

A close-up photograph of a male doctor with glasses, wearing a white lab coat over a blue shirt. He is smiling slightly and holding a bright red, glossy heart-shaped object in the palm of his right hand, which is extended towards the camera. The background is softly blurred, showing a clinical setting.

HOW TO
**Treat
Sleep
Apnea**
IN YOUR
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Failure
Patients**

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HOW TO **Treat Sleep Apnea** IN YOUR **Heart Failure Patients**

New findings on ASV use in particular patient groups mean the best sleep clinicians weigh more data than ever in determining what device to try.

By Lena Kauffman

In 2015, SERVE-HF study data led to a profound shift in the prescribing of adaptive servo-ventilation (ASV) for congestive heart failure patients with central sleep apnea. The study identified a statistically significant increased risk of cardiovascular mortality for a subset of patients who received ASV therapy compared to those in the control group.¹ Based on findings from this 1,325-patient study, ASV is contraindicated for patients with a left ventricular ejection fraction (LVEF) of less than or equal to 45% and predominant central sleep apnea (CSA).²

At the same time, prescribing ASV to patients who are not in the contraindicated group—such as those with central or complex sleep apnea and heart failure but with a preserved ejection fraction—became more intricate.

Clinicians can prescribe CPAP, but research indicates that for nearly half of patients with CSA, continuous positive

airway pressure does not adequately control their sleep-disordered breathing.³ Similarly, in patients who have both obstructive and central sleep apnea (also known as “complex sleep apnea”), CPAP is ineffective or even causative for the appearance of the central apneas. ASV typically works better—but the potential benefits must be balanced against a long-term need to also review their clinical status at regular intervals to ensure that heart failure does not evolve, placing them into the contraindicated population.

Sorting patients into those who might benefit and those who might be harmed is the type of complexity in prescribing confronting many specialties today. Medical treatments are increasingly tailored to specific patients’ needs in a “precision medicine” world. As a sleep medicine physician, managing this complexity is challenging, but it is also a sign of how medicine is changing to serve

patients better, says Teofilo Lee-Chiong, MD, professor of Medicine at National Jewish Health in Denver and at the University of Colorado Denver School of Medicine, as well as chief medical liaison at Philips, an ASV device developer.

“The science of medicine has changed tremendously,” Lee-Chiong says. “Part of it is driven economically. Part of it is driven by access to information by our heart failure patients and their families. But it is also partly because the way we have practiced medicine was inadequate for the needs of the patients.”

The traditional prescriptive approach to medicine is one where patients see specialists individually and each prescribes a standard treatment for the diagnosed conditions—according to clinical guidelines without a lot of discussion between the various specialists or between specialists and the patient and patient’s family. But research is



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In a precision medicine world, sleep physicians must weigh benefits and harms of therapy modalities using each patient's specific circumstances.

increasingly leading to more personalized, precise treatments as well as greater choice for patients. Providing the highest level of care for sleep medicine patients will increasingly require staying informed about the latest research developments, sharing decision making with patients to take into account their goals and desires, and working as part of multidisciplinary patient management teams, Lee-Chiong says. In sleep, ASV is one example of this in action.

“Every clinician should advocate first and foremost for the patients,” he says. “I think it’s our duty and our responsibility to manage our patients the best we can. And the only way we can do that is to keep updated or abreast of the ongoing research. We cannot simply stop learning. So we need to understand and keep up with the ASV research as it unfolds.”

WHY USE ASV

There is considerable evidence that untreated OSA and CSA pose risks.^{4,5,6} Patients who have untreated sleep-disordered breathing typically either have or are at risk for:

- Intermittent hypoxemia–reoxygenation;
- Hypercapnia–hypocapnia;
- Increased sympathetic activity;
- Reduced LVEF;
- Excessive arousals;
- Shift to light sleep stages, with many being unable to reach REM sleep;
- Large negative swings in intrathoracic pressure;
- Excess morbidity;
- Greater hospital readmission rates; and
- Higher mortality rates.

And then there is an opportunity to improve health-related quality of life. When sleep apnea is controlled and patients sleep better, there is often a marked improvement in quality of life.⁷ Patients have more energy, and this in turn may help them tackle difficult lifestyle changes needed to get back to activities they enjoy.

An estimated 5.7 million people in the United States have heart failure,⁸ and between 40% and 60% of them have a preserved ejection fraction.^{9,10} Having a LVEF above 45% means that ASV is considered safe to adequately control their apnea-hypopnea index (AHI), provided they are regularly monitored for changes in cardiovascular status. But the remaining group faces challenges because there is not the same range of treatments available for them, explains Salma Imran



Trying to understand the physiological process behind the findings could identify whether the results of SERVE-HF were due to a product class effect or to a device-specific effect.

