Servo-ventilation Is Still An Option

Sponsored by
PHILIPS
RESPIRONICS

Published and written by
Sleep Review
THE JOURNAL FOR SLEEP SPECIALISTS

Some providers may have overreacted to the results of a prominent study that identified an at-risk group for ASV therapy. Sleep physicians and researchers say a consequence is now some patients who need the advanced therapy—and are not in the at-risk group—are not receiving it. Paradoxically, this overreaction imperils, rather than increases, the safety of several sleep-disordered breathing patient populations.

By Lena Kauffman

Before adaptive servo-ventilation (ASV) was developed a little over a decade ago, treating patients with the highly variable breathing patterns found in cases of central sleep apnea and complex sleep apnea was difficult. Patients whose sleep breathing patterns swung between apneas, hypopneas, hyperventilation, and periods of normal breathing would be uncomfortable with CPAP or even the more advanced bilevel PAP treatment. They also got little relief from symptoms like daytime sleepiness and consequently frequently abandoned their therapy after a short period of time.

ASV offered new hope. These devices use advanced algorithms that analyze the patient's breathing rate as well as inspiratory and expiratory pressure. They calculate the level of breathing support in response to what the patient is actually doing. If the patient has a period of apnea or hypopnea, the inspiratory air pressure support goes up. If the patient has a period of normal breathing or hyperventilation, the pressure support goes down. In particular, ASV seemed like a possible breakthrough for a particular subset of central sleep apnea patients, those with heart disease. After all, if a patient's heart is already struggling to keep his body properly oxygenated, then adding oxygen disruption via sleep-disordered breathing at night would seem to make matters worse.

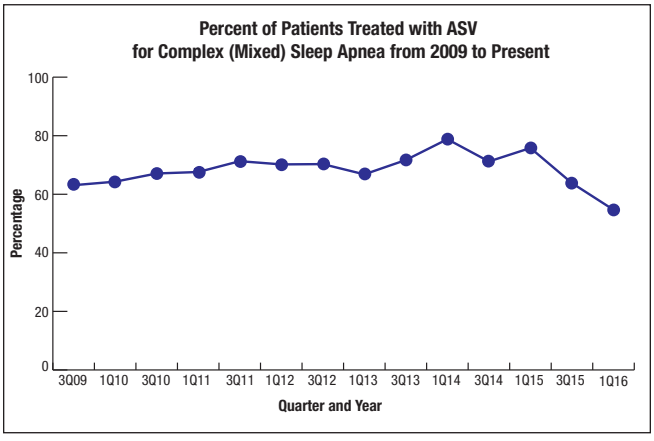


Figure 1. A semi-annual *Sleep Review* survey has data for servo-ventilation usage for complex sleep apnea patients from as early as the third quarter of 2009, when ASV was prescribed for 63.1% of patients with complex sleep apnea. Prescriptions peaked in the first quarter of 2014 at 78.8%, with a second smaller peak of 75.8% in the first quarter of 2015. As of the first quarter of 2016 (the most recent data that is available), prescriptions have dropped to 54.7%, the lowest since the survey began.

So it shook the sleep medicine community when, a little over a year ago, researchers on the SERVE-Heart Failure (SERVE-HF) study announced the trial did not meet its primary endpoint. According to SERVE-HF data, the heart failure patients in the ASV treatment arm of their randomized study were dying at a higher rate than the patients in the non-treatment arm who were not on ASV.

The evidence did not trigger a US Food and Drug Administration recall because the higher mortality rate was a secondary finding to the study's primary design. However, all three manufacturers of ASV devices—ResMed, Philips Respironics, and Weinmann*—prudently issued field notices in May 2015. The American Academy of Sleep Medicine (AASM) also issued a special safety notice.[1] As everyone in the industry is now aware, the notices alerted physicians to not prescribe ASV for patients with three criteria: symptomatic chronic heart failure (New York Heart Association class 2 to 4 heart failure), reduced left ventricle ejection fraction equal to or less than 45%, and moderate to severe predominant central sleep apnea. The *New England Journal of Medicine* published the results of the "Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure" study on September 17, 2015.[2] By then, sleep physicians were already combing their records and reaching out to patients previously prescribed ASV to see if they needed an echocardiogram or should come off the device due to a prior diagnosis of heart failure.

