CHEST Online Supplement

Apneas of Heart Failure and Phenotype-Guided Treatments

Part One: OSA

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e-Appendix 1.

Overview of the prevalence, clinical presentation and cardiovascular consequences of OSA

• Prevalence:

An early, although exceedingly detailed, systematic prospective study in HFrEF involved 100 of 114 ambulatory male patients with stable, treated HF[1]. Using an apnea–hypopnea index (AHI) of ≥15 events/ h of sleep as the threshold, 49% of the 100 patients had moderate to severe SDB. In this study only10% of the patients were taking β-blockers, yet the prevalence of SDB remains similar to many more recent studies published after β-blockers became part of the standard armamentarium of HF management [2,10]. Recent studies from the U.S. report a higher prevalence of OSA than CSA[3], although data from investigators in Germany continue to report that CSA remains the predominant disorder.[4]

• Clinical Presentation:

Sleepiness: Patients with HF and OSA generally do not complain of daytime sleepiness. When patients with OSA/HFrEF are asked about daytime sleepiness using a questionnaire similar to that used by Young and colleagues[5], about one third of the patients reported subjective sleepiness [8]. Surprisingly there were no significant difference in comparisons among patients with severe OSA, severe CSA, and those without significant SDB [1]. Multiple later studies using Epworth Sleepiness Scale (ESS) have reported similar findings [6].

Discordance between subjective vs. objective daytime sleepiness: There is dissociation between subjective and objective daytime sleepiness, such that when HF patients undergo multiple sleep latency testing (MSLT), electroencephalographic sleepiness in terms of mean sleep latency (MSL) is well documented. The disconnect between subjective vs. objective daytime sleepiness had been previously shown in HFrEF patients with CSA (See part 2), and this appears to be the case in HFrEF patients with OSA[7]. In a study of 26 HFrEF patients (mean LVEF = 34%) and a wide spectrum of OSA severity (AHI = 34 ± 27, mean ± SD), we obtained a number of biomarkers along with sleep studies. There was no significant association of MSL and ESS (−0.36, −0.81 to 0.09, P = .11). Notably, 22 of 26 patients (85%) had an MSL < 10 minutes, consistent with objective daytime sleepiness. Further, seven patients (28%) had an MSL < 5 minutes indicative of pathological daytime sleepiness, similar to the MSL in patients with

narcolepsy. In contrast, mean ESS was 8 and only 4 patients (15%) scored above 10, a score generally recognized as indicative of subjective sleepiness. The most significant finding was a correlation of MSL with interleukin-6 which persisted in adjusted models[7]. Also, as noted above, 7 subjects had an MSL less than 5 minutes, and 6 of them had the highest plasma levels of TNFα. In contrast, there was no significant associations between MSL vs, plasma adrenaline or noradrenaline. We concluded that pathways associated with inflammation, but not increased sympathetic tone, could explain a mechanism leading to objective sleepiness. These data are inconsistent with the suggestion that in HF, sympathetic overactivity is the driver for the lack of subjective sleepiness [6]. Paradoxically, therefore, patients with HFrEF, with either OSA or CSA are objectively sleepy, but do not endorse symptoms of sleepiness.

Role of the overlap in symptoms of chronic heart failure and SDB: This overlap may account for inability of OSA patients to endorse hypersomnia. We have been of the opinion that the lack of subjective daytime sleepiness is related to chronic shared nocturnal symptoms between the two disorders which could include paroxysmal nocturnal dyspnea (reflecting hyperventilation following apnea or hypopnea), cough, nocturia, awakenings and insomnia, restless sleep, and leg movements (which occur in patients with heart failure with or without SDB), unrefreshing sleep, and finally, daytime fatigue, lethargy and, in some, overt sleepiness.

