Effects of Short-Term Continuous Positive Airway Pressure on Myocardial Sympathetic Nerve Function and Energetics in Patients with Heart Failure and Obstructive Sleep Apnea: A Randomized Study

Running title: Hall et al.; CPAP and Cardiac SN Function and Energetics

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Abstract

**Background**—Heart failure with reduced ejection fraction (HFrEF) and obstructive sleep apnea (OSA), two states of increased metabolic demand and sympathetic nervous system activation, often co-exist. Continuous Positive Airway Pressure (CPAP), which alleviates OSA, can improve ventricular function. It is unknown whether this is due to altered oxidative metabolism or pre-synaptic sympathetic nerve (SN) function. We hypothesized that short-term (6-8 weeks) CPAP in patients with OSA and HFrEF would improve myocardial SN function and energetics.

**Methods and Results**—Forty-five patients with OSA and HFrEF (LVEF 35.8±9.7%; mean±SD) were evaluated using echocardiography, ^11^C-acetate and ^11^C-hydroxyephedrine (HED) positron emission tomography (PET) before and approximately 6-8 weeks after randomization to receive short-term CPAP (N=22) or no CPAP (N=23). Work metabolic index (WMI), an estimate of myocardial efficiency, was calculated as: \(\text{stroke-volume-index} \times \text{heart rate} \times \text{systolic BP} \div k\)-mono, where k-mono is the mono-exponential function fit to the myocardial ^11^C-acetate time-activity data, reflecting oxidative metabolism. Presynaptic SN function was measured using the ^11^C-HED retention index. CPAP significantly increased HED retention vs. No-CPAP (Δretention: +0.012 (0.002,0.021) vs. -0.006 (-0.013,0.005) min^−1, p=0.003). There was no significant change in WMI between groups. However, in those with more severe OSA (Apnea Hypopnea Index >20 events/hr), CPAP significantly increased both WMI and systolic BP (p<0.05).

**Conclusions**—In patients with HFrEF and OSA, short-term CPAP increased HED retention, indicating improved myocardial SN function, but overall did not affect energetics. In those with more severe OSA, CPAP may improve cardiac efficiency. Further outcome-based investigation of the consequences of CPAP is warranted.

**Clinical Trial Registration Information**—clinicaltrials.gov. Identifier: NCT00756366.

**Key words:** heart failure, imaging, metabolism, sleep, sympathetic nervous system
Introduction

Obstructive sleep apnea (OSA), present in approximately a third of all patients with heart failure (HF) with reduced ejection fraction (HFrEF), is an independent predictor of mortality. Common to both HFrEF and OSA are sympathetic nervous system (SNS) activation and impaired myocardial energetic efficiency.

Myocardial efficiency estimates the capacity of the heart to convert oxygen into effective forward stroke work. The non-invasively derived cardiac work-metabolic index (WMI) estimates efficiency by quantifying forward minute-work of the left ventricle (LV), corrected for the rate of oxidative metabolism measured using $^{11}$C-acetate positron emission tomography (PET). Oxidative metabolism represents the utilization of substrates via the tricarboxylic acid cycle for the production of adenosine triphosphate and is directly linked to myocardial oxygen consumption.

HFrEF is an energy-deplete state, in which increased metabolic oxidative demand exists at the expense of forward stroke work, which causes further reflex-mediated increases in efferent sympathetic discharge and norepinephrine (NE) release. In OSA, acute upper airway obstruction generates greater negative intra-thoracic pressure (i.e. increased afterload) and causes hypoxia, hypercapnia and arousal from sleep. These several stimuli increase simultaneously both metabolic demand and sympathetic discharge. Thus, during sleep these interactions between OSA and HFrEF will perturb the myocardial oxygen supply-demand ratio, impacting adversely LV performance.

One might posit then, that abolition of OSA by nocturnal continuous positive airway pressure (CPAP) therapy would restore cardiac autonomic balance and improve myocardial efficiency and LV systolic performance. Indeed, in a randomized controlled trial involving...
HFrEF patients with moderate to severe OSA, 1 month of CPAP improved daytime LV ejection fraction and arterial baroreflex modulation of heart rate and lowered heart rate, systolic blood pressure and sympathetic vasoconstrictor discharge directed at skeletal muscle. However, the mechanism by which nocturnal CPAP improves daytime LV systolic function is presently unclear. If CPAP improved cardiac contractility but increased cardiac sympathetic drive and myocardial oxygen consumption, this would indicate reduced efficiency and could lead to detrimental consequences such as those induced by sympathomimetic inotropic therapies. The present investigation was stimulated by our previous exploratory non-randomized study of 7 patients with OSA and HFrEF, in whom CPAP increased cardiac efficiency. Although consistent with an energy sparing effect, a definitive test of these concepts would require a larger cohort evaluated in a randomized controlled trial, accompanied by concurrent evaluation of myocardial SNS activity. In patients with decreased LV function, reduced cardiac presynaptic nerve function, measured using myocardial retention of $^{11}$C-hydroxyephedrine (HED) on PET or $^{123}$I-MIBG washout imaging, has been shown to predict the severity of arrhythmias and adverse outcomes.

