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Comparison of Physiological Performance of Four Adaptive Servo Ventilation Devices in Patients with Complex Sleep Apnea

To the Editor:

Adaptive servo ventilation (ASV) increased the risk for mortality in the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure) trial, but the underlying mechanisms are unclear (1–3). Conceivably, device algorithms controlling respiratory rate and pressure support may have led to high $\dot{V}_E$ that caused hypocapnia and consequent arrhythmias (2, 4, 5). Whether such findings are a result of a device algorithm–based effect ("device-effect") or apply to all servo-algorithm devices ("class-effect") is uncertain (2, 6). We compared the performance of various ASV devices on measures of respiration and electrocardiography. Some of the results of these studies have been previously reported in the form of an abstract (7).

Methods

We performed a randomized controlled crossover physiological experiment of patients with complex sleep apnea with preserved cardiac contractility (left ventricular ejection fraction >45% by echocardiography) who were adherent to ASV therapy. Patients with untreated sleep disorders such as insomnia, periodic limb movement syndrome (leg movement index >10/h in prior laboratory-based polysomnography [PSG]), or restless legs syndrome were excluded. Patients were randomly assigned to 4 nights of PSG while receiving the device used in the SERVE-HF trial (ResMed S7 VPAP Adapt [ResMed]; hereafter, "S7 device"), a later version of the S7 device (ResMed S9 VPAP Adapt [ResMed]; hereafter, "S9 device"), a Philips ASV device (System One; Philips-Respironics, Inc.), and a later version of Philips ASV device (Dreamstation; Philips-Respironics, Inc.). For all devices, the expiratory positive airway pressure level was set from 4 to 15 cm H_2O; the minimum pressure support was set at the lowest level possible (3 cm H_2O for the S7 device and 0 cm H_2O for all other devices); and maximum pressure support was 15 cm H_2O, with maximum total pressure of 25 cm H_2O with automatic back-up rate, whereas patients used the same mask interface on all nights. Conventional PSG with two electroencephalography leads each for frontal, occipital, and temporal; right and left electro-oculography; chin electromyography; lead II electrocardiography; finger pulse-oximetry; and respiratory signals derived from the device pneumotachograph output (airflow, V_T, and their derivatives: instantaneous respiratory rate [respiratory rate = 1/total respiratory cycle time] and $\dot{V}_E$ [product of V_T and respiratory rate]) were collected. Electrocardiography signals (200 Hz sampling rate) were analyzed for heart rate and QTc interval (MATLAB software). Patients were blinded to the device, and blinded observers scored PSG, respiratory, and electrocardiographic signals (8). Statistical analysis was performed by individuals blinded to study condition through numerical coding of the device using ANOVA or generalized linear model with repeated measures with adjustment for multiple comparisons (generalized linear model with Holm-Bonferroni correction that adjusts for control of family-wise error rate; IBM SPSS v25.0; IBM Corp.).

Fourteen patients underwent PSG on 4 nights while receiving treatment from four different devices. $\dot{V}_E$ was greater during treatment with the S7 device when compared with all other devices during wakefulness ($P < 0.0001$; Figure 1). The $\dot{V}_E$ for the entire night when receiving therapy with the S7 device was greater than the $\dot{V}_E$ for the entire night when receiving therapy with any of the other devices ($P < 0.02$; right upper panel of figure). Respiratory rate was greater with the S7 device when compared with the S9 device for the entire night ($P < 0.0001$; Table 1). During wakefulness, pressure support level was greater during S7 device therapy when compared with S9 device ($P = 0.002$; Table 1) and tended to be greater than pressure support level administered by the S9 device during sleep ($P = 0.085$). QT interval corrected for heart rate (QTc) during S7 therapy was not different than that during any of the other therapy nights ($P = 0.24$). The tendency for greater frequency of premature ventricular beats during S7 nights when compared with any other night was observed but did not reach statistical significance ($P = 0.20$). There were three episodes of nonsustained ventricular tachycardia during the entire study: two episodes during the S7 nights and one during a System One night. The total apnea–hypopnea index and apnea index were not different across the different devices ($P > 0.6$). The central apnea index tended to be lower in the S7 and S9 devices when compared with the System One and Dreamstation devices (ANOVA; $P = 0.08$).

