment. Patients were excluded if they had any the following: known diabetes mellitus, heart failure, coronary artery disease, use of illicit drugs or excessive alcohol consumption, active smoking, advanced lung disease, use of inhalers, prior treatment with CPAP, or any contraindication to MRI such as ferromagnetic foreign body, orbital metal, cerebral aneurysm clip, pacemaker, defibrillator, neurostimulator, allergy to gadolinium-based contrast, or severe claustrophobia. Patients with hypertension were included only if they have been well-controlled (defined as a systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg) and have been on a stable dose of medications for at least a month. Written informed consent was obtained from
all the subjects to participate in this Institutional Review Board-approved protocol. Venous blood samples were collected prior to baseline CMR imaging. After baseline CMR examination, all patients initiated CPAP treatment with an objective compliance card embedded in the machine and returned for monthly visits with the sleep disorders specialist for CPAP therapy optimization followed by repeat CMR at 3 month follow-up. The prescribed CPAP pressure was based on a CPAP titration study that eliminated respiratory events and improved oxyhemoglobin saturation during sleep.

Polysomnography

All patients underwent standard diagnostic overnight PSG. Airflow was measured by monitoring of nasal pressure via a nasal cannula. Sleep stages were scored in 30-second epochs using standard criteria. Each epoch was analyzed for the number of apneas, hypopneas, electroencephalographic (EEG) arousals, and oxyhemoglobin desaturation. Apnea was defined as the absence of airflow for at least 10 sec. Hypopnea was defined as a visible reduction in airflow lasting at least 10 sec associated with at least a 4% decrease in arterial oxyhemoglobin saturation. The apnea hypopnea index (AHI) was defined as the number of apneas and hypopneas/hr of sleep.

Cardiac Magnetic Resonance Examination

All subjects underwent identical CMR examination completed on a 1.5 Tesla clinical magnetic resonance scanner (MAGNETOM Avanto, Siemens Medical Solutions, Inc., Erlangen, Germany) using a 12-element cardiac phased array coil. The CMR protocol included: (i) cine acquisitions in standard planes including contiguous short-axis slices to measure RV and LV free
wall thickness, end-diastolic volumes, end-systolic volumes, and ejection fractions; (ii) first-pass myocardial perfusion imaging during intravenous administration of 140 mcg/kg adenosine using 0.1 mmol/kg gadolinium-DTPA contrast and rest perfusion imaging 15 minutes after stress; and (iii) late post-gadolinium acquisitions in standard planes for myocardial scar visualization 5-10 minutes after rest perfusion imaging was completed. Standard 12-lead electrocardiography was performed prior to and after each CMR examination.

Image Analysis

Left and right ventricular volumes and ejection fractions were computed from short axis cine images (Figure 1) using standardized semi-automated segmentation software (Argus, Siemens Medical Solutions). Briefly, endocardial contours at end-systole and end-diastole delineated the left and right ventricle in each slice; using Simpson’s rule, the volumes from each short axis slice (area × slice thickness) were summed to obtain ventricular volumes. Ejection fraction was computed as the stroke volume (end-diastolic volume - end-systolic volume) divided by end-diastolic volume. Quantification of myocardial perfusion was performed using semi-automatic delineation of endocardial and epicardial left ventricular borders throughout the phases of first-pass perfusion with respiratory motion correction as needed (CMRTools, London). Rest and stress myocardial perfusion slopes were derived using Fermi-fitting of signal intensity versus time and normalized to the LV blood pool slope as well as heart rate. A Myocardial Perfusion Reserve Index (MPRI), calculated for each subject, was defined as the ratio of stress to rest normalized myocardial perfusion slope. Thickness of the interventricular septum (IVS) was measured at the mid-ventricular level from an end-diastolic long axis image. All image analysis was performed blinded to subject history.
**Statistical Analysis**

All continuous variables are expressed as mean ± standard deviation (SD). Volumes are reported normalized to body surface area (mL/m²). Stata/SE 8.1 (Stata Corp., College Station, TX) was used for statistical analysis. The Mann-Whitney Two Sum Rank test was used to compare values pre- and post-CPAP therapy. P-value <0.05 was considered significant.

**Results**

Fifteen patients age 27 to 66 years were enrolled; two could not complete CMR examination, one due to claustrophobia and another due to morbid obesity. The average body mass index (BMI) was 35.3 ± 7.6 kg/m². All had severe OSA, with AHI ranging from 30 - 102 events/hr associated with mild to moderate oxyhemoglobin desaturations during sleep with a nadir of 80 + 6%. Oxyhemoglobin saturation by pulse oximetry during wakefulness was > 95% in all patients. Only five of the thirteen patients (38%) were on anti-hypertensive medications and these patients all had good blood pressure control during the study period. None of the patients had an elevated B-type natriuretic peptide (BNP) level. Except for three patients (34, 36, and 51 pg/ml), all patients had BNP levels of <30 pg/ml which is the lower limit of detection in our laboratory. The clinical characteristics are summarized in Table 1. There was no significant change in body weight from baseline to after 3 months of CPAP treatment (baseline: 110.0 ± 21 versus three mo: 112.0 ± 22.6 kg, p=NS) and no changes in medications occurred during this time period. Patients were compliant with CPAP therapy with an average use of 5.3 ± 1.6 hrs per night (time at effective pressure) throughout the study period. Subjective sleepiness measured by
the Epworth sleepiness score significantly decreased with CPAP treatment (baseline: 15 ± 3 versus three mo: 6 ± 3, p<0.0001).