We therefore hypothesized that in patients with OSA and HFrEF, treatment of OSA by nocturnal CPAP for 6 to 8 weeks would increase daytime myocardial WMI, an estimate of efficiency, measured using $^{11}$C-acetate and echocardiography, and at the same time improve presynaptic sympathetic neuron (SN) function, as quantified using $^{11}$C-HED PET.

Methods

Study Design

The study was a single center, unblinded, randomized controlled trial with balanced
randomization ratio (1:1). The trial was designed to determine the short-term (6-8 weeks) effects of CPAP on cardiac energetic and sympathetic nerve function in patients with OSA and HFrEF. The study was approved by the University of Ottawa Heart Institute Human Research Ethics Board. All patients provided informed consent.

**Experimental Protocol**

Forty-five patients with HFrEF and OSA were consecutively recruited with the following inclusion criteria: a) LV systolic dysfunction [left ventricular ejection fraction (LVEF) <45% by echocardiography, radionuclide or contrast ventriculography]; b) NYHA Class ≥II dyspnea; c) stable condition with optimally tolerated medical therapy, unchanged for >4 weeks; d) OSA defined on nocturnal polysomnogram as an apnea/hypopnea index (AHI) >10 events/hr with a predominantly obstructive pattern (≥80%). Exclusion criteria were patients with: a) unstable angina or myocardial infarction within 4 weeks prior to study enrollment; b) a requirement for revascularization; c) transmural scar known to be >25% of the LV on prior perfusion imaging; d) severe valvular dysfunction; e) life expectancy <1 year from other co-morbidities; f) significant obstructive or restrictive lung disease; g) use of tricyclic antidepressants, cocaine or drugs which may alter catecholamine uptake; or hypnotic, benzodiazepine, SSRI, neuroleptic, narcotic or other medications which may alter sleep or sleep-disordered breathing; h) central sleep apnea; i) other primary sleep disorders; j) debilitating daytime somnolence.

Eligible and consenting patients were randomized and underwent baseline measurements including: clinical exam, electrocardiography (ECG), blood work, echocardiography, $^{11}$C-acetate and $^{11}$C-HED PET imaging.

**Randomization**

A stratified (by ischemic or non-ischemic etiology) block randomization scheme was used.
Ischemic etiology was defined based on prior perfusion imaging, coronary angiography or prior history of MI or revascularization. Within each stratum, eligible patients were randomly assigned to CPAP (group A: CPAP) or no CPAP therapy (group B: No-CPAP) with the block size of 4. Baseline measurements were repeated approximately 6-8 weeks after initiation of therapy (CPAP or no–CPAP).

**Sleep Studies**

Overnight polysomnogram was performed using the Alice system (Respironics, Murrysville, PA). Sleep staging was determined by standard four-channel EEG (C4A1, C3A2, O4A1, O3A2, plus two EEG leads for arousals: F4A1, F3M2), 2-channel electro-oculogram, and submental EMG. Continuous measures of airflow by thermistor and nasal/oral pressure transducer, ribcage and abdominal motion by impedance plethysmography, oxygen saturation by finger oximetry and movement by leg EMG were recorded and analyzed in a standardized fashion. ECG recorded heart rate and rhythm. Sleep stages were scored using standard Rechtschaffen and Kales criteria as modified by AASM 2007. An obstructive apnea was defined as cessation of airflow for >10 seconds with persistent respiratory effort as seen in the ribcage or abdomen signals; hypopnea (option A) was defined as a decrease in airflow, ribcage or abdominal motion by >50% of the baseline signal, for >10 s with a ≥4% fall in O2 saturation. The AHI quantifies the number of events per hour of scored sleep.

**CPAP Titration and Therapy**

Patients assigned to CPAP had a CPAP titration sleep study scheduled approximately 1-2 weeks after the baseline PET and echocardiography studies. Therapeutic CPAP pressure was determined as per clinical guidelines for the manual titration of positive airway pressure in adult patients with sleep apnea so that apneas, hypopneas and respiratory effort-related arousal in all...
sleep stages were abolished. Patients were instructed to use CPAP at the determined pressure every night for at least 6 hours. Whenever possible, CPAP compliance was assessed using the machines’ hour usage meters and patients were contacted approximately biweekly to optimize mask tolerance, fit and compliance during the study period in order to optimize CPAP compliance.

**Echocardiography**

Echocardiographic examinations were performed using an HP 5500 or ie33 ultrasound system equipped with a 2-to 4-MHz transducer (Philips, Andover, Massachusetts). LVEF was calculated using the bi-plane method of disks (modified Simpson’s rule). Forward stroke volume (SV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and LV outflow tract diameter. Stroke volume index (SVI) was derived by dividing the SV by the body surface area. Those performing the echocardiographic measurements (SYC, IGB) were blinded to patient clinical data and OSA status.