The outpouring of concern for patient welfare from researchers, manufacturers, and sleep physicians is laudable. But, paradoxically, other patients—those not in an identified at-risk group—may have been put in jeopardy by losing access to their ASV devices as a result of broad corrective action. Data now suggests that many providers stopped prescribing ASV to patients who are not in the identified at-risk group; as a result some sleep-disordered breathing patients are not receiving adequate treatment because they were prescribed less advanced devices such as CPAP or bilevel PAP. "The nuances of this [study] are

Central sleep apnea (CSA) occurs when a patient's brain does not send correct signals to the muscles that control breathing. CPAP therapy may manage CSA; however, when CSA is CPAP-resistant, advanced therapies such as ASV are needed.

not broadly appreciated in medicine," explains Sairam "Sai" Parthasarathy, MD, director of the Center for Sleep Disorders at the University of Arizona College of Medicine. Parthasarathy says too many providers are looking at ASV safety concerns as black-and-white, and missing the nuanced shades of gray for all of the patients for whom ASV is still the best option.

Parthasarathy, who researches sleep in heart failure patients and treats patients with ASV therapy, says he is concerned that an overabundance of caution in ASV use is leading clinicians to not prescribe ASV for any patients, including those not in the identified at-risk group. Many of these patients may really need ASV to be properly treated. However, they are now either "making do" with a less suitable treatment option, such as bilevel PAP, or going without any treatment at all, he says.

EVIDENCE THAT ASV IS BEING UNDERUTILIZED

Patients with complex sleep apnea (also known as mixed sleep apnea; referring to a combination of both obstructive and central sleep apnea symptoms) are not in the group considered at risk, so did use of ASV in this patient population go down after the publication of the SERVE-HF study? Yes, it did.

A joint *Sleep Review* and Needham & Company survey shows that ASV prescriptions for complex sleep apnea cases decreased from a peak of 78.8% of total prescriptions in the first quarter of

Educating Cardiologists

The interaction between sleep-disordered breathing and cardiovascular disease continues to be a new frontier in sleep clinical practice. Electrophysiologists (cardiologists who specialize in heart rhythms) and sleep medicine physicians in particular are beginning to work together to see if treating sleep-disordered breathing may improve outcomes for atrial fibrillation (Afib) cardiac ablation treatments. Will the finding that adaptive servo-ventilation (ASV) treatment increased mortality in another group of cardiology patients have a chilling effect on the burgeoning relationship between the sleep and cardiology disciplines?

"The results of this trial certainly didn't help the field in that regard," notes Douglas Bradley, MD, director of the Sleep Research Laboratory at the Toronto Rehabilitation Institute. "I think that is a major concern."

Shahrokh Javaheri, MD, a sleep physician at TriHealth Sleep and Bethesda North Hospital, as well as professor emeritus of medicine at the University of Cincinnati College of Medicine in Cincinnati, Ohio, is a clinician and researcher who receives about a third of his sleep patient referrals from cardiologists. Although he has not seen a drop-off in referrals from cardiologists in his own practice, he believes it could be happening elsewhere.

"We need to keep educating physicians, both sleep and heart failure doctors, because they have heard about this ASV trial that failed and they are generalizing this to all heart failure patients, including AFib patients," he says. "We need to go back to step one, which is saying that this is one cause of central sleep apnea, but we have all of these other potential causes and if patients don't respond to CPAP—which is the key—we need to educate them to start using a device that works for them."

Just like Javaheri, Sairam "Sai" Parthasarathy, MD, director of the Center for Sleep Disorders at the University of Arizona College of Medicine, has been lecturing about ASV safety and appropriate use. "A lot of people are busy and it is our job as clinical researchers who have one leg in research and one leg in clinical medicine to do the appropriate translation because the world of clinical research is a different world from the world of clinical medicine," Parthasarathy says. "When we translate, show the data, show the rebuttal, then they can make up their own minds and make a better judgment."

2014 to 54.7% of total prescriptions in the first quarter of 2016 (see Figure 1). "We suspect that the decline has been driven by the results from ResMed's SERVE-HF trial that were disclosed in May 2015, although the trial was focused on patients with heart failure and central sleep apnea rather than complex sleep apnea," the authors write.[3]

Parthasarathy says, "People are worried, and prescribing ASV now requires extra work in terms of screening the appropriate patients to make sure they get the appropriate device. I think there are some people in sleep practice that 'play it safe' and also may not want to do the extra legwork, in my opinion."