Patients’ right ventricular volumes were significantly reduced with CPAP therapy (Figures 2 and 3): right ventricular end-diastolic volume index (RVEDVI) decreased from 57.6 ± 11.4 mL/m² to 47.8 ± 14.4 mL/m² (p<0.05), and right ventricular end-systolic volume index (RVESVI) decreased from 30.0 ± 7.7 mL/m² to 22.2 ± 5.5 mL/m² (p <0.05). There was a trend toward improved right ventricular ejection fraction with CPAP therapy that did not achieve statistical significance (47.5 ± 12.1% vs. 52.5 ± 8.6%, p=0.33). There was also no significant change in the RV free wall thickness (p=0.53). In this cohort, CPAP did not produce any significant change in left ventricular volumes, ejection fraction, or LV free wall thickness. Similarly, myocardial perfusion index did not change significantly (0.94 ± 0.14 vs. 0.83±0.63, p=0.14). No OSA patient had left ventricular hypertrophy; thickness of the interventricular septum was normal at baseline and did not change significantly at 3 months follow-up (7.9 ± 2.2 mm vs 8.0 ± 2.4 mm, p=NS).

**Discussion**

In a cohort of patients with severe OSA, we found mild improvements in right ventricular volumes and a trend toward improved RV ejection fraction with short-term CPAP treatment. No significant change was seen in LV volumes, LV ejection fraction, myocardial perfusion reserve index, or thickness of the IVS, RV and LV free wall in this study population. By excluding patients with any history of tobacco use, diabetes, atherosclerotic heart disease, or heart failure, we studied a group of OSA subjects whose cardiac parameters were close to normal at baseline. Still, we found improvements in RV volumes with CPAP treatment. This suggests that prior to
the development of overt cardiovascular disease and prior to demonstrable LV dysfunction, the right heart is the first to undergo adverse remodeling due to OSA.

This is the first study that has utilized CMR in assessing the effects of CPAP on cardiac structure and function. A prior small study involving five OSA patients used CMR but imaging was not performed after CPAP therapy 25. We have shown that in our current study of obese subjects, excellent quality images can be obtained for a precise and comprehensive noninvasive assessment of cardiac structure and function. Prior studies examining the effects of CPAP treatment uniformly employed echocardiography with its inherent limitations in obtaining adequate images in predominantly obese subjects. In addition, the CMR also allows assessment of rest and stress myocardial perfusion in the same examination. This, as well as the small sample size requirement afforded by the higher reproducibility of CMR, would be important in future studies examining the effects of CPAP treatment in OSA patients with pre-existing cardiovascular disease, or in OSA patients at increased cardiovascular risk due to diabetes and hypertension.

RV remodeling in OSA may result from repetitive nocturnal elevations in pulmonary artery pressure that results in intermittent RV pressure overload 26,27 and also by increased sympathetic discharges during apneic episodes 5. CPAP treatment for 3 months has been shown to decrease pulmonary artery systolic pressure 28. Our patients had mild to moderate oxyhemoglobin desaturations during sleep prior to treatment, and despite the absence of clinical symptoms of RV dysfunction had improvements in their RV volume after a relatively short period of CPAP therapy. We speculate that our findings may, in part, be due to the reduction in sympathetic nervous system activity that is known to occur with CPAP treatment. It is possible that we could have seen more improvements in the right heart function if our patient population
included OSA subjects with more severe oxyhemoglobin desaturations during sleep prior to treatment.

We did not find any significant changes in LV structure and function with CPAP treatment. LV abnormalities has been associated with OSA in some 29, but not all studies 30,31. Differences in the results of these studies, including ours, may in part be due to the fact that other studied populations may have had more significant hypertension, which is known to adversely affect LV structure and function. We specifically enrolled patients either without hypertension or whose blood pressure was well-controlled and had been on a stable dose of medications.

Our study has several limitations. Our sample size was relatively small, but we were able to show significant differences in RVEDVI and RVESVI after 3 months of CPAP therapy. It is not known whether a larger sample size would allow for the noted trend of an increase in RVEF to be statistically significant. We did not include a group of untreated OSA patients. Therefore, we cannot totally exclude that unknown confounding factors such as regression to the mean could potentially explain our findings. Given our results, a randomized controlled trial would be appropriate to assess ventricular structure and function using CMR in OSA patients. Finally, we included only a group of patients without co-existing co-morbidities such as atherosclerotic heart disease or LV dysfunction. Further studies are required using CMR to determine the effects of CPAP on ventricular structure and function in OSA patients with LV dysfunction and/or atherosclerotic heart disease.