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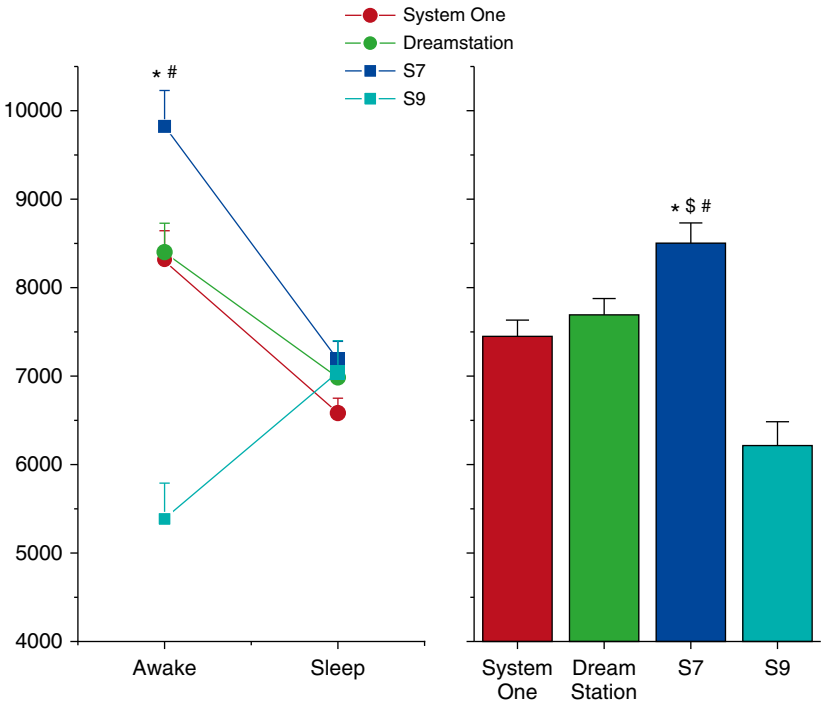

Figure 1. $\dot{V}_E$ by sleep–wakefulness state (left panel) and $\dot{V}_E$ for the entire night (right panel) are plotted for nights when undergoing laboratory-based polysomnography performed while receiving four different ASV devices: ResMed S7 VPAP Adapt (S7 device), a later version of the S7 device (ResMed S9 VPAP Adapt; S9 device), a Philips ASV device (System One), and an updated version of the Philips ASV device (Dreamstation). Mean and SE bars are plotted. Note that $\dot{V}_E$ for most devices was greater during wakefulness when compared with sleep. Also, the greatest $\dot{V}_E$ is during wakefulness while receiving therapy via the S7 device. There was no order effect for randomization sequence with regard to the $\dot{V}_E$ findings. $^{*}P < 0.05$ when compared with Dreamstation device; $^{\#}P < 0.05$ when compared with S9 device; and $^{\$}P < 0.05$ when compared with System One. ASV = adaptive servo ventilation.

Discussion

There were significant differences in $\dot{V}_E$ delivered by various ASV devices. During wakefulness, $\dot{V}_E$ was 15–40% greater during S7 night than with other devices. Moreover, the difference in $\dot{V}_E$ during wakefulness versus sleep states was greater for the S7 device ($+2.64 \pm 0.46$) than any other device (System One [$+1.73 \pm 0.37$]; Dreamstation [$+1.42 \pm 0.37$]; and S9 device [-1.6 ± 0.1 L/min]; $P < 0.0001$). Such amplification factors of the wakefulness drive to breathe can create respiratory instability and potentiate central apneas, which, in turn, would require greater pressure support and respiratory rate by the servo mechanism and/or respiratory drive (9). Such increases in $\dot{V}_E$ during wakefulness cause hypocapnia (respiratory alkalosis), which, in turn, could cause hypokalemia (10). Hypokalemia resulting from nighttime intracellular shifts in potassium ions can prolong QT interval and lead to potentially life-threatening cardiac arrhythmias (10). Conceivably, nighttime alkalosis resulting from excessive ventilation may lead to daytime hypokalemia and QTc prolongation through renal loss of potassium at night, with consequent arrhythmogenic effects during the daytime. Although the observed QTc prolongation during S7 therapy was small in magnitude and not statistically significant, such effects may be magnified in patients with heart failure who develop metabolic alkalosis resulting from loop diuretics. We did not, however, measure CO_2 levels or potassium levels, which is a study limitation. Future research needs to be performed with adequate sample size to distinguish such differences.

