



## Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

V.L. is a 63 yo morbidly obese woman (BMI 44.9) with NICM, CHF (EF 20-25%) s/p BiV/AICD, HTN, HL, pHTN, and COPD/asthma on home O<sub>2</sub> presents with multiple falls in recent months of unknown etiology at home, with no associated LOC, lightheadedness, vision changes, paresthesias, CP, palpitations, N/V, or diarrhea. She presented to the ED with hypertensive urgency and marked dyspnea, and found to have BNP >4000 and pulmonary vascular congestion on CXR, suggesting acute on chronic CHF exacerbation. She was started on aggressive diuresis with improvement in symptoms. One morning, she was found to be somnolent, breathing noisily, transiently arousable with shaking, A&O x 1.5. ABG revealed mild CO<sub>2</sub> retention. Out of concern for OSA, she was started on CPAP. Inpatient sleep study was then obtained, showing severe Cheyne-Stokes respiration (CSR), with a small element of OSA during REM, though this may have been underestimated as the study was limited by position. CPAP was trialed and found to be ineffective, while adaptive servo-ventilation was very effective at ameliorating CSR and improved her quality of sleep.

Clinical Question: What is the benefit of using adaptive servo-ventilation (ASV) over CPAP in a patient with heart failure and likely mixed central and obstructive sleep apnea?

### Search Strategy

**Database:** Pubmed

**Search terms:** “adaptive servo-ventilation”, “auto servo-ventilation”, “central sleep apnea”, “obstructive sleep apnea” → 4 primary results and 2 additional results (in section “Titles with your search terms”)

**Limits:** Clinical Trial, English Language

### Journal Article

Randerath, W. J., G. Nothofer, et al. (2012). "Long-term auto servo-ventilation or constant positive pressure in heart failure and co-existing central with obstructive sleep apnea." *Chest*.

### **Background:**

- Sleep-disordered breathing is prevalent in patients with HF (CSA/CSR 30-50%, OSA 20-40%).
- Associated increase in mortality related to heightened sympathetic activity, exaggerated negative intrathoracic pressure during apnea, asphyxia, and vascular wall injury.
- CSA/CSR is a form of periodic breathing, a manifestation of respiratory instability that might arise from prolonged circulatory time in HF leading to delayed ventilatory response, hypersensitivity of ventilatory chemoreceptors, and low PaCO<sub>2</sub> related to pulmonary congestion.
- CPAP known to suppress sympathetic overactivity and improve LVEF, but CanPAP trial evaluating long-term efficacy in patients with CSA showed no improvement in transplant-free survival<sup>1</sup>
- Post-hoc analysis suggested that CPAP might improve survival if CSA is sufficiently controlled (AHI < 15/h)<sup>2</sup>
- Apnea-hypopnea index (AHI): 5–15/hr = mild; 15–30/hr = moderate; and > 30/h = severe
- Adaptive servo-ventilation: Fixed or flow-triggered EPAP with flow-triggered IPAP
  - Most studies are industry sponsored and different algorithms used by different manufacturers, so generalizability is a problem.
  - Some evidence exists showing improvement in AHI, LVEF, QOL, and improved compliance compared to CPAP<sup>3,4</sup>, but studies have small sample sizes and no long-term or survival data.



**Senior Medicine Rotation: Evidence-Based Medicine Project (Cont)**

<b>Group</b>	<b>Criteria or definition</b>	<b>n</b>
Population screened.	Consecutive patients with HF and co-existing OSA and CSA recruited at University of Witten/Herdecke (single center)	?
Inclusion criteria	1) Age $\geq$ 18 2) HF (EF $\geq$ 20%, NYHA II-III) under optimal medical treatment 3) Co-existing OSA and CSA (AHI $\geq$ 15/h, central $\leq$ 80%, obstructive 20-25%) confirmed by full-night, inpatient polysomnography	70
Exclusion criteria	1) MI, unstable angina, or cardiac surgery within 3 months 2) Pregnancy	70
Conventional Therapy	Continuous positive airway pressure (CPAP), optimally titrated once at start of study and continued for 12 months	36
Alternative Therapy	Auto servo-ventilation (ASV), optimally titrated once at start of study and continued for 12 months	34

**Primary endpoints:**

- 1) Change in central AHI on treatment at 12 months.

**Secondary endpoints:**

- 1) Changes in other polysomnographic parameters, BNP level, echocardiographic parameters and compliance with treatment at 3 months and 12 months compared to baseline performed at start of study.
- 2) Quality of life measurements using Minnesota Living with Heart Failure self-administered questionnaire (MLHFQ) at 6 and 9 months of treatment compared to baseline.

