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SCIENTIFIC INVESTIGATIONS

Characterizing respiratory parameters, settings, and adherence in real-world patients using adaptive servo ventilation therapy: big data analysis

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Study Objectives: There is minimal guidance around how to optimize inspiratory positive airway pressure (IPAP) levels during use of adaptive servo ventilation (ASV) in clinical practice. This real-world data analysis investigated the effects of IPAP and minimum pressure support settings on respiratory parameters and adherence in ASV-treated patients.

Methods: A United States-based telemonitoring database was queried for patients starting ASV between August 1, 2014 and November 30, 2019. Patients meeting the following criteria were included: United States-based patients aged ≥ 18 years; AirCurve 10 device (ResMed); and ≥ 1 session with usage of ≥ 1 hour in the first 90 days. Key outcomes were mask leak and residual apnea-hypopnea index at different IPAP settings, adherence and therapy termination rates, and respiratory parameters at different minimum pressure support settings.

Results: There were 63,996 patients included. Higher IPAP was associated with increased residual apnea-hypopnea index and mask leak but did not impact device usage per session (average > 6 h/day at all IPAP settings; 6.7 h/day at 95th percentile IPAP 25 cm H_2O). There were no clinically relevant differences in respiratory rate, minute ventilation, leak, and residual apnea-hypopnea index across all possible minimum pressure support settings. Patients with a higher 95th percentile IPAP or with minimum pressure support of 3 cm H_2O were most likely to remain on ASV therapy at 1 year.

Conclusions: Our findings showed robust levels of longer-term adherence to ASV therapy in a large group of real-world patients. There were no clinically important differences in respiratory parameters across a range of pressure and pressure support settings. Future work should focus on the different phenotypes of patients using ASV therapy.

Keywords: treatment adherence, adaptive servo ventilation, minute ventilation, pressure support, big data analysis

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Although patients with reduced ejection fraction had worse outcomes when randomized to adaptive servo ventilation (ASV) in a large randomized controlled clinical trial, other patient groups might still benefit from ASV therapy. However, there is a lack of guidance around optimization of ASV settings in ASV-treated patients. Therefore, this big data analysis investigated the real-world application of ASV and determined the effects of different inspiratory positive airway pressure and minimum pressure support settings on respiratory parameters and adherence.

Study Impact: Good usage of ASV can be achieved in clinical practice, and use of first-generation ASV devices with minimum pressure support of 3 cm H_2O appears unlikely to contribute to negative outcomes associated with hyperventilation.

INTRODUCTION

Obstructive sleep apnea (OSA) is estimated to affect approximately 1 billion people worldwide.[1] Central sleep apnea (CSA) is also a common problem, particularly in patients with congestive heart failure, opioid use, and other conditions.[2–7] The treatment of choice for OSA is continuous positive airway pressure (CPAP) therapy.[8] However, the optimal treatment for CSA is less well defined. Treatment for CSA involves addressing underlying issues, including optimization of congestive heart failure medications and reduction or withdrawal of opioids.[9] However, despite these measures, sleep-disordered breathing (either OSA or CSA) frequently persists and positive airway pressure (PAP) therapy may be helpful for some patients.[10]