How much of the ASV prescription drop is a legitimate reaction to the safety concerns that surfaced in SERVE-HF and how much is an overreaction from providers who do not understand or want to work through the nuances? It is hard to say with exact certainty. One estimate says the identified at-risk group is about 15% to 20% of total pre-SERVE-HF ASV prescriptions, but that the drop-off in prescriptions is more than double that amount.

But generalizing a finding from one study on one specific subset of patients to *all* patients who could be candidates for ASV therapy can actually be the less safe option, if it removes a needed and appropriate therapy from patients not in an at-risk group, Parthasarathy says. "Time and again in history, we see that knee-jerk responses to situations oftentimes don't lead to good. Instead, they lead to more harm," he says.

According to both Parthasarathy and sleep physician Shahrokh Javaheri, MD, when patients are prescribed a device not designed to fully handle their complex or central sleep apnea, their symptoms may persist. In addition to the long-term consequences of inadequately treated apneas, using a device that's not up to the treatment task also puts patients at greater risk of abandoning treatment, which in turn could pose additional risks for their health.

"There are some people who need the [ASV] device and don't have the contraindications with regard to heart failure," Parthasarathy says. "It is up to us to figure out who those people are and distinguish them from the people who don't have such problems, because at the end of the day, it is the patient that loses out if we are being risk averse or lazy or a combination of both."

Patients for whom ASV continues to be appropriate include those who suffer from complex sleep apnea patients (measured in the Needham-*Sleep Review* study), as well as three other categories. ASV is also still appropriate for:

1. Patients with opioid-induced central sleep apnea. Chronic use of opioids (generally prescribed for chronic pain management) has been linked with central sleep apnea that is CPAP-resistant.[4]
2. Patients with heart disease with preserved ejection fraction who belong to either of two subgroups. The first group is patients with atrial fibrillation (Afib) with dilated left atrium who have been found to have central sleep apnea and obstructive sleep apnea in a sleep study and whose central sleep apnea did not improve with CPAP. The second group is patients with diastolic heart failure with preserved ejection fraction.

Opioids have been linked to CPAP-resistant CSA that responds to ASV. With 259 million prescriptions for opioid painkillers written in 2012, this means there are many patients potentially in the population of opioid-induced CSA.

3. Patients with idiopathic (primary) central sleep apnea. This is fairly rare, but does happen in certain cases, such as in those who have had a stroke or renal failure. As the name implies, this diagnosis is reserved for central sleep apnea cases in which the cause is unknown.

About a third of Javaheri's referrals come from cardiologists. The sleep physician at TriHealth Sleep and Bethesda North Hospital and professor emeritus of medicine at the University of Cincinnati College of Medicine in Cincinnati, Ohio, has published several studies examining ASV. He continues to prescribe ASV for patients not in an at-risk group. He encourages other clinicians to do the same even if the patients require closer monitoring and possibly more work. "Unfortunately, with the publication of SERVE-Heart Failure, a lot of people got frightened and they are underutilizing this very intelligent and important device," he says.

Among Javaheri's patients are those with opioid-related central sleep apnea. In his experience, this type of central sleep apnea generally cannot be managed with CPAP alone, and the potential patient population is much larger than many sleep physicians may realize. According to the U.S. Centers for Disease Control and Prevention, 259 million prescriptions for opioid painkillers were written in 2012.[5] "There are many, many patients with opioid-induced central sleep apnea that if they are tested and CPAP doesn't work, they need to go on ASV," Javaheri says.

Another important group to consider for treatment with ASV are patients with Afib or diastolic heart failure. "This is important because both Afib and diastolic heart failure are epidemic in the older population," Javaheri says. "The only groups we should not be using ASV in at this time are the patients with central sleep apnea and low ejection fraction."

MANAGING PATIENTS WHO REFUSE TO STOP ASV

After they began contacting patients about the ASV safety notice, some sleep physicians found a number in an at-risk group who refused to come off the therapy. This happened with some of Javaheri's cardiology patients.

"A number of them are going to say 'I'm doing so well and I'm sleeping so much better, I don't want to come off this device,'" Javaheri says. One religious patient even told Javaheri he believed God meant for him to continue on ASV.

Since a physician cannot easily force a patient to discontinue a therapy, Javaheri instead works with his patients who refuse to come off the device to closely monitor their condition. He makes sure they first meet with him to be fully informed about possible risks. They must sign a document explaining the risks of continuing on ASV therapy outside of a closely monitored clinical study. Finally, the patient must regularly come in for measuring of the ejection fraction. "If the ejection fraction is going down, they should definitely come off the device," Javaheri says.