**11C-Acetate PET Protocol and Analysis**

Immediately following echocardiography, patients were positioned supine in a quiet and awake state in the Siemens/CTI ECAT-ART PET (Knoxville, TN) or GE Discovery 690 PET/VCT (Waukesha, WI) scanner. A transmission scan was performed using isotope sources or x-ray CT to correct for photon attenuation. Immediately following the transmission scan, 10-15mCi (370-550 MBq) 11C acetate was administered intravenously and a 30-minute dynamic PET scan was initiated (10 frames x10 seconds; 2x30s; 5x100s; 3x180s, 2x300s).

Images were reconstructed using filtered-back-projection with a 12 mm Hann window of the ramp filter. Automatic reorientation of the images, and extraction of mean myocardial and cavity time-activity curves were performed using our FlowQuant© software [Ottawa, Canada].

DOI: 10.1161/CIRCULATIONAHA.113.005893
A mono-exponential function \([k_{\text{mono}} \text{ (min}^{-1})]\) was fit to the myocardial time activity data, as described previously\(^9\). The mono-exponential fit started at the point when the blood pool was stable (usually 2 to 4 min after injection). All data were analyzed blinded to the clinical data, the OSA status and the randomization group.

**Assessment of myocardial efficiency**

The \(^{11}\text{C}\)-acetate clearance rate was combined with the stroke work data to estimate myocardial efficiency using the LV work metabolic index (WMI), as described previously: \(\text{WMI} = \text{SVI} \times \text{SBP} \times \text{HR} \div k_{\text{mono}}\); where SVI is the stroke volume index determined by echocardiography, SBP is systolic blood pressure, HR is heart rate, and \(k_{\text{mono}}\) is the mono-exponential rate constant for C-11 clearance from the myocardium\(^6\)-\(^9\). This equation is a modification of the minute-work-to-oxygen consumption relationship originally defined as mechanical efficiency\(^5\).

**\(^{11}\text{C}\)-HED PET Protocol and Analysis**

\(^{11}\text{C}\)-HED was produced from \(^{11}\text{C}\)-methyl iodide and metaraminol free base using standard methods in high purity and specific activity\(^35\). Two hours after \(^{11}\text{C}\)-acetate injection (allowing for decay of \(^{11}\text{C}\); \(t_{1/2}=20 \text{ min}\)), the patient was repositioned in the scanner and underwent a transmission scan as noted above for attenuation correction followed by the administration of 10-15 mCi (370-550 MBq) of \(^{11}\text{C}\)-HED and a 40 minute dynamic PET acquisition (\(10x10s;1x60s;5x100s;3x180s;4 \times 300s\))\(^36\).

Tracer retention rate (\(R \text{ (min}^{-1})\)) was used as an index of \(^{11}\text{C}\)-HED uptake and calculated as: \(R = \text{Myocardium Activity (t}_{30-40\text{min}}) \div \int \text{Blood Activity (t}_{0-40\text{min}}\)\(^27\), \(^37\). The \(^{11}\text{C}\)-HED data was also displayed using our standard retention polar map software, FlowQuant\(^\text{©}\) [Ottawa, Canada]\(^38\).
Sample size and Statistical Analysis

When designing the study, a sample size calculation was used which considered the estimates based on the best available evidence at the time (LV oxidative metabolism (k=0.046±0.009 min\(^{-1}\)) and the WMI (6.1±1.7x10\(^6\) mmHg*ml/m\(^2\)) from data in our laboratory in patients with heart failure\(^7\)). We calculated that a sample size of 40 patients (20 patients per group) would provide 80% power to detect a delta difference of 0.009 min\(^{-1}\) in oxidative metabolism or a delta difference of 1.53x10\(^6\) mmHg*ml/m\(^2\) in the WMI for patients with CPAP using a two sample t-test with a two sided alpha level of 0.05. Enrolment of 45 patients would allow for an 11% dropout rate.

Continuous variables are presented as means and standard deviations or median with interquartile range (IQR) where appropriate. Categorical variables are presented as frequencies with percentages. For the analysis of patient baseline characteristics, Wilcoxon rank-sum tests were used for continuous variables and Fisher exact tests were used for categorical variables. The change of continuous variables measured at baseline and after 6-8 weeks of CPAP or no-CPAP was compared between the two groups using Wilcoxon rank-sum tests. To include the patients with incomplete follow-up data, a repeated measure growth curve model which treated the within-group effect of time as a continuous variable, the treatment group (CPAP vs. no-CPAP) and an interaction term (treatment-time) as a fixed effect along with random intercept and slope was used to evaluate the effect of CPAP on myocardial energetics parameters from baseline to follow-up between treatment groups assuming that missing data is missing at random (MAR). The effects of treatment group, time and the interaction of treatment group and time were evaluated by F tests. The analysis was performed using PROC MIXED (SAS version 9.2). The general linear regression model was used to test for interaction between the OSA severity
and treatment group to evaluate if the treatment effect of CPAP on the change of continuous variables was equal between different OSA severity groups. A subgroup analysis was performed for more severe OSA group (AHI>20) if a significant interaction was detected. Finally the linear regression was used to assess whether the OSA severity was correlated to the change in WMI and HED retention with CPAP in a subset of patients with automated confirmation of CPAP compliance. A p value of 0.05 was considered a statistically significant difference. The analysis was performed using SAS software (version 9.2, SAS Institute, Inc., Cary, North Carolina).