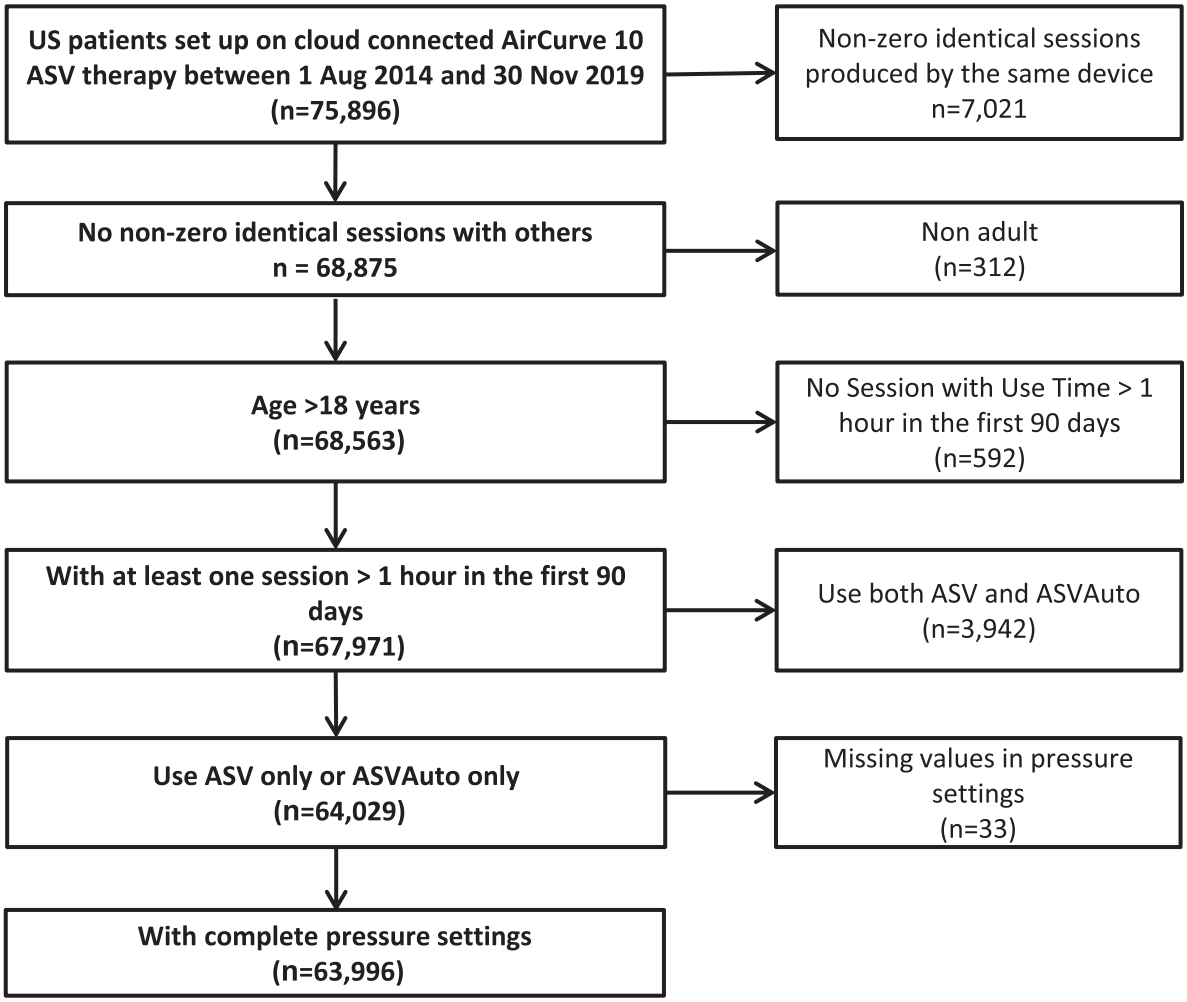
The use of PAP is complicated in a subset of patients. Approximately 10% of OSA patients develop CSA while on PAP therapy, an entity known as treatment-emergent central apnea.[11] Although treatment-emergent central apnea is often self-limiting, it may be associated with poor adherence to therapy.[12] For patients with CSA at baseline, PAP therapy has variable efficacy, meaning that adherence may

again be compromised by residual apnea. In large data sets, we and others have observed that residual apnea can persist in 1%–4% of patients treated with CPAP.[13,14] In such cases, switching from CPAP to adaptive servo ventilation (ASV) has been associated with improvements in residual apnea and PAP adherence. However, guidelines on the clinical use of ASV are lacking, perhaps due to evidence gaps.[15]

One prominent study using ASV in congestive heart failure patients with reduced left ventricular ejection fraction reported adverse outcomes in patients randomized to ASV compared with optimal medical therapy alone.[16] That study included patients with predominant CSA and heart failure with reduced ejection fraction and therefore its findings are only relevant to a fairly narrow segment of the population with sleep apnea. Nonetheless, the study's publication resulted in general reluctance within the clinical community to use ASV, perhaps due to theoretical concerns about general adverse events of the device.[17] However, other studies, including those conducted in patients with heart failure and preserved ejection fraction or acute congestive heart failure, showed possible improvements in outcomes with ASV,[18] providing some reassurance that the ASV device per se was not harmful and highlighting the importance of the clinical scenario in which it is used.