MANAGING NEW PATIENTS

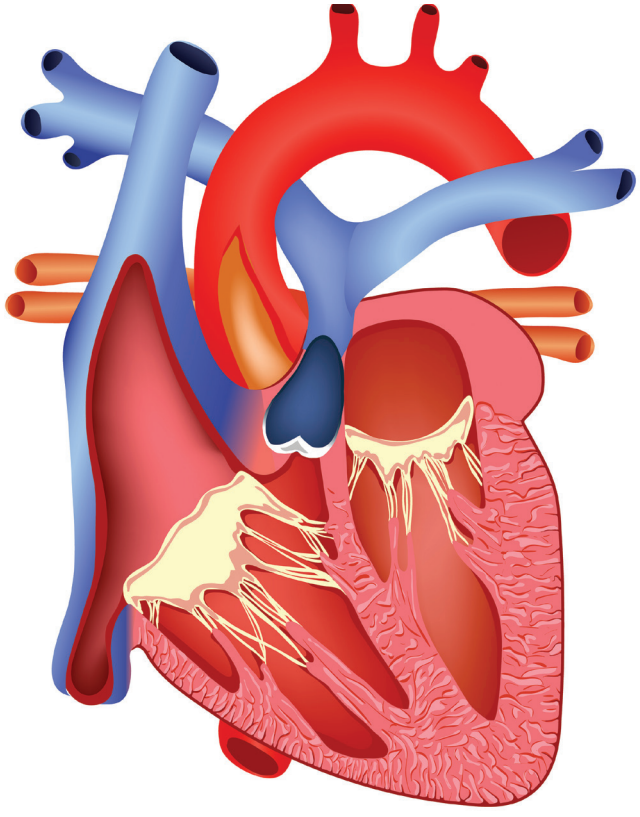
Another larger group of patients to manage are those who, through a sleep study, are discovered to have complex or central sleep apnea and respond best to ASV. Here it becomes critical to know if they could be in an at-risk group.

Parthasarathy and Javaheri stress that until more research is done, all sleep physicians should follow the AASM recommendation to not use ASV in patients with left ventricle heart failure and a reduced ejection fraction (45% or less). But that still leaves a lot of other patients for whom ASV might be a very helpful therapy—or even the only therapy if they fail on CPAP or bilevel PAP. "Whether it is CPAP or ASV needs to be determined and if CPAP is not working, then ASV is the right way to go," Javaheri says.

Parthasarathy shares how he and his colleagues approach the issue at the University of Arizona sleep center. Their first step is to make sure patients who could potentially be in an at-risk group are identified before an ASV prescription can be written. To do this, the sleep center has changed its workflow so patients are no longer automatically prescribed ASV unless the medical record shows they had an echocardiogram within the past year that shows the heart function is OK. Absent that, if the sleep technician identifies ASV as the most appropriate therapy during the sleep study, the patient must first be seen in clinic for heart function testing and education, Parthasarathy explains.

In addition, the University of Arizona integrated health system's electronic medical record (EHR) allows Parthasarathy to identify all the health system patients currently on ASV who may need follow-up. The EHR system also can add alerts to ensure patients in an at-risk group are not prescribed ASV by mistake.

Practices that see few patients who may be ASV candidates and lack the resources to do the appropriate monitoring, should consider conferring with colleagues about the right treatment, Javaheri adds.



Notices alerted physicians to not prescribe ASV for patients with three criteria: symptomatic chronic heart failure, reduced left ventricle ejection fraction equal to or less than 45%, and moderate to severe predominant central sleep apnea. Ejection fraction refers to the percentage of blood leaving a patient's heart each time it contracts. It is usually measured in the left ventricle because that is the heart's main pumping chamber.

WHAT COMES NEXT

Douglas Bradley, MD, director of the Sleep Research Laboratory at the Toronto Rehabilitation Institute, currently heads a large multi-site randomized study called "Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure," or ADVENT-HF for short. His team is examining if ASV can reduce the rate of cardiovascular hospitalizations and death in subjects with both heart failure and sleep apnea. The study is sponsored by the Toronto Rehabilitation Institute with collaboration from the Canadian Institutes of Health Research and Philips Respironics. So far, Bradley and his team have not found the same issue of greater mortality in the ASV treatment arm that the SERVE-HF study found. Bradley says more research is the only way to truly know who ASV is viable and not viable for. "We can't ignore the facts of the SERVE trial," he says. "But I think that further testing is required in the setting of a randomized trial, like we are doing, to find out whether this effect was specific to one device or whether it was a class effect for all ASV devices."