Results

The baseline demographics of the 45 study patients shown in Table 1 indicate similar characteristics of the two randomized groups (A: short-term CPAP therapy vs. B: No-CPAP) with the exception of body surface area (BSA) and history of hyperlipidemia (p<0.05).

Of the 22 patients in whom baseline data was obtained within the CPAP treatment arm, one dropped out after baseline evaluation and another after 1 week because of test scheduling conflicts. In the No-CPAP arm, 1 patient was withdrawn because they required an ICD implantation. Thus, 20 patients in the CPAP arm and 22 in the No-CPAP arm completed follow-up (Figure 1).

CPAP compliance data was available in all 20 treated patients; compliance was confirmed in 15 by automatic verification, 3 by self-reporting and 1 partly self-reported, partly automatic. One patient was non-compliant. Prior studies have considered, as acceptable compliance for clinical trial purposes, a mean CPAP use per night of >4.5 hours or between 3.6-4.3 hours per day\(^{39,40}\). Excluding the patient who was clearly non-compliant, the median (IQR) time of CPAP use/night was 4.22 (3.05,6.00) hours and the median (IQR) sleep time on
CPAP,total baseline sleep on polysomnogram was 1.17 (0.83,1.46) hours.

In the CPAP group, the median (IQR) time between baseline studies and CPAP start was 7.0 (2.0,14.0) days. The median (IQR) time between CPAP start and follow-up PET studies was 40.5 (36.5,52.0) days. The median (IQR) follow-up times, in days between baseline and the follow-up procedure dates for the non-CPAP group was 42 (35,54) days.

**Effects of CPAP on LV parameters and Myocardial Energetics**

There were no significant changes in any hemodynamic, LV or energetics parameters in the whole study population (Table 2, Figure 2A). There appeared to be a positive directional change in the WMI in the CPAP arm compared to the non-CPAP arm, but this was not statistically significant by comparing the delta change (p= 0.574) and using a repeated measures growth curve model (p=0.417).

**Pre-synaptic Sympathetic Nerve Function**

The effect of CPAP therapy on pre-synaptic 11C- retention in the whole study population is shown in Table 3. In the CPAP-arm, one patient lacked baseline 11C-HED data due to technical issues. Two patients who dropped out lacked follow-up 11C-HED data. In the non-CPAP arm, two patients did not have follow-up 11C-HED data: one who dropped out and another due to technical issues with tracer production. A significant increase in 11C-HED retention occurred with the CPAP arm compared to the non-CPAP arm (p=0.003) (Table 3, Figure 3). A significant increase in 11C-HED retention in the CPAP arm was also found in the whole study population using a repeated measure growth curve mixed model (p=0.002).

The interaction analysis between CPAP and OSA severity with the change in 11C-HED retention indicated that the beneficial effect of CPAP was independent from the OSA severity (p=0.892).
Post-Hoc Analysis of Subgroup with severe OSA

Since the OSA severity was identified as an effect modifier to the treatment effect of CPAP on the change of SBP (p=0.016) and WMI (p=0.026) from the interaction analysis, a post-hoc analysis was applied to the subset of patients who had severe OSA (AHI >20 events/hour). Of these, 9 were randomized to CPAP and 16 were in the untreated group. There were no significant differences in any baseline parameters between the two groups (Table 4). CPAP therapy was accompanied by a significant increase in WMI (p=0.037) and SBP (p=0.024) (Table 5, Figure 2B). The change of WMI and SBP remained significantly different between the two groups (p=0.010, 0.013, respectively) using a repeated measure growth curve mixed model, which included the patients with incomplete follow-up.

Correlations Between OSA Severity and Change in WMI and HED Retention with CPAP in Sub-set of Patients with Confirmation of CPAP Compliance

Sustained abolition of OSA would be anticipated in patients with automated verification of CPAP compliance19. In this group, there was a significant correlation between severity of OSA at baseline and subsequent changes in WMI (r=0.54, p=0.037, Figure 4), but not for concurrent changes in HED retention.

Discussion

In this randomized trial, we demonstrated a significant increase in ¹¹C-HED retention in those allocated to CPAP, indicating improved pre-synaptic SN function. We did not, however, demonstrate significant favorable alterations in myocardial function nor energetics in the treated group overall. Our findings suggest that short term CPAP therapy in patients with HFrEF and OSA improves myocardial sympathetic dysregulation, but not myocardial energetics.
In post-hoc analysis, when we focused on patients with more severe OSA, cardiac efficiency (estimated by the WMI) did improve with CPAP. Due to the limitations of post-hoc analysis, definitive conclusions regarding this finding cannot be made, but may direct future investigations in this area to target those with HF and more severe OSA.

**Impact of CPAP Therapy on Myocardial Energetics in Patients with HF and OSA**

Heart failure has been described as an ‘energy depleted state’\textsuperscript{11, 12}. Drug therapies with energy sparing effects are associated with improved outcomes\textsuperscript{11}, while those which improve performance at the expense of oxygen consumption often yield long-term detrimental effects\textsuperscript{41, 42}. The metabolic and energetic effect of therapies such as CPAP is less well known.