It has been suggested that specific ASV device settings may have an impact on clinical outcomes. For example, some investigators speculated that devices using algorithms that are prone to high levels of inspiratory positive airway pressure (IPAP) could result in high minute ventilation. Because augmented minute ventilation can lead to hypocapnia, the possibility that excessive IPAP could worsen central apnea has been suggested.[19] In addition, hypocapnia has been shown to trigger laryngeal closure reflexes and might therefore worsen OSA.[20,21] Thus, high levels of IPAP may be problematic for a number of reasons. For the practicing clinician, these details are important because there is currently minimal guidance around how to optimize IPAP levels in ASV-treated patients.

Figure 1—Flowcharts for patient inclusion in the study.



ASV = adaptive servo ventilation.

Another important point is the evolution of technologies over time. For example, earlier devices did not provide autotitration of expiratory positive airway pressure (EPAP), so a fixed EPAP was delivered. Therefore, in theory, inadequate EPAP could lead to repetitive upper airway collapse and associated poor outcomes. Inspiratory pressure settings are also important, because earlier devices allowed a minimum pressure support level (ie, IPAP minus EPAP) of 3 cm H_2O, whereas some would argue that lower levels of pressure support ventilation may be needed, especially in the context of hyperventilation and resultant hypocapnia.[22] However, newer devices allow more flexibility in these settings such that both auto EPAP and a minimum pressure support (PSmin) of zero are both now readily available. In this context, we used a big data source of cloud-connected devices from a United States national database to describe the real-world application of ASV and determine the effects of different IPAP and PSmin settings on respiratory parameters and adherence.

METHODS

Database

A United States PAP telemonitoring database was queried to obtain data for this study. The telemonitoring database is a Health Insurance Portability and Accountability Act (HIPAA)-compliant web-based tool for health care professionals that receives data from cloud-connected PAP devices. Patients with devices connected to the database are being managed by private and academic sleep centers, home medical equipment providers, and primary care practices. When patients sign up to use the cloud-connected interface, their consent is obtained to have their data transmitted to the telemonitoring database and for use of deidentified data for research purposes. All data communication and storage is encrypted to meet required international privacy and security standards. The study was reviewed by an Institutional Review Board (Advarra [reference number Pro00037770]) and deemed exempt from Institutional Review Board oversight.

Data extraction

Inclusion criteria for the study were as follows: US-registered adult patients; use of the AirCurve 10 ASV device (ResMed, San Diego, CA); therapy initiation between August 1, 2014 and November 30, 2019; valid data entry; wireless data only; and at least 1 session with device usage of ≥ 1 hour in the first 90 days of therapy. Patients who were deemed to have invalid data entry if age was invalid and patients who had identical sessions produced by the same device were excluded. Data cut-off date was December 1, 2020, with the last observation on December 31, 2020.

Outcomes

The main outcomes were as follows: mask leak and the residual apnea-hypopnea index (AHI) at different IPAP settings, adherence (device usage, rates of Centers for Medicare & Medicaid Services compliance, and therapy continuation rates at 1 year), and respiratory parameters (respiratory rate, minute ventilation, residual AHI, and leak) at different PSmin levels.

Data analysis

All data were anonymized and analyzed in a secure database that was separate from the main telemonitoring database server. Statistical analyses were performed using R language (R development core team), RStudio version 1.0.153. Missing compliance data were imputed as zero. The first day of therapy was considered as the patient setup date in the telemonitoring database. For other data fields, including clinical metrics and respiratory events, missing data were not imputed and not included in calculations of mean and standard deviation values and proportions. Data on mask leak, residual AHI, and other respiratory parameters were analyzed using analysis of variance and presented as median values with interquartile range. Centers for Medicare & Medicaid Services compliance rates were analyzed using the chi-squared test. A Cox proportional hazards model, including patient age, pressure and pressure support settings, residual AHI, and leak, was created to determine predictors of ASV adherence.

RESULTS

Population

Of the 75,896 patients screened, 63,996 met all inclusion criteria and were included in the analyses (**Figure 1** and **Table 1**).

Table 1—Patient demographic and ASV therapy characteristics (n = 63,996).