In our study, we found lower sleep efficiency (greater awake time) during S9 therapy nights when compared with other devices, including the S7 device night (Table 1). Specifically, the proportion of wakefulness time during S7 device therapy nights was better than that during S9 device nights (generalized linear model, $P < 0.0001$; Holm-Bonferroni correction, $P = 0.0002$). In fact, the proportion of time during wakefulness during S9 therapy was worse than that during any other device night. In contrast to our study finding, Teschler and colleagues (11) performed an elegant study in which improvements in central apnea index and sleep architecture (notably greater REM sleep and slow wave sleep) was observed when performing a randomized crossover trial of ASV, continuous positive airway pressure, bilevel positive airway pressure, and oxygen treatment for central sleep apnea. In our study, we compared four different types of ASV devices and noticed differences in $\dot{V}_E$ and sleep architecture across such devices, although there were no appreciable differences in central apnea index. Interestingly, we found that the magnitude of $\dot{V}_E$ was inversely related to proportion of time spent awake (Pearson $R^2 = -0.93$; $P = 0.031$). Conceivably, hypocapnia-induced cerebral vasoconstriction and reduced arousability may have played a role in such a finding (12, 13).

The internal validity of the study is reflected by the expected greater $\dot{V}_E$ during wakefulness than during sleep, regardless of device. Moreover, the observation that the S7 device delivers greater

Table 1. Breath Components and Pressure Assist Levels

Device and Sleep Stage	V_T (*ml*)	Respiratory Rate (*bpm*)	PS Level (*cm H_2O*)	Sleep Stage (%)	QTc Interval (*ms*)	CAI (*Events/h*)
System One						
Awake	570 ± 33	14.9 ± 0.6	2.0 ± 0.4	22.8 ± 4.2	396.1 ± 6.2	6.3 ± 2.6
Sleep	462 ± 17	14.7 ± 0.3	3.7 ± 0.2	14.9 ± 1.8 (N1) 41.9 ± 3.7 (N2) 9.7 ± 1.4 (REM) 10.6 ± 2.1 (SWS)	397.2 ± 5.4	
Dreamstation						
Awake	568 ± 33	15.3 ± 0.6	2.3 ± 0.4	29.0 ± 4.2	391.5 ± 6.4	4.2 ± 1.3
Sleep	512 ± 17	14.2 ± 0.3	4 ± 0.2	16.0 ± 1.8 (N1) 38.8 ± 3.7 (N2) 7.9 ± 1.4 (REM) 8.1 ± 2.1 (SWS)	401.5 ± 5.4	
S7						
Awake	624 ± 41	15.8 ± 0.8	2.6 ± 0.5	19.2 ± 5.2	400.9 ± 6.0	2.2 ± 1.1*
Sleep	460 ± 21	16 ± 0.4	2.6 ± 0.3	12.0 ± 2.2 (N1) 45.0 ± 4.5 (N2) 9.2 ± 1.7 (REM) 14.6 ± 2.6 (SWS)	403.5 ± 5.1	
S9						
Awake	459 ± 41	12.0 ± 0.8	0.0.1 ± 0.5	49.8 ± 5.2†	393.1 ± 6.2	2.2 ± 1.0*
Sleep	415 ± 24	11.1 ± 0.7	0.9 ± 0.4	5.1 ± 2.2 (N1) 28.5 ± 4.5 (N2) 7.9 ± 1.7 (REM) 8.6 ± 2.6 (SWS)	395.9 ± 5.5	

Definition of abbreviations: bpm = breaths/min; CAI = central apnea index; N1 = non-REM sleep, stage 1; N2 = non-REM sleep, stage 2; PS = pressure support; SWS = slow wave sleep.
Data are shown as mean ± SE.
*$P = 0.08$ when compared to other devices.
†$P < 0.05$ when compared with other devices for wakefulness state.

ventilation is similar to that observed in the SERVE-HF trial (1, 4), whereby device algorithms that control rate and pressure support were compounded by a minimum default pressure support of 3 cm H_2O that provided high levels of $\dot{V}_E$ (external validity) (4).

