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Central Sleep Apnea with Heart Failure: Two Bad Bedfellows

Shahrokh Javaheri[1], Winfried J. Randerath, M.D.[2], and Lee K. Brown, M.D.[3]

[1]Division of Pulmonary and Sleep Medicine, Bethesda North Hospital, Cincinnati, Ohio; [2]Bethanien Hospital Clinic of Pneumology and Allergology, Center for Sleep Medicine and Respiratory Care, Institute of Pneumologie at the University of Cologne, Solingen, Germany; and [3]Division of Pulmonary, Critical Care, and Sleep Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico

ORCID IDs: 0000-0002-5010-8461 (W.J.R.); 0000-0002-4009-457X (L.K.B.).

In this issue of *AnnalsATS*, Agrawal and colleagues (pp. 450–455) present a comprehensive exploration of a "big data" source, an increasingly popular approach to inform medical decision making given the ubiquity of large datasets (1). Using a Veterans Affairs (VA) database, the authors extracted data for patients initially diagnosed with either central sleep apnea (CSA) or obstructive sleep apnea (OSA) during a 1-year period beginning in 1999 and followed their status through December 1, 2021. During this period, 25% of patients with CSA had died, whereas the mortality for patients with OSA was significantly lower at 15%. Moreover, when patients with CSA were evaluated for factors that predicted reduced survival, the presence of heart failure (HF), cerebrovascular disease, hemiplegia (probably also representing cerebrovascular disease), and low body mass index (BMI) ($<$18.5 kg/m^2) emerged as being highly relevant.

The result of the current report showing increased mortality of veterans with HF and comorbid CSA is consistent with another systematic and most detailed VA study (though small; $n = 88$) (2), as well as several other non-VA studies (3–5), all showing an association of CSA with mortality in HF.

As a subject that is still controversial, we were particularly interested in the findings of the current study (1) exhibiting significantly higher mortality in patients with HF with CSA than with OSA, a finding consistent with previous large studies by Khayat and colleagues (4) and Oldenburg and colleagues (3). The latter study, incorporating a larger number of subjects, (3), revealed a 5-year survival for those with CSA (as estimated from the Kaplan-Meier curve) of approximately 50%, compared with those with OSA of about 70%. In the current study, estimating from the graphically depicted Kaplan-Meier curves, the 5-year survival rate for subjects with CSA and HF was approximately 67% (compared with 92% for subjects with CSA without HF).

How then do the results of the current VA study compare with the mortality figures of the published randomized controlled trials (RCTs) involving patients with HF and CSA from which 5-year survival rates can also be extracted? In the first RCT, the CANPAP (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure) trial (6), the control group enrolled 130 patients diagnosed with CSA and HF with reduced ejection fraction (HFrEF) and reported an approximately 50% 5-year survival rate. However, that study took place during a period of major changes in guideline-directed therapy for HF, and the trial was terminated before reaching the enrollment numbers required by the power analysis. Data are available from the control group of the SERVE-HF (Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure) trial (7). The cumulative 5-year survival (Kaplan-Meier analysis was not performed because of competing risks; rather, the graphic depicts cumulative incidence curves determined by Aalen-Johansen estimates) was approximately 60% in the 578 members of the control group. This cohort received contemporary guideline-based medical therapy.

We congratulate the authors on the monumental effort involved in using the

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huge VA database to clarify the effect of CSA (and OSA) on mortality. What is striking is the similarity between the 5-year survival figures derived from the current study (1) and the two RCTs (6, 7). Nevertheless, the results (1) must be interpreted with due regard for the advantages and disadvantages inherent in the analysis of big data. Such analyses involve statistical methods that are not as easily understood as those used in other forms of investigation. Proponents of big data point out that electronic medical records (EMRs) or administrative databases can incorporate a far larger number of variables, almost all of which are entered during the normal course of medical care and administration. Moreover, it is assumed that erroneous data are of limited impact because of the huge number of individual records being analyzed (8). We note, however, that the gold-standard approach remains that of the prospective RCT. RCTs are designed to overcome potential biases in observational studies, ensuring that groups who are treated are otherwise comparable to control groups. When properly planned and performed, one can trust that the results could be generalizable, statistically robust, and clinically valid.

In the current observational study (1), it is not reported whether patients with CSA were treated or not, although during the study period, it is likely that few patients with HFrEF received treatment with adaptive servo-ventilation, given the proscription against this modality engendered by the SERVE-HF study (7). Similarly, transvenous phrenic nerve pacing was not widely available. It is conceivable, however, that some were treated with supplemental nocturnal oxygen, which has been used to treat CSA at VA medical centers (9, 10).

Other limitations of the current study (1) are emphasized, with the hope that the authors can obtain missing data from the EMRs of the enrolled participants, which should be available in the VA data set. Important variables include segregating subjects with preserved ejection fraction from those with HFrEF because CSA is most common in HFrEF and OSA in HF with preserved ejection fraction (11). In this context, echocardiographic findings including left systolic and diastolic function are valuable.

The source of the polysomnogram (PSG) data entered into the database appears to have been limited to that extracted from PSG reports from sleep testing performed at different sleep laboratories. Almost 20% of sleep studies were performed outside of VA facilities, and we are particularly concerned that there may exist the potential for lack of uniformity in classifying the respiratory events based on the American Academy of Sleep Medicine scoring manual criteria distinguishing central from obstructive hypopneas. PSG recordings from patients with HF frequently demonstrate a combination of CSA and OSA (12), and distinguishing central hypopneas from obstructive hypopneas is quite difficult, resulting in hypopneas of both types being lumped into the obstructive hypopnea category (13). Perhaps studies performed outside of a VA facility should have been excluded. Moreover, the distribution of events across various sleep stages (CSA is most common in non–rapid eye movement sleep) and the severity of sleep disordered breathing could be added by reviewing individual PSGs.

We note that in the current study (1) cerebrovascular disease and having BMI $<$ 18.5 were among the highest predictors of survival. Both these conditions predispose to CSA. The association of cerebrovascular disease with CSA is well known, and in this group of patients information regarding left ventricular systolic function noted above is of importance (14). Interestingly, a low BMI and associated reduced metabolic rate (CO_2 production) may increase the loop gain by decreasing the plant gain predisposing to CSA (15). Such interactions between these conditions and CSA would be valuable to explore.

The prevalence of CSA in the VA database was surprisingly low. Only 0.2% of the patients were classified with a diagnosis of CSA. Several aspects may be responsible for the unexpectedly low CSA figures; this includes the phenomenon that CSA is often associated with mild or unspecific symptoms, including lack of excessive daytime sleepiness (12, 16, 17). The symptoms of the underlying diseases may frequently outweigh any clinical signs of CSA. Patients and physicians may only search for the classic OSA symptoms, such as obesity, snoring, and daytime sleepiness, whereas patients with CSA, particularly those with HF, are often thin and do not snore as much as obese patients (12). Without systematic screening in risk groups, CSA may often be missed. The low proportion of patients with CSA may represent a selection of more severe or symptomatic patients. The authors only sophistically validated the charts of patients with CSA, but it cannot be excluded that an unknown number of patients with OSA were misclassified in the original dataset.

Given the detailed information contained within the VA database and EMRs, most if not all of the aforementioned limitations could be rectified and be the subject of a future analysis. Even so, the current study reinforces the already compelling evidence that CSA is an important factor leading to mortality in HF. By extending their analysis as outlined above, even more factors may be revealed that can help make treatment decisions when CSA complicates HF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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