In a hypothesis–generating pilot study of 7 non-randomized patients with HFrEF and OSA, we previously demonstrated an energetics benefit of 6 weeks of CPAP therapy, specifically, reduced myocardial oxidative metabolism and improved cardiac efficiency\textsuperscript{9}. This led us to test our hypothesis in the current study, with a larger study population and a more rigorous randomized design. The primary outcome of the current study did not support this previous work. The current study was somewhat underpowered to detect significant differences given the small changes and larger standard deviations observed.

An improvement in LVEF with chronic CPAP therapy has been reported in some, but not all prior studies\textsuperscript{15, 43}. We did not observe a statistically significant improvement in LVEF with CPAP vs. no-CPAP. One explanation is that the mean EF in the current study (LVEF 35.8 \%±9.7) was not as severely depressed as it was in prior studies of patients with OSA and HF, in which LVEF averaged 25\%\textsuperscript{19, 39}. As such, the potential for improvement in LVEF in this cohort may have been less than in previous trials. Alternatively longer time periods may have been required to demonstrate a change in energetics and LV function in this cohort. Longer term
studies, such as ADVENT (NCT01128816), a sub-study of which will be evaluating energetics and sympathetic function, are ongoing and may help address this.

Patients entering this study had variable severity of OSA as defined by their AHI, with a small portion having more severe disease. As the detrimental cardiac impacts of OSA may be correlated with its severity, it is possible that the impact of therapy on the heart may vary with baseline OSA severity. In the small previous non-randomized pilot study, where CPAP was observed to improve energetics, most of the patients (5/7) had AHI >20. The subgroup data in the current study is consistent with this previous work, suggesting that CPAP therapy might have benefit by improving energetics in patients with more severe OSA and HF, but given this was a post-hoc analysis definitive conclusions cannot be made. The findings support the need for further study.

**Impact of CPAP Therapy on Myocardial SNS Activity in Patients with HF and OSA**

CPAP therapy has been previously demonstrated to decrease fibular muscle SNS activity (MSNA) and improve HR variability in patients with HF and OSA. Impaired baroreflex sensitivity, also linked to excess SNS activity, in patients with HF and OSA improves with CPAP therapy.

Previous studies involving patients with cardiomyopathy and sleep disordered breathing have identified increased myocardial sympathetic drive using semi-quantitative scintigraphic analysis of $^{123}$I-MIBG washout rates. A recent non-randomized study suggested that adaptive servo-ventilation (ASV) improved cardiac sympathetic nerve function measured using $^{123}$I-MIBG in 10 patients with central sleep apnea and HF. To our knowledge, however, the current study is the first to evaluate the effects of CPAP therapy on myocardial SN function using a randomized design, quantified using $^{11}$C-HED PET and concurrently with the evaluation...
of energetics in patients with OSA and HF. CPAP increased $^{11}$C-HED retention, consistent with improved myocardial SN function with decreased myocardial NE and/or decreased SN firing. Indeed, measurements of SN function in the myocardium may be more sensitive to early changes in HF than systemic measurements and may have greater prognostic value$^{27,46,47}$.

Benefits of CPAP in patients with OSA and HF may be due not only to a normalizing impact on systemic sympathetic activity, as demonstrated by others$^{17,18,44}$, but also to a possible SNS benefit in the myocardium as shown in the current study. The potential importance of a beneficial effect of CPAP therapy on SN function is emphasized by the findings of a recent study by Fallavollita et al which indicate that reduced $^{11}$C-HED retention is associated with increased risk of sudden death in patients with LV dysfunction$^{28}$.

Of note, the magnitude of HED retention improvement with CPAP therapy in the current study was greater than the test-retest SD reported previously, albeit in different patient populations$^{48,49}$. Our finding are consistent with improvement in sympathetic nerve function following CPAP therapy. Whether this translates into meaningful clinical outcome benefit requires further investigation and was not within the scope of the current study. To our knowledge there are no studies to-date linking changes in HED retention to clinical outcomes. However, this question may be answered in ongoing RCTs.

It is noteworthy that the interaction analysis between CPAP and OSA severity with changes in $^{11}$C-HED retention was not significant, indicating that CPAP’s beneficial effects on SN function does not depend on OSA severity. Whether this represents an independent benefit of CPAP in HF requires further study.

**Study Limitations**

The sample size may have limited the ability to detect a significant difference in energetics...
parameters in the whole study population, but was sufficient to enable detection of differences in
the $^{11}$C-HED retention in response to CPAP. Despite randomization, there were some between-
group differences in baseline characteristics. The etiology of HF was mixed ischemic and non-
ischemic. It is possible that failing hearts of differing pathogenesis may respond differently to
CPAP therapy.

We did not perform follow-up sleep studies to evaluate the efficacy of CPAP. If CPAP
did not uniformly abolish OSA, such heterogeneity may have limited our ability to detect the full
range of responses to effective CPAP therapy$^{39}$.