Lack of hypersomnolence and under-diagnosis of SDB: The limited association of OSA with sleepiness in this population likely contributes to the under-diagnosis of sleep apnea in HF, as well as poor adherence to therapy. In a large cohort of Medicare beneficiaries, only 2% of the 30,000 newly diagnosed HF patients were referred for objective testing for SDB [8]. The co-morbidity of OSA should always be considered in patients with HF, and when such signs or symptoms as obesity, snoring, awakening with respiratory symptoms (to be distinguished from paroxysmal nocturnal dyspnea), or morning headache are present, the denial of sleepiness should not be a deciding factor in pursuing SDB evaluation.

• Cardiovascular consequences of OSA in HF:

OSA has a bidirectional relation with HF: The acute overnight adverse (Figure 1) and long-term pathobiological consequences of OSA are well known[9]. On one hand, the prospective Sleep Heart Health study, has shown that obstructive sleep apnea is associated with incident coronary heart disease and

heart failure [16] with OSA being integral to the metabolic syndrome, can cause hypertension and worsen glucose intolerance and dyslipidemia, all factors that accelerate the progression of cardiovascular disease into HF[10,11]. On the other hand, HF is associated with venous congestion and hypoxemia that can destabilize control of breathing particularly in the presence of obesity. If lower extremity edema is present, OSA may worsen during the course of the night[17,18] due to a caudal fluid shift from the edematous lower extremities during the recumbent positions of sleep. This may lead to fluid accumulation in and around the upper airway and decrease upper airway luminal dimensions, increasing the severity of OSA. Further, in the face of periodic breathing, pharyngeal collapse occurs at the nadir of ventilation.

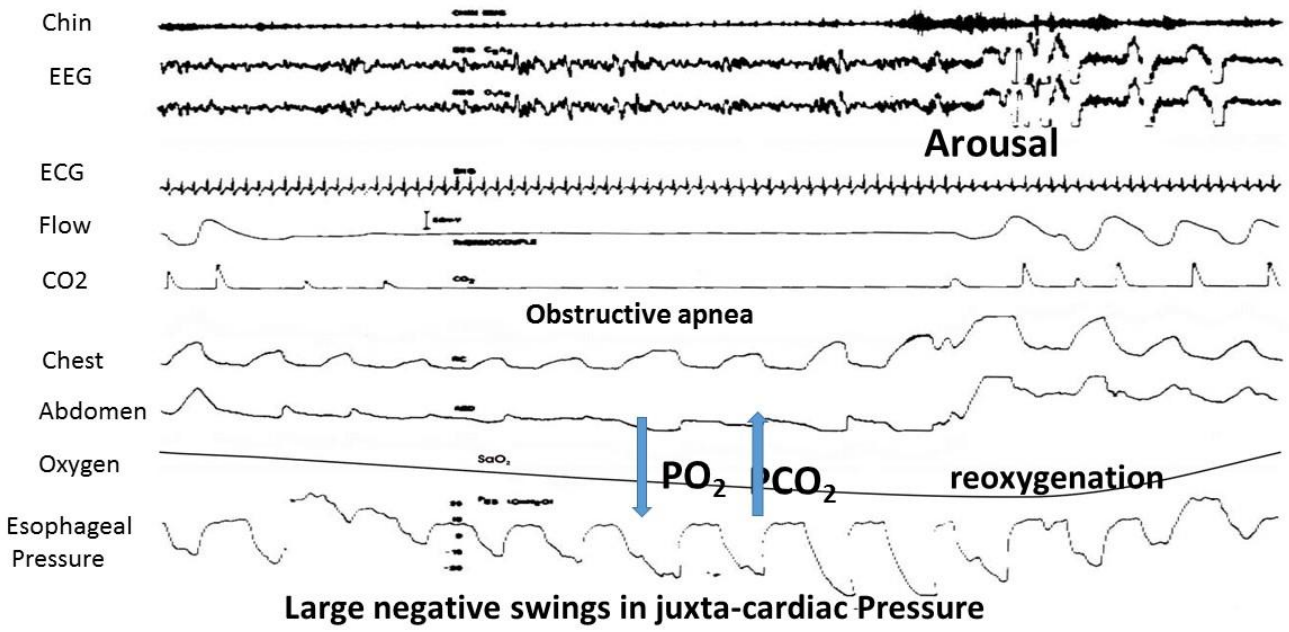
Readmissions and mortality: Large cohort studies from the U.S. have shown that OSA is independently associated with excess re-hospitalization and premature mortality. In a large prospective study[12,13] of patients hospitalized with HF, newly diagnosed OSA was an independent predictor of post discharge readmissions and mortality. The study found decreased mortality in patients who elected PAP therapy. In the large Medicare observational study of 30,000 HF subjects[8], SDB was independently associated with excess hospitalization, excess cost and excess mortality. In contrast, those HF patients who were treated with CPAP had improved survival (Fig 3).