Patel, MD, MPH, assistant professor of medicine at the University of Arizona College of Medicine in Tucson.

Among those with sleep apnea and heart failure with a reduced LVEF, around a third will have CSA and another 12% to 30% will have OSA.^{11,12} (By comparison, heart failure patients with preserved LVEF have a lower incidence of CSA, 23%, but a higher incidence of OSA, 25%.¹³) The obstructive sleep apnea group usually responds well to CPAP, but many in the central sleep apnea group do not have their AHI adequately controlled with CPAP alone.³ “We need other therapies to treat patients who have heart failure with CSA,” Patel says.

An analysis of insurance claim data on 1,324,414 heart failure patients conducted by Patel and colleagues showed a statistically significant reduction in hospitalizations in patients on all types of

positive airway pressure therapy (bilevel, CPAP, and bilevel-spontaneous timed) compared to patients without positive airway pressure therapy.¹⁴ What’s more, preliminary results from a study on US Veterans Administration patients hospitalized with acutely decompensated heart failure show a reduction in 30-day hospital readmission rates for those who received ASV therapy compared to the patients who only received usual medical management.¹⁵

Additionally, it should be noted that the Cardiovascular Improvements with Minute Ventilation-targeted Adaptive Servo-Ventilation Therapy in Heart-Failure (CAT-HF) trial published in 2017 did not find improved cardiovascular outcomes for hospitalized patients who had moderate-to-severe sleep-disordered breathing and received ASV at the six month follow-up interval. But the researchers were intrigued by how ASV was linked with

substantial reductions seen in left atrial volume among patients with both reduced and preserved LVEF, which could indicate improved diastolic function.¹⁶

For Patel, her own findings and those of others underscores the urgency of finding out why ASV was associated with higher mortality in some patients in the SERVE-HF study and figuring out if it is a correctable issue so that ASV might be put back into the mix for all heart failure patients with sleep-disordered breathing.

KNOWING WHAT WE DON'T KNOW

One of the biggest questions ASV prescribers face is why a treatment that was so helpful for some patient groups was also linked to a higher mortality rate in a subset of congestive heart failure patients with predominant CSA. Sairam Parthasarathy, MD, professor of medicine, chief of the Division of Pulmonary,

Allergy, Critical Care and Sleep Medicine, and director of the Center for Sleep and Circadian Sciences at the University of Arizona, became interested in finding out.

A failed experiment, meaning one where you do not get the results you were expecting, is not really a failure or the end of the story, he believes. Rather, it is a clue to the next important finding.

Parthasarathy and Patel have been investigating whether there are features of the ASV device used in the SERVE-HF study that might lead to theories behind the results. In March of 2019, Parthasarathy and colleagues published results of a comparison of four ASV devices,¹⁷ including the ASV device utilized in the SERVE-HF trial. He had 14 patients with CSA with LVEF of greater than 45% receive ASV over four nights in a sleep lab. Each night, the device was swapped and then hidden so that neither the patient nor the sleep study scorers could tell which device was being used. Everything but the device, including the mask interface and device settings, was the same each night. What the researchers found was different physiological performances between the devices. Specifically, the device in the SERVE-HF trial had the greatest minute ventilation and respiratory rate of all the tested devices (including a more technologically advanced later-generation device from the same manufacturer).

“What we found was that the minute ventilation, not during sleep but during wakefulness, was different in those devices,” he says. “Why does that matter? It matters because when you go to sleep, you’re not completely 100% asleep...you wake up transiently and you slip right back to sleep. That’s exactly what was happening in these patients. And when it happened, the minute ventilation suddenly bounced up by about 30% to 40% and then tried to settle down when they fell back asleep. But that kind of oscillation causes an instability in the breathing that of itself can perpetuate central apnea, and the machine is programmed to take care of central apnea. So what it does is it gives more pressure and more ventilation to reduce the instability. But every time the patient wakes up, now their breathing can overshoot even more.

And because the breathing is unstable, the machine cranks up a little bit higher. So what’s happening is a closed loop. It’s like a runaway phenomenon.”

Newer devices have more advanced algorithms with guardrails on them to prevent this type of feedback loop from leading to over-ventilating the patient, Parthasarathy explains. But prior to 2015, when the SERVE-HF study was conducted, this potential issue had not yet been fully understood.

Finding out if the device could have been over-ventilating patients is important, Parthasarathy says, because it opens up at least two possible theories on how the device might have harmed patients. One is that the greater minute ventilation led to more pressure from the lungs on the heart. In someone who has a weak heart, this added pressure may interfere with fluid coming back into the heart so that the heart cannot refill with blood between beats the way it is supposed to.