Likewise, we were not able to determine relationships between reductions in OSA with
changes in WMI or SN function. However, when we evaluated patients for whom we had
objective evidence (via automated measurements) of CPAP compliance, we observed that there
was a relationship between the baseline severity of OSA and the change in WMI. (This is
supported by our findings that patients with worse OSA derive energetics benefit from CPAP
therapy). For the same compliant group, there was no significant relationship with changes in
HED retention. This may suggest the benefit of CPAP on SN function may be independent of
OSA severity and relate to other mechanisms. However, without interval efficacy studies, these
results must be interpreted with caution. Definitive conclusions would require additional studies
that were not part of this project, but should be considered in the future.

The current study focused on patients with concomitant OSA and HFrEF. Whether
CPAP might impart such benefits to patients with HFrEF without OSA merits consideration in
future studies.

**Therapeutic Implications and Conclusions**

The most effective therapies in HF have two common features, namely they improve cardiac
performance without increasing oxygen consumption and second, they favorably affect
neurohormonal activation\textsuperscript{11,42}. The findings of this study indicate that overall, short term CPAP
therapy in patients with HFrEF and OSA increases \textsuperscript{11}C-HED retention, reflecting improved SN
function, but does not appear to affect myocardial energetics in this cohort. Provocative findings
from post-hoc subgroup analysis may suggest an energetics benefit for HF patients with more
significant OSA, but this needs further study. Larger, outcome-based randomized trials are also
warranted and are underway.

\textbf{Acknowledgments:} The authors express their gratitude to the patients who participated; the
National Cardiac PET Centre team including May Aung, RTNM, Kim Gardner, RTNM,
Monique Pacquette, RN and Patricia Grant, RN; Xing Liu in the Echocardiography laboratory
and Lyne Babineau in the Sleep Laboratory; and for the statistical advice and assistance of Dr.
G.A. Wells.

\textbf{Funding Sources:} This project was supported in part by Heart and Stroke Foundation of Ontario
Grant-in-Aid (HSFO\# T 6426 and NA 7158) and in part by the IMAGE-Heart Failure Team
Grant (Canadian Institute of Health Research team grant \# CIF 99470). R.B. is a career
investigator supported by the Heart and Stroke Foundation of Ontario and Tier 1 Chair in
Cardiovascular Research supported by the University of Ottawa. JF is a Tier 1 Canada Research
Chair in Integrative Cardiovascular Biology. MCZ and KY were supported in part by HSFO
(Program Grant \#PRG6242) and the University of Ottawa International Fellowship Award.

\textbf{Conflict of Interest Disclosures:} RB is a consultant for Lantheus Medical Imaging and
JubilantDRA\textsuperscript{X}Image (JDI). RB and RdK have received grant funding from a
government/industry research program (partners: GE Healthcare, Nordion, Lantheus Medical
Imaging, and JDI). RdK is a consultant for, and receives research funding from JDI, and royalty
revenues from rubidium generator technology and FlowQuant software licenses. Related
products were not used in this study.
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Table 1. Patient Baseline Characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=22)</th>
<th>No CPAP (N=23)</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD, N (%)</td>
<td>Mean ± SD, N (%)</td>
</tr>
<tr>
<td>Age</td>
<td>57.8 ± 11.2</td>
<td>64.9 ± 13.4</td>
</tr>
<tr>
<td>Male</td>
<td>17 (77%)</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (82%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19 (86%)*</td>
<td>13 (57%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>16 (73%)</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (45%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>13 (59%)</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>4 (18%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Ischemic Etiology HF</td>
<td>14 (64%)</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.3 ± 0.2*</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>AHI (#/hr)</td>
<td>27.0 ± 18.6</td>
<td>27.4 ± 15.4</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>10.7 ± 6.2</td>
<td>9.6 ± 4.7</td>
</tr>
<tr>
<td>Drugs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>21 (95%)</td>
<td>19 (83%)</td>
</tr>
<tr>
<td>- Beta blocker</td>
<td>19 (86%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td>- Diuretic</td>
<td>15 (68%)</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67.3 ± 11.4</td>
<td>63.5 ± 8.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.9 ± 16.3</td>
<td>119.9 ± 22.1</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>70.1 ±17.4</td>
<td>69.2 ± 18.9</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>30.7 ± 7.0</td>
<td>33.6 ± 8.6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35.1 ± 9.9</td>
<td>36.5 ± 9.7</td>
</tr>
<tr>
<td>Kmono (min⁻¹)</td>
<td>0.044 ± 0.011</td>
<td>0.048 ± 0.012</td>
</tr>
<tr>
<td>WMI (mmHg mL/m² x 10⁻⁵)</td>
<td>55.6 ± 19.2</td>
<td>55.8 ± 20.8</td>
</tr>
<tr>
<td>HED retention (min⁻¹)**</td>
<td>0.114 ± 0.040</td>
<td>0.126 ± 0.040</td>
</tr>
</tbody>
</table>