Age, y	65.5 ± 13.4
Average median IPAP/EPAP, cm H_2O	12.6 ± 3.0/8.0 ± 2.5
Average 95th percentile IPAP/EPAP, cm H_2O	16.3 ± 3.1/8.7 ± 2.6
Average minimum EPAP setting, cm H_2O	7.9 (5.0–9.0)
Average maximum EPAP setting, cm H_2O	10.0 (7.0–15.0)
Average PSmin, cm H_2O	3.1 ± 1.6
Average PSmax, cm H_2O	13.4 ± 3.0
Average median RR, breaths/min	13.3 ± 2.8
Average median minute ventilation, L/min	7.1 ± 1.8
Average residual AHI, events/h	2.4 (1.0–5.3)
Average median leak, L/min	3.9 (1.0–10.2)
Average 95th percentile leak, L/min	19.3 (9.2–34.7)
Mean CMS compliance rate, %	77.7
Average daily usage over all d, h/d	4.8 ± 2.8
Average usage per session, h/d	6.2 ± 2.2
Proportion of d with usage ≥ 4 h, %	61.2 ± 34.0

Values are mean ± SD or median (interquartile range). AHI = apnea-hypopnea index, ASV = adaptive servo ventilation, CMS = Centers for Medicare & Medicaid Services, EPAP = expiratory positive airway pressure, IPAP = inspiratory positive airway pressure, PSmax = maximum pressure support, PSmin = minimum pressure support, RR = respiratory rate, SD = standard deviation.

Overall ASV usage was good in all patients, with an adherence rate of 78% and average device usage of 4.8 ± 2.8 h/day over all days (**Table 1**).

Pressures

Overall, 56.6% of patients used fixed EPAP and 43.4% used auto-adjusting EPAP. Of note, the average median minute ventilation was the same for those patients using ASV with fixed EPAP (7.1 ± 1.8 L/min) vs auto-adjusting EPAP (7.1 ± 1.8 L/min). Median length of time with the device before dropout or censoring was 560 days (interquartile range 179–1001). The maximum default pressure setting of 25 cm H_2O was met in 40.5% of patients (n = 25,926) and average 95th percentile IPAP delivered reached this maximum device pressure in 0.3% of patients. Residual AHI, mask leak, and average usage per session increased significantly as average 95th percentile IPAP increased from below 20 cm H_2O to the maximum device pressure setting of 25 cm H_2O (**Table 2**). Both residual AHI and mask leak also increased significantly as maximum IPAP increased, whereas device usage decreased (**Table 2**). Mask leak noticeably increased as the maximum EPAP setting increased, residual AHI increased slightly, and device usage decreased (**Table 2**). Device usage per session was > 6 h/day at all maximum IPAP and EPAP settings, and the variation in usage between different settings was < 0.5 h/day (**Table 2**). There were significant positive correlations between 95th percentile IPAP and PSmin, maximum EPAP setting, and maximum IPAP setting, and a weak negative correlation between PSmin and the maximum EPAP setting.

Pressure support

Overall, PSmin setting was 0 cm H_2O in 12.3% of patients (n = 7,897), 1 in 2.2% (n = 1,405), 2 in 4.7% (n = 3,014), 3 in 42.3% (n = 27,068), 4 in 18.5% (n = 11,871), 5 in 11.9% (n = 7,596), and 6 in 8.0% (n = 5,145). Although some between-group differences achieved statistical significance, there were no clinically important differences in respiratory rate, minute ventilation, leak, and residual AHI based on PSmin setting (**Table 3**). Variations in the proportion of patients achieving Centers for Medicare & Medicaid Services compliance criteria, average daily ASV device usage, and the proportion of days with ≥ 4 hours of ASV usage between the different PSmin groups were not clinically relevant (**Table 3**). Of all the patients who started ASV therapy, more than 3/4 (76%–79%) were still using ASV at 1 year; a slightly higher proportion of those with a PSmin of 3 cm H_2O remained on therapy at 360 days (65.4% vs 62.3% for patients with a PSmin of 2) (**Figure 2**).

Table 2—Mask leak and residual AHI at different pressure settings during ASV.