The excess mortality of HF patients with OSA has been confirmed by observational studies from Canada, Japan and Brazil, albeit involving smaller numbers of patients. In a recent prospective study from Brazil [22], Uchoa and colleagues followed 104 patients with acute cardiogenic pulmonary edema (ACPE) for a mean of one year. Most of the study cohort demonstrated HFpEF rather than overt systolic HF. Sixty-four patients (61%) had OSA with an average AHI of 33/h vs 9/h in the remaining patients. In a Cox proportional hazards regression analysis, OSA was independently associated with ACPE recurrence, incidence of myocardial infarction, cardiovascular and total death.

In a Canadian study, Wang and colleagues[14] followed HF patients with a wide spectrum of OSA severity and were able to demonstrate that those with moderate or severe OSA had significantly higher mortality than those with mild or no OSA. Similarly, a Japanese study[23] showed that HF patients with severe OSA were prone to excess premature mortality and that treatment with CPAP, when adherence and control of SDB were satisfactory, improved survival.

References

1. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol.* 2006;106(1):21-28.
2. MacDonald M, Fang J, Pittman SD, White DP, Malhotra A. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. *J Clin Sleep Med.* 2008;4(1):38-42.
3. Khayat RN, Jarjoura D, Patt B, Yamokoski T, Abraham WT. In-hospital testing for sleep-disordered breathing in hospitalized patients with decompensated heart failure: report of prevalence and patient characteristics. *J Card Fail.* 2009;15(9):739-746.
4. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail.* 2007;9(3):251-257.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328(17):1230-1235.
6. Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med.* 2006;166(16):1716-1722.
7. Mehra R, Wang L, Andrews N, et al. Dissociation of Objective and Subjective Daytime Sleepiness and Biomarkers of Systemic Inflammation in Sleep-Disordered Breathing and Systolic Heart Failure. *J Clin Sleep Med.* 2017;13(12):1411-1422.
8. Javaheri S, Caref EB, Chen E, Tong KB, Abraham WT. Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure. *Am J Respir Crit Care Med.* 2011;183(4):539-546.
9. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *J Am Coll Cardiol.* 2017;69(7):841-858.
10. Brooks B, Cistulli PA, Borkman M, et al. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *J Clin Endocrinol Metab.* 1994;79(6):1681-1685.
11. Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. *Am J Respir Crit Care Med.* 2011;184(3):355-361.
12. Khayat R, Jarjoura D, Porter K, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J.* 2015;36(23):1463-1469.
13. Khayat R, Abraham W, Patt B, et al. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. *J Card Fail.* 2012;18(7):534-540.
14. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. *J Am Coll Cardiol.* 2007;49(15):1625-1631.



e-Figure 1. Immediate Consequences of OSA. Please note that during obstructive apnea, airflow is absent while breathing effort continues. Breathing resumes with the onset of arousal. Chin: Chin electromyogram; EEG: electroencephalogram; ECG: electrocardiogram; Flow: oral thermocouple signal; CO2: end tidal CO2: Chest: rib cage effort; Abdomen: abdominal teffort; oxygen: saturation. Reprinted with permission from Javaheri (9). OSA = obstructive sleep apnea. From reference 9. With permission from JACC.