In conclusion, patients with severe, untreated OSA without cardiovascular disease have shown modest but significant improvements in right ventricular structure after initiation of CPAP therapy. We have shown that in this group of obese subjects with OSA, high quality images using CMR can be obtained for a precise and comprehensive noninvasive assessment of cardiac
structure and function. Ongoing longer-term follow-up and comparison to OSA patients with more significant cardiac dysfunction may yield additional insights into the relationship between OSA and cardiovascular disease.

**Abbreviations List**

AHI = apnea-hypopnea index  
BMI = body mass index  
CMR = cardiac magnetic resonance  
CPAP = continuous positive airway pressure  
EF = ejection fraction  
IVS = interventricular septum  
LV = left ventricle  
LVEDVI = left ventricular end diastolic volume index  
LVESVI = left ventricular end systolic volume index  
OSA = obstructive sleep apnea  
PSG = polysomnography  
RV = right ventricle  
RVEDVI = right ventricular end diastolic volume index  
RVEDSI = left ventricular end systolic volume index  
MPRI = myocardial perfusion reserve index
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Figure Legends

Figure 1. Representative CMR mid-ventricular short axis slice in one OSA patient shown at end-diastole (left) and end-systole (right). The contours indicate semi-automated delineation of endocardial and epicardial contours around the left ventricular (LV) myocardium, and endocardial contours delineating the inner surface of the right ventricular (RV) myocardium. Knowing the areas of these contours and the thickness of the slice allows calculation of the volume in each slice; summing over the slices that cover the heart yields total ventricular volumes.
Figure 2. Right ventricular end-diastolic volume indexed to body surface area (RVEDVI, mL/m²) decreased significantly after 3 months of CPAP treatment (p<0.05). Box plots of the RVEDVI are shown. The lower and upper bars represent the lowest and highest values, respectively; the lower and upper boundaries of the box represent the first and third quartiles, while the line within the box represents the median value.
Figure 3. Right ventricular end-systolic volume indexed to body surface area (RVESVI, mL/m²) decreased significantly after 3 months of CPAP therapy (p<0.05).
Figure 4. Right ventricular ejection fraction (RVEF, %) shows a trend toward improvement after 3 months of CPAP therapy in patients with OSA.
### Tables

Table 1. Patient characteristics at baseline**.

<table>
<thead>
<tr>
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<th>Patients (N=13)</th>
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<tbody>
<tr>
<td>Males (%)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48.8 ± 10.8</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>35.3 ± 7.6</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>121 ± 12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>15.0 ± 3.0</td>
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<tr>
<td>AHI (events/hr)</td>
<td>60.2 ± 23.7</td>
</tr>
<tr>
<td>Obstructive apneas (% of total events)</td>
<td>48.4 ± 27.3</td>
</tr>
<tr>
<td>Central apneas (% of total events)</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>Hypopneas (% of total events)</td>
<td>49.7 ± 28.2</td>
</tr>
<tr>
<td>SpO₂ during wakefulness (%)</td>
<td>97 + 1</td>
</tr>
<tr>
<td>SpO₂ nadir during sleep (%)</td>
<td>80 + 6</td>
</tr>
<tr>
<td>CT90 (min)</td>
<td>8.3 ± 6.3</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>92 + 8</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>162 + 37</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>&lt; 60</td>
</tr>
</tbody>
</table>

AHI = apnea-hypopnea index  
SpO₂ = oxyhemoglobin saturation by pulse oximetry  
CT90 = cumulative time below 90% during sleep  
**Values represent mean + standard deviation
Table 2. CMR baseline and follow-up measurements**.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>After 3 Months of CPAP</th>
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<tbody>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>54.2 ± 19.5</td>
<td>50.4 ± 8.1</td>
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<tr>
<td>LVESVI (mL/m²)</td>
<td>22.4 ± 9.0</td>
<td>20.5 ± 3.5</td>
</tr>
<tr>
<td>LV free wall (mm)</td>
<td>8.0 ± 1.1</td>
<td>8.0 ± 1.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.5 ± 8.2</td>
<td>58.9 ± 5.4</td>
</tr>
<tr>
<td>RVEDVI (mL/m²)</td>
<td>57.6 ± 11.4</td>
<td>47.8 ± 14.4*</td>
</tr>
<tr>
<td>RVESVI (mL/m²)*</td>
<td>30.0 ± 7.7</td>
<td>22.2 ± 5.5*</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>47.5 ± 12.1</td>
<td>52.5 ± 8.6</td>
</tr>
<tr>
<td>RV free wall (mm)</td>
<td>4.4 ± 1.3</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>7.9 ± 2.2</td>
<td>8.0 ± 2.4</td>
</tr>
<tr>
<td>MPRI</td>
<td>0.94 ± 0.14</td>
<td>0.83 ± 0.63</td>
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*P<0.05 compared to baseline measurements. See text for abbreviations.

** Values represent mean + standard deviation.