	Average AHI, Events/H	Average 95th Percentile Mask Leak, L/min	Average Usage per Session, h
Average 95th percentile IPAP, cm H_2O			
≤ 20	2.2 (0.9–4.7)	17.9 (8.5–31.9)	6.3 (4.7–7.6)
21	4.4 (2.0–8.4)	29.7 (15.1–49.5)	6.5 (5.0–7.8)
22	5.2 (2.4–9.6)	32.9 (15.5–54.5)	6.4 (4.9–7.7)
23	5.8 (2.7–11.1)	37.2 (17.8–62.0)	6.5 (5.1–7.9)
24	6.0 (2.7–11.8)	40.6 (20.0–65.2)	6.6 (5.4–7.9)
25	5.4 (2.7–11.1)	46.0 (25.9–69.0)	6.7 (5.6–8.0)
Maximum IPAP setting, cm H_2O			
< 20	2.4 (1.1–4.9)	16.5 (7.9–29.2)	6.4 (4.9–7.6)
20	2.1 (0.9–4.7)	16.3 (7.8–29.1)	6.5 (4.9–7.7)
21	2.3 (0.9–5.0)	17.5 (8.4–30.5)	6.4 (4.9–7.6)
22	2.4 (1.0–5.2)	19.2 (8.8–33.8)	6.4 (4.8–7.6)
23	2.5 (1.1–5.5)	20.1 (9.5–35.8)	6.4 (4.8–7.6)
24	2.8 (1.2–6.2)	20.9 (10.1–38.0)	6.3 (4.7–7.6)
25	2.5 (1.0–5.6)	21.6 (10.2–39.0)	6.3 (4.7–7.6)
Maximum EPAP setting, cm H_2O			
< 6	1.9 (0.8–4.0)	14.2 (6.7–24.7)	6.5 (4.9–7.6)
6 to < 9	2.2 (0.9–4.8)	17.5 (8.2–30.9)	6.4 (4.9–7.7)
9 to < 12	2.7 (1.2–5.7)	21.1 (10.2–37.3)	6.3 (4.8–7.6)
12 to < 15	3.1 (1.3–6.5)	22.7 (10.9–42.0)	6.2 (4.7–7.6)
15	2.5 (1.0–5.5)	21.4 (10.2–38.4)	6.3 (4.7–7.6)

Values are median (interquartile range). AHI = apnea-hypopnea index, ASV = adaptive servo ventilation, EPAP = expiratory positive airway pressure, IPAP = inspiratory positive airway pressure.

Table 3—ASV therapy metrics and adherence at different minimum pressure support settings.

	Average PSmin, cm H_2O						
	0	1	2	3	4	5	6
Average residual AHI, events/h	2.4	3.0	2.5	2.2	2.6	2.7	2.9
	(1.0–5.1)	(1.3–6.4)	(1.1–5.5)	(0.9–4.9)	(1.1–5.6)	(1.1–5.9)	(1.2–6.1)
Average median leak, L/min	3.8	3.7	3.9	3.6	4.0	4.4	4.7
	(1.0–9.6)	(1.1–10.0)	(1.0–10.1)	(0.9–9.4)	(1.1–10.5)	(1.2–11.6)	(1.3–12.4)
Average median RR, breaths/min	14.0	13.7	13.5	13.4	12.8	12.4	11.8
	(12.1–16.0)	(11.9–15.6)	(11.7–15.4)	(11.6–15.2)	(11.1–14.7)	(10.6–14.3)	(10.0–13.7)
Average median MV, L/min	6.9	6.8	6.8	6.9	7.0	7.2	7.3
	(5.8–8.0)	(5.6–7.9)	(5.8–8.0)	(5.9–8.1)	(5.9–8.2)	(6.0–8.4)	(6.1–8.6)
Average daily usage, h	5.2	4.9	5.0	5.3	5.1	5.1	5.2
	(2.4–7.1)	(2.4–6.8)	(2.2–7.0)	(2.4–7.2)	(2.2–7.1)	(2.3–7.0)	(2.4–7.2)
Proportion of d with usage ≥ 4 h, %	72.4	68.4	70.8	73.9	69.8	71.4	71.7
	(31.3–92.8)	(28.8–91.1)	(27.0–92.3)	(30.5–93.4)	(28.0–92.7)	(28.8–9.27)	(30.7–93.1)
CMS compliance rate, %	78.8	76.6	76.3	77.9	76.8	77.6	77.5

Values are median (interquartile range) or mean percentage of patients. ASV = adaptive servo ventilation, CMS = Centers for Medicare & Medicaid Services, MV = minute ventilation, PSmin = minimum pressure support, RR = respiratory rate.