*p<0.05 vs. no-CPAP; **one patient was missing baseline HED retention in CPAP.
Table 2. Impact of Short-term CPAP Therapy on Myocardial Energetics Parameters Measured via \(^{11}\)C-acetate PET and Echocardiography.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPAP mean±sd</th>
<th>No CPAP mean±sd</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=22</td>
<td>N=23</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>67.3 ± 11.4</td>
<td>63.5 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>64.1 ± 9.1</td>
<td>60.5 ± 6.3</td>
<td>0.907</td>
</tr>
<tr>
<td>Delta*</td>
<td>-1.88 (-6.25,2.96)</td>
<td>-2.38 (-6.25,1.50)</td>
<td>0.735</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>115.9 ± 16.3</td>
<td>119.9 ± 22.1</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>116.5 ± 18.7</td>
<td>113.9 ± 22.1</td>
<td>0.141</td>
</tr>
<tr>
<td>Delta*</td>
<td>-0.88 (-10.88,12.38)</td>
<td>-2.50 (-10.50,1.50)</td>
<td>0.308</td>
</tr>
<tr>
<td>SV (mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70.1 ±17.4</td>
<td>69.2 ± 18.9</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>78.9 ± 20.0</td>
<td>75.2 ± 19.2</td>
<td>0.835</td>
</tr>
<tr>
<td>Delta*</td>
<td>8.20 (-4.82,16.28)</td>
<td>1.03 (-5.32,18.65)</td>
<td>0.755</td>
</tr>
<tr>
<td>SVI (mL/m(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30.7 ± 7.0</td>
<td>33.6 ± 8.6</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>34.1 ± 8.2</td>
<td>36.8 ± 9.3</td>
<td>0.868</td>
</tr>
<tr>
<td>Delta*</td>
<td>3.81 (-3.11,6.80)</td>
<td>0.83 (-2.29,8.11)</td>
<td>0.970</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>35.1 ± 9.9</td>
<td>36.5 ± 9.7</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>40.4 ± 10.9</td>
<td>40.3 ± 12.0</td>
<td>0.566</td>
</tr>
<tr>
<td>Delta*</td>
<td>5.5 (0.5,8.5)</td>
<td>3.0 (-4.0,8.0)</td>
<td>0.356</td>
</tr>
<tr>
<td>K(_{mono}) (min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.044 ± 0.011</td>
<td>0.048 ± 0.012</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.044 ± 0.010</td>
<td>0.04 ± 0.011</td>
<td>0.805</td>
</tr>
<tr>
<td>Delta*</td>
<td>-0.001 (-0.006,0.007)</td>
<td>-0.001 (-0.005,0.004)</td>
<td>0.871</td>
</tr>
<tr>
<td>WMI (mmHg mL/m(^2) x 10(^3))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55.6 ± 19.2</td>
<td>55.8 ± 20.8</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>60.1 ± 19.4</td>
<td>54.5 ± 15.6</td>
<td>0.417</td>
</tr>
<tr>
<td>Delta*</td>
<td>3.33 (-6.25,13.32)</td>
<td>0.005 (-6.46,10.36)</td>
<td>0.574</td>
</tr>
</tbody>
</table>

*reported as median (IQR) based on N=20 in CPAP and N=22 in nonCPAP; ** for each parameter in table 2,3,5 the first p value was generated using a repeated measures growth curve mixed model by comparing the effect of CPAP from baseline to follow-up between two groups; the second p value was generated using Wilcoxon rank-sum test by comparing the delta between two groups.

Table 3. Impact of Short-term CPAP Therapy on Myocardial \(^{11}\)C HED Retention as a Measure of Pre-Synaptic SN Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPAP mean±sd</th>
<th>No CPAP mean±sd</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=21*</td>
<td>N=23</td>
<td></td>
</tr>
<tr>
<td>HED retention (min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.114 ±0.040</td>
<td>0.126 ±0.040</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.127 ±0.039</td>
<td>0.121 ±0.041</td>
<td>0.002</td>
</tr>
<tr>
<td>Delta**</td>
<td>0.012 (0.002,0.021)</td>
<td>-0.006 (-0.013,0.005)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*One patient was missing baseline HED retention in CPAP; **reported as median (IQR) based on N=19 in CPAP and N=21 in nonCPAP.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=9) Mean ± SD, N (%)</th>
<th>No CPAP (N=16) Mean ± SD, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.7 ± 10.5, 9 (100%)</td>
<td>63.5 ± 14.4, 12 (75%)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (89%), 1 (1%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (67%), 5 (56%)</td>
<td>10 (63%), 8 (89%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (89%), 8 (89%)</td>
<td>9 (56%), 14 (88%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>6 (67%), 5 (56%)</td>
<td>10 (63%), 7 (44%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (56%), 5 (56%)</td>
<td>7 (44%), 6 (67%)</td>
</tr>
<tr>
<td>Family history</td>
<td>5 (56%), 7 (75%)</td>
<td>4 (25%), 7 (50%)</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>2 (22%), 4 (44%)</td>
<td>2 (12%), 11 (69%)</td>
</tr>
<tr>
<td>Ischemic Etiology HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td>2.3 ± 0.3, 6 (67%)</td>
<td>2.1 ± 0.2, 10 (63%)</td>
</tr>
<tr>
<td>AHI (#/hr)</td>
<td>42.8 ± 20.4, 5.46 (-1.50,16.13)</td>
<td>33.4 ± 14.8, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>9.6 ± 7.0, 9 (100%)</td>
<td>10.2 ± 4.3, 8 (89%)</td>
</tr>
<tr>
<td>Drugs: - ACEi/ARB</td>
<td>8 (89%), 1 (1%)</td>
<td>14 (88%), 15 (94%)</td>
</tr>
<tr>
<td>- Beta blocker</td>
<td>9 (100%), 9 (100%)</td>
<td>15 (94%), 12 (100%)</td>
</tr>
<tr>
<td>- Diuretic</td>
<td>8 (89%), 8 (89%)</td>
<td>12 (75%), 9 (100%)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65.8 ± 10.8, 5.46 (-1.50,16.13)</td>
<td>63.9 ± 8.3, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>117.5 ± 13.4, 5.46 (-1.50,16.13)</td>
<td>117.2 ± 21.4, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>Stroke Volume (mL)</td>
<td>64.0 ± 17.6, 5.46 (-1.50,16.13)</td>
<td>68.6 ± 18.9, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31.0 ± 8.1, 5.46 (-1.50,16.13)</td>
<td>33.2 ± 9.4, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>SVI (mL/m²)</td>
<td>28.0 ± 6.3, 5.46 (-1.50,16.13)</td>
<td>32.6 ± 8.3, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>kmono (min⁻¹)</td>
<td>0.045 ± 0.011, 5.46 (-1.50,16.13)</td>
<td>0.046 ± 0.010, -4.00 (-13.75,0.50)</td>
</tr>
<tr>
<td>WMI (mmHg mL/m² x 10⁵)</td>
<td>49.3 ± 13.3, 5.46 (-1.50,16.13)</td>
<td>55.3 ± 19.1, -4.00 (-13.75,0.50)</td>
</tr>
</tbody>
</table>