In conclusion, there were significant differences in $\dot{V}_E$ and sleep architecture while receiving ASV therapy from various available devices, and higher $\dot{V}_E$ was associated with small but statistically nonsignificant QTc prolongation. We speculate that the mechanisms underlying the adverse effects of ASV may be secondary to excessive ventilation resulting from a device-based effect rather than a class effect. ■

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James Knitter, B.S.
Omavi F. Bailey, M.D.
Chithra Poongkunran, M.D.
Aylene Flores Martinez, B.A.
Linka Martinez, B.A.
Ume Kobayashi, B.S.
Daniel Combs, M.D.
Richard Lane, M.D., Ph.D.
University of Arizona
Tucson, Arizona

Wojciech Zareba, M.D.
University of Rochester
Rochester, New York

Sairam Parthasarathy, M.D.*
University of Arizona Health Sciences Center for Sleep and Circadian Sciences
Tucson, Arizona

*Corresponding author (e-mail: spartha1@email.arizona.edu).

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Airway Pressure Monitoring May Improve Small Airway Flow, Hemodynamics, and Tissue Oxygenation

To the Editor:

We would like to congratulate Scales and Kavanagh (1) for their insightful comments reported in the editorial accompanying the study by Grieco and colleagues (2). It is true that research on resuscitation made early gains, but recent progress has been slow because of the dispersion of researchers to aspects other than elucidating the physiology and pathophysiology of cardiac arrest and resuscitation.

Although our understanding of the interaction between chest compression and mechanical ventilation remains limited, expert opinions will probably continue to rely on flawed studies that neither report nor take into consideration, when interpreting the results, the method of postintubation ventilation (self-inflating bag or ventilator), while suggesting simultaneously that early intubation during cardiopulmonary resuscitation (CPR) does not improve, or even decreases, survival (3). Ventilation with a self-inflating bag in intubated patients usually results in excessive ventilation volume and rate, thus aggravating oxygenation and hemodynamics, and surprisingly, it continues to be a major limitation in resuscitation studies.

Cordioli and colleagues (4) demonstrated that ventilation during CPR by using currently recommended chest compression rates takes place entirely below FRC and is associated with negative intrathoracic pressures during decompression. Although the thoracic pump theory is not widely accepted among the resuscitation community, the study of Cordioli and colleagues suggests that both cardiac pump and thoracic pump have a role in forward blood flow and tissue oxygenation. In this context, the study by Grieco and colleagues (2) strengthens the evidence-based notion that the harmony between circulation and ventilation during CPR is critical. Achieving the correct balance between too little and too much ventilation is of major importance for optimizing survival, and theoretically, there must be an intrathoracic pressure limit at which the effect of a thoracic pump should be maximal. Above this limit, intrathoracic pressure would be deleterious, and under this limit, ventilation may not provide adequate blood oxygenation because of small airway closure, increasing pulmonary vascular resistance and impairing pulmonary and systemic blood flow.

Our group has recently shown an association between mean airway pressure and outcome of CPR in mechanically ventilated patients, with a value of 42.5 mbar being associated with return of spontaneous circulation (5). In our patients, simultaneous positive pressure ventilation in time with each chest compression prevented a loss of intrathoracic pressure via the airway, and probably kept the small airways open. In this study, we found no difference in end-tidal carbon dioxide between survivors and nonsurvivors, probably because of the maintenance of flow in small airways and the improvement in minute-volume ventilation during CPR (6). Of note, the rise in intrathoracic pressure in mechanically ventilated patients undergoing CPR is transmitted equally to all intrathoracic structures and squeezes out the pulmonary vessels, which increases forward blood flow, arterial oxygen partial pressure, and aortic pressure. Moreover, as hemodynamics may be aggravated in prolonged CPR because of vascular tone deterioration, the pressing effect of positive pressure ventilation and increased intrathoracic pressure on aortic wall may increase aortic resistance and retrograde volume loading, therefore enhancing the compression-related blood flow (5).

Collectively, the study by Grieco and colleagues and our findings highlight the favorable effects of the thoracic pump and the importance of intubation and mechanical ventilation in patients with cardiac arrest, supporting our deduction that the interplay between ventilation and chest compression during CPR is a key point to optimize outcomes (6). As proper timing of compression and ventilation seems to be the key for improving the circulation, the focus of the resuscitation community must immediately return to the elucidation of the physiology and pathophysiology of cardiac arrest and resuscitation. ■

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

Athanasios Chalkias, Ph.D.*
University of Thessaly
Larisa, Greece
and
Hellenic Society of Cardiopulmonary Resuscitation
Athens, Greece

Theodoros Xanthos, Ph.D.
Hellenic Society of Cardiopulmonary Resuscitation
Athens, Greece
and
European University Cyprus
Nicosia, Cyprus

*Corresponding author (e-mail: thanoschalkias@yahoo.gr).

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