Predictors of ASV adherence

Cox proportional hazards model analysis (**Figure 3**) showed that age, 95th percentile IPAP, and 95th percentile EPAP were significantly associated with an increased likelihood of ASV usage at 1 year. Conversely, maximum pressure support, residual AHI, and median mask leak were significantly associated with lower likelihood for patients to still be using ASV at 1 year. There was no association between PSmin settings and 1-year adherence to ASV therapy.

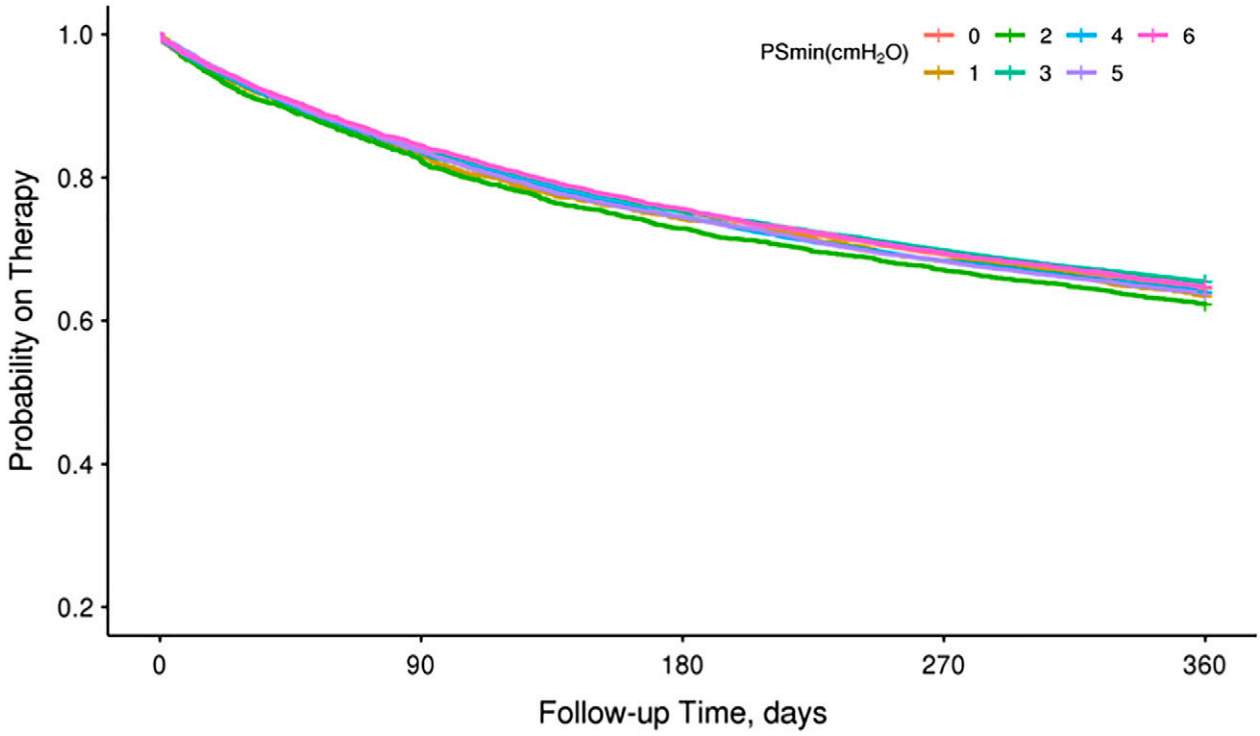
DISCUSSION

The results of this study showed that increasing IPAP was associated with increases in residual AHI and mask leak and that PSmin setting did not have any clinically relevant effects on ventilatory parameters (including minute ventilation) in patients receiving ASV in routine clinical practice. Device usage was high, averaging nearly 5 h/day in all patients studied. In addition, changes in usage across all categories of 95th percentile IPAP, maximum IPAP, maximum EPAP, and PSmin were < 0.5 h/day and were therefore unlikely to be clinically relevant.[23]

These findings are important for a number of reasons. First, adherence to ASV therapy was excellent compared with previously published big data looking at standard CPAP.[13,24] This finding provides reassurance that patients are actually using their ASV device, suggesting self-perceived improvements and, therefore, the potential to achieve the associated health benefits. Second, the lack of any important impact of PSmin settings on respiratory parameters suggests that use of ASV devices with a PSmin of greater than 0 cm H_2O is unlikely to have contributed to negative outcomes associated with hyperventilation. Thus, one might speculate that the excess mortality reported previously in the literature with ASV[16] may not have been driven by device-related hyperventilation. Finally, there were no major pressure differences between manual EPAP and auto EPAP, suggesting that repetitive upper airway collapse from inadequate EPAP was not a systematic problem during ASV therapy.