Bradley notes that, when evaluating research, readers should keep in mind study design, overall quality of the data, and whether there are other plausible explanations for the findings. The SERVE HF-trial did have some confounding factors, he adds. For example, not all patients were compliant with their ASV therapy during the study. Some patients moved back and forth between the treatment arm and the control group. In addition, a portion of the patients in the study had heart pacemakers, which means there were actually two types of devices in the study (ASV and pacemakers). Finally, Bradley wonders if the particular device used may have made a difference as the devices do not use the same algorithm to attempt to normalize breathing patterns.

Bradley and other sleep researchers (including Parthasarathy, who is also participating in the ADVENT-HF study) have published responses to SERVE-HF where they put forth alternate theories as to why the patients on ASV could have had a higher mortality rate in the SERVE-HF study. ADVENT-HF may ultimately provide additional clarity.

While awaiting results from these two efforts, sleep physicians can also enroll their patients with heart failure and a reduced ejection fraction in a clinical study if the patient has failed on CPAP/bilevel PAP and may only be helped by ASV. Considering what is known about the links between sleep-disordered breathing and worsening of cardiac outcomes, receiving ASV as part of a carefully monitored study may indeed be preferable if the other choice is no therapy.

There are still many patients who benefit from ASV and are not in an identified at-risk group. Patients should be closely monitored to confirm they are benefiting from the therapy and, if they have heart failure, to ensure their ejection fraction does not fall to 45% or less (in which case, they should discontinue ASV use).

Clinical trials can be located through clinicaltrials.gov. Bradley notes that, after recruitment for the ADVENT-HF study was initially halted for patient safety review following publication of SERVE-HF, the study is now once again recruiting briskly.

"If you are interested in finding out if this really works or not and if different devices behave differently, then send your patients for randomization into a clinical trial," Bradley says.

Javaheri is hopeful that as clinicians become more educated about what researchers have actually found out about ASV safety, they will begin to understand the nuances about when ASV is appropriate and when it is not. At that point, the number of prescriptions for ASV may start to normalize.

"The key is education, education, education," he says. "We need to keep educating not only cardiologists but also primary care physicians that this particular study finding has come out, but it is only unique to heart failure with reduced ejection fraction. We have epidemics of opioid use, atrial fibrillation, and diastolic heart failure, and these patients deserve to have the best device that works for them. " **SR**

Lena Kauffman is a freelance writer and former Sleep Review *editor based in Ann Arbor, Mich.*

**Weinmann Medical Technology is based in Hamburg, Germany. It does not have significant sales of an ASV device in the US market.*

REFERENCES

1. Special Safety Notice: ASV therapy for central sleep apnea patients with heart failure. American Academy of Sleep Medicine. 15 May 2015. www.aasmnet.org/articles.aspx?id=5562

2. Cowie M, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med* 2015;373:1095-1105.

3. Matson M, Roy S. First Quarter 2016 Sleep Center Survey Results. *Sleep Review.* www.sleepreviewmag.com/2016/05/first-quarter-2016-sleep-center-survey-results. Accessed 5/12/16.

4. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. *J Clin Sleep Med.* 2014;10(6):637-643.

5. Opioid Painkiller Prescribing. Centers for Disease Control and Prevention. www.cdc.gov/vitalsigns/opioid-prescribing. Accessed 5/16/16.

WWW.SLEEPREVIEWMAG.COM

Download "BiPAP AutoSV for Treating Sleep-Disordered Breathing Clinical Update" at www.sleepreviewmag.com/bipap-autosv-treating-sleep-disordered-breathing-clinical-update. It includes a bibliography of research studies about ASV in specific patient populations.

Watch the free on-demand webinar "Supplementary Applications for Auto Servo-ventilation" at www.sleepreviewmag.com/supplementary-applications-auto-servo-ventilation.

Learn more at **philips.com/dreamfamily**

1 Than their prescribed mask; survey of U.S. patients
2 In a retrospective review conducted by Philips Respironics of approximately 15,000 patients using System One, those patients who used DreamMapper demonstrated 22% greater adherence to the therapy than patients who did not use DreamMapper. To see a list of compatible DreamMapper devices, go to www.sleepmapper.com/compatible.

PHILIPS
RESPIRONICS