Table 5. Impact of Short-term CPAP Therapy on Myocardial Energetics Parameters Measured via \(^{11}\)C-acetate PET in Subset of Patients with More Severe OSA (AHI>20).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPAP mean±sd N=9</th>
<th>No CPAP mean±sd N=16</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>Baseline 117.5 ± 13.4</td>
<td>117.2 ± 21.4</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Follow-up 124.3 ± 21.7</td>
<td>107.6 ± 16.9</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Delta* 5.46 (-1.50,16.13)</td>
<td>-4.00 (-13.75,0.50)</td>
<td>0.024</td>
</tr>
<tr>
<td>WMI (mmHg mL/m² x 10⁵)</td>
<td>Baseline 49.3 ± 13.3</td>
<td>55.3 ± 19.1</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Follow-up 65.3 ± 19.6</td>
<td>51.6 ± 11.9</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Delta* 14.91 (6.37,22.10)</td>
<td>-1.57 (-8.24,10.36)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*reported as median (IQR) based on N=8 in CPAP and N=15 in nonCPAP)
Figure Legends:

**Figure 1.** Protocol and Patient Flow.

**Figure 2.** Kmono (upper) and WMI (lower) for CPAP (left) and No-CPAP (right) groups. Figure 2A shows the Box Whisker plot of non-significant changes in $K_{\text{mono}}$ and WMI with short-term CPAP therapy in patients with HF and OSA; Figure 2B shows the non-significant changes in $K_{\text{mono}}$ and significant increase in WMI with short-term CPAP therapy in patients with HF and more severe OSA, AHI >20; *p <0.05.

**Figure 3.** A) Example of increased $^{11}$C-HED retention in a study patient with short-term CPAP therapy at baseline and follow-up. Mean global HED retention values: Baseline=0.0631; Follow-up=0.0893; Delta=0.0262 min$^{-1}$. A=anterior, P=posterior, L=lateral, S=septal territories of the LV. B) Change in HED retention: baseline to 6-8 weeks for CPAP therapy and the No CPAP group. *p=0.003 versus No CPAP group.

**Figure 4.** Graph showing a significant correlation between the change in WMI (y-axis) with OSA severity (represented by AHI, x-axis) in 15 patients with automated confirmation of compliance with CPAP therapy. r=0.54, p=0.037.
548 Assessed for Eligibility

503 Excluded
254 Not meeting inclusion criteria
71 No OSA
49 EF criteria
134 Other exclusion criteria
140 Declined
109 Other reasons
65 Enrolled in other study
38 MD preference
6 Travel Distance

45 Randomized (HF with OSA)

22 Allocated to CPAP
15 compliance (confirmed automatic verification)
1 compliance (partly automatic, partly self-report)
3 compliance by self-report
1 compliance failed
2 dropped out after 1 week or less

23 Allocated to No-CPAP

20 Completed Follow-up
2 withdrew (personal preference)

22 Completed Follow-up
1 withdrew (ICD implant)

22 Intention-To-Treat Analysed

23 Intention-To-Treat Analysed

Figure 1
Figure 2B
Figure 3B
Figure 4
Effects of Short-Term Continuous Positive Airway Pressure on Myocardial Sympathetic Nerve Function and Energetics in Patients with Heart Failure and Obstructive Sleep Apnea: A Randomized Study

Circulation. published online July 3, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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