After steps have been taken to address any conditions contributing to sleep-disordered breathing, it is not always clear what the optimal strategy for PAP therapy should be. However, this decision most likely depends on the underlying etiology. The condition of patients with CSA specifically, and sleep-disordered breathing in general, is often dynamic and the optimal therapy may vary between patients and in the same patient over time.[25] There are now technologies available to help manage and overcome these issues. Information provided by telemonitoring can be used by clinicians to optimize PAP therapy. For example, if a previously adherent patient suddenly stops using therapy, a call or a visit could be scheduled to address the underlying issue. Similarly, the development of residual apnea could be detected remotely and in turn could trigger a search for potential corrective actions (eg, optimization of PAP settings, changing heart failure medications, decreasing opioid dosages). As previously acknowledged, the patient populations most likely to benefit

Figure 2—Kaplan-Meier plot of probability of remaining on ASV therapy in patient subgroups based on PSmin setting.



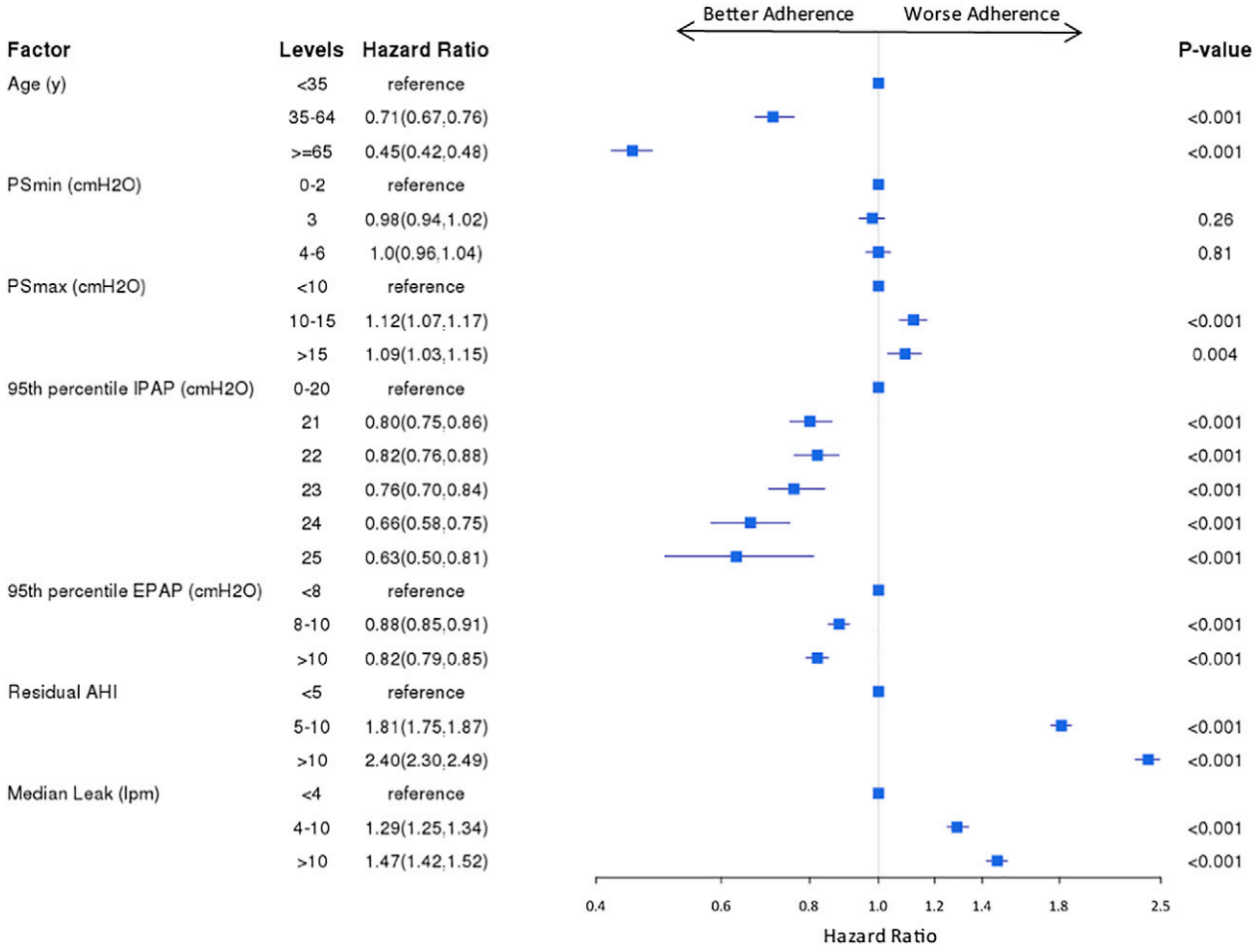
ASV = adaptive servo ventilation, PSmin = minimum pressure support.