- Are the Results of the Trial Valid?
  - **Randomized?** Yes. After a full-night, inpatient polysomnography, patients meeting inclusion criteria were randomized to receive CPAP or ASV for 1 year. Sample size calculated as 35 patients per treatment group, so 70 consecutive patients were recruited. However, one patient did not receive allocated intervention (withdrew consent before initiation and changed from ASV to CPAP arm).
  - **All patients accounted for at end?** No. One patient in each treatment group was lost to follow-up; 8 patients in each group discontinued intervention early in the study.
  - **Intention to treat?** Yes. Per-protocol data set was also analyzed (51 patients).
  - **Blinding?** Possibly. Patients and data analysts were blinded to therapy allocation; however, it is not clear how patients and investigators were blinded to the actual therapy (did the machines and settings look different?).
  - **Groups similar at start of trial?** Yes, there was no significant difference between the CPAP vs. ASV groups in age, sex, BMI, polysomnographic parameters (total AHI, central AHI, etc.), or cardiac parameters (BNP, LVEF, etc.).
  - **Equal treatment of groups?** Yes. After allocation of intervention, both groups stayed 3 consecutive nights in the sleep laboratory, 2 for titration to optimal settings (CPAP to 8-13; ASV to EPAP  $\geq$  7, IPAP  $\geq$  7 to  $\geq$  15) for suppression of events, and 1 additional night for observation under optimal settings. At 3-month and 12-month f/u, inpatient polysomnography was performed. At 6-month and 9-month f/u, patients received a telephone call and self-administered questionnaires.
  - **Did randomization work?** Yes.

- Are the Results of the Trial important?
  - **Size of treatment effect of primary endpoint?** Central AHI was reduced significantly by ASV (~75%) compared to CPAP (~50%) at 3 months and 12 months; obstructive AHI was decreased in both groups; and total AHI was also more significantly reduced at 3 months in ASV group (intention-to-treat analysis).
  - **Precision of the estimate of the effect?** Small sample size, large standard deviations.
  - **Secondary endpoints?** BNP level significantly improved in ASV group in per-protocol analysis. However, echocardiographic parameters (per-protocol analysis), compliance (>4h/d), MLHFQ score, and self-assessed symptoms (reduced dyspnea and fatigue) did not differ between the two groups.

	Baseline		3 Months		12 Months	
	CPAP	ASV	CPAP	ASV	CPAP	ASV
Age (y)	67.4 ±8.1	65.3 ±10.0				
Sex (m/f)	32/2	31/5				
BMI (kg/m <sup>2</sup> )	30.3 ±4.8	32.2 ±6.8				
AHI total (/h)	40.8 ± 17.1	46.8 ± 23.6	16.5 ± 17.3 <sup>***</sup>	10.8 ± 11.3 <sup>###</sup>	17.0 ± 17.9 <sup>***</sup>	11.1 ± 11.6 <sup>***</sup>
AHI central (/h)	21.8 ± 11.7	23.1 ± 13.2	10.9 ± 7.8 <sup>***</sup>	6.9 ± 8.3 <sup>###</sup>	10.7 ± 8.7 <sup>***</sup>	6.1 ± 7.8 <sup>###</sup>
AHI periodic (/h) <sup>1</sup>	12.3 ± 13.9	13.9 ± 14.7	3.8 ± 5.4 <sup>***</sup>	0.3 ± 0.9 <sup>#####</sup>	3.5 ± 5.6 <sup>**</sup>	0.5 ± 1.1 <sup>#####</sup>
AHI obstructive (/h)	11.7 ± 7.0	15.8 ± 9.8	3.7 ± 7.0 <sup>***</sup>	3.4 ± 5.9 <sup>***</sup>	4.1 ± 7.0 <sup>***</sup>	4.6 ± 6.9 <sup>***</sup>
AHI mixed (/h)	7.2 ± 10.7	7.9 ± 11.6	1.9 ± 7.3 <sup>***</sup>	0.4 ± 1.0 <sup>***</sup>	2.1 ± 7.3 <sup>***</sup>	0.5 ± 1.4 <sup>#####</sup>
NT-proBNP (ng/l)	686.7 ± 978.7	537.3 ± 891.8	644.2 ± 1015.3	426.0 ± 712.5 <sup>#</sup>	847.3 ± 1848.1	230.4 ± 297.4 <sup>#</sup>
LVEF (%)	43.2 ± 16.4	47.4 ± 15.9	48.5 ± 14.0	42.6 ± 13.8	48.1 ± 11.9	45.5 ± 16.0

- Can I apply these results to my patient?
  - **Comparison of my patient to trial patients.** My patient meets all inclusion criteria and does not violate any exclusion criteria. My patient is female (vs. 63/70 patients male), age 63 (vs. mean age 66.3), BMI 44.9 (vs. mean BMI 31.3), and shows primarily CSA/CSR (vs. mean CSA/CSR 54.7%), but her OSA component is likely underestimated. However, she has more severe HF than average patients in this study; less severe HF is one possible reason suggested for why no difference in LVEF and QOL was seen. Respironics ASV used in this trial as well as with my patient.
  - **All clinically important outcomes considered.** Did not measure cardiovascular events or survival, maybe due to small sample size.
  - **Likely benefits outweigh potential harms and cost?** Yes, there was significant improvement in CSA/CSR suppression with ASV over CPAP and improvement in total AHI. No harm related to use of ASV vs. CPAP was discussed (one patient in ASV group had sudden cardiac death). Cost of ASV is many-fold greater than that of CPAP and is not widely available at institutions.

#### References:

- <sup>1</sup>Bradley, T. D., A. G. Logan, et al. (2005). "Continuous positive airway pressure for central sleep apnea and heart failure." *N Engl J Med* 353(19): 2025-2033.
- <sup>2</sup>Arzt, M., J. S. Floras, et al. (2007). "Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP)." *Circulation* 115(25): 3173-3180.
- <sup>3</sup>Philippe, C., M. Stoica-Herman, et al. (2006). "Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period." *Heart* 92(3): 337-342.
- <sup>4</sup>Kasai, T., Y. Usui, et al. (2010). "Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration." *Circ Heart Fail* 3(1): 140-148.