from ASV and the optimal usage in these populations remain unclear but may be informed by ongoing randomized controlled trials.

Our study had a number of strengths including a large sample size and the analysis of real-world data, providing good external validity. However, we acknowledge a number of limitations. We acknowledge that our cloud-based analyses reflect only those patients who have access to health care and who are able to obtain an ASV device. Thus, the data may not pertain to individuals who either refuse a device or do not have sufficient access to health care to acquire one. The nature of the study dataset means that there is a lack of granular data regarding the patients' medical history, including absence of information about the reasons for prescription of the particular treatment modality and pressure settings. The outcomes in the current study were considered to be clinically relevant, but were obtained via the PAP device, without supporting patient-centric clinical outcomes such as the occurrence of myocardial infarction or stroke. As a result, adequately powered studies assessing objective clinical outcomes are required to provide robust data on which to base future clinical practice. Furthermore, although the large sample size is one strength of our study, it could also be argued that this approach does not highlight the unique preferences and responses for individual patients. Thus, although auto EPAP and manual EPAP yielded very similar settings, there are likely to be individuals who would prefer one approach over another (ie, a specific type of device). For example, some individuals with highly variable pressure requirements (eg, rapid eye movement vs non-rapid eye movement sleep or supine vs lateral sleep-disordered breathing) may benefit from autotitration EPAP rather than being manually titrated to the maximum required value. In addition, given the nature of variability in respiratory mechanics and breathing patterns, there may well be individuals who respond to lower PSmin settings, although in aggregate we did not see an important impact of the PSmin variable. Finally, our analyses were limited to ASV devices that target minute ventilation and therefore we cannot draw any meaningful conclusions about other devices or strategies using different algorithms. Although our sample included a large number of patients who are likely to be representative of a larger group, we are supportive of further mechanistic research to identify and characterize important subsets who may respond differently to this therapy.

In conclusion, the robust level of adherence to ASV therapy documented in this big data analysis provides some reassurance about potential concerns that ASV may be poorly tolerated. In addition, respiratory rate, pressure settings, and minute ventilation data suggest that ASV-treated patients in this study did not experience hyperventilation. Although further research is needed in this area, the current findings provide some guidance for clinicians regarding what can be expected during ASV therapy and suggest that ASV therapy may have utility in patients who meet current eligibility criteria and have no contraindications to this form of positive airway pressure treatment.

Figure 3—Forest plot showing predictors of adherence to ASV therapy.



Data show hazard ratio (squares) with 95% confidence interval (lines). AHI = apnea-hypopnea index, ASV = adaptive servo ventilation, EPAP = expiratory positive airway pressure, IPAP = inspiratory positive airway pressure, lpm = liters per minute, PSmax = maximum pressure support, PSmin = minimum pressure support.

ABBREVIATIONS

AHI, apnea-hypopnea index
ASV, adaptive servo ventilation
CPAP, continuous positive airway pressure
CSA, central sleep apnea
EPAP, expiratory positive airway pressure
IPAP, inspiratory positive airway pressure
IRB, institutional review board
OSA, obstructive sleep apnea
PAP, positive airway pressure
PSmin, minimum pressure support

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