“It is the same reason women who are pregnant and full term are advised to sleep on their side instead of their back because the pressure of the baby can obstruct the veins in the back of the abdominal cavity and reduce the amount of blood that goes to the heart so much that a woman can pass out just lying down, especially if she is carrying twins or triplets,” Parthasarathy says.

Another theory is that over-ventilation might make the body blow off too much carbon dioxide (CO₂). Carbon dioxide is acidic and if there is less of it in the blood, the blood becomes more alkaline, which in turn can interfere with the electrical signals in the heart and brain. This pathway of hypocapnia (respiratory alkalosis) leading to hypokalemia leading to cardiac arrhythmias is well known among cardiologists.

“When the blood gets very alkaline, the electrical system in the heart can cause arrhythmias, the electrical system in the neurons in the brain can cause seizures,” Parthasarathy says. “We know this because when we take care of ICU [intensive care unit] patients on ventilators, and a patient goes into an arrhythmia or other things, we look at where their blood alkaline level is and see if we are blowing off too much CO₂. If so, we go back down on the minute ventilation

so that we make sure that we are not inciting that particular situation.”

Trying to understand the physiological process of how ASV could be correlated with an increased mortality will both help make future ASV devices safer and could show whether the results of the SERVE-HF study were due to a product class effect (meaning it is common to all ASV devices) or due to a device-specific effect (meaning related to a particular feature of a single device and not necessarily true for all ASV devices).

APPROACHES TO COMPLEX PRESCRIBING

Parthasarathy, who is also medical director of the Center for Sleep Disorders at Banner — University Medical Center in Tucson, sees staying on top of the latest research developments and clearly explaining to patients what we know and don’t know about the effect of ASV treatment on heart failure as an important part of responsibly caring for these patients. However, he also recognizes that different physicians will have different approaches to prescribing ASV and managing the complexity of when and when not to prescribe it.

It will be a while, he says, before sleep medicine is as comfortable with complex prescribing scenarios as specialties like oncology are, where treatments are increasingly tailored to patients’ specific tumor characteristics and unique genetic risk factors. He is confident sleep medicine will get there because the alternative, in his view, is practicing less than the best quality medicine. “It’s doable but it’s going to get very complex and people better get ready for it,” he says. “It’s going to get hot in the kitchen, and if you can’t handle it, get out of the kitchen.”

Lee-Chiong agrees. “When you look at the ASV dilemma, we have a technology that works for periodic breathing but might have different outcomes for different patients,” he says. “So what we need today is (A) to figure out whether we can improve the ASV technology and (B) to figure out whether we can identify patients who will benefit versus those who cannot benefit or who would actually suffer from, the treatment. It is a rather complex problem.”

In the clinical setting, Parthasarathy and Patel manage this with informed decision making discussions with their patients and close ongoing patient monitoring. It is very important not to prescribe ASV for any patient with heart failure and a reduced LVEF, they say. But both do prescribe ASV for heart failure with a preserved ejection fraction as it is not contraindicated in that group and research supports positive outcomes like reduced hospital readmissions.

Parthasarathy is aware that some physicians categorically refuse to prescribe ASV. He says, “They stay miles away from this device being adopted into their practice. But in those people for which it is not contraindicated, I feel that they’re being shorted for a particular treatment if we don’t offer it. We talk about precision medicine in healthcare, but when it comes to practicing precision medicine, it is a lot of hard work and so some clinicians don’t end up doing it...Here’s an opportunity to practice precision sleep medicine.”

When a patient is not in the contraindicated group and could potentially have their AHI better controlled with ASV, Parthasarathy has an open discussion with them about the potential risks and benefits. He explains that a large study found a risk of higher mortality for patients who have heart failure but only in a subgroup of which they are not currently a part. He then stresses that unless new findings come out that would change the earlier study’s findings, it is important their heart function be tested regularly.

If their ejection fraction reduces, they could become a part of the group that ASV may be harmful for and they will need to stop using the device.

“If you ever have a change in your heart condition or medical condition that relates to the heart, then this contraindication may now apply to you, in which case you need to talk to your doctor and ask to be referred back to us so that we can actually do an assessment,” Parthasarathy says he tells patients.

Although some clinicians may worry that patients may not understand and be able to follow their more complex directions, in Patel’s experience, this is not something that has been a problem. Indeed, she’s found patients are typically open to frank discussions about research and how to weigh potential risks and benefits.

“Most patients are pretty sophisticated and they can understand basic stuff that we explain in terms like, ‘You have sleep apnea, you have heart failure, but if your heart pumping function isn’t good, then maybe this device isn’t a good fit you,’” she says. “They can generally follow that train of thought and then you



Patients may appreciate having a conversation with you about how study findings relate to their sleep apnea subgroup.

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Sleep Medicine Could Lower Cardiovascular Disease Costs

According to the Centers for Disease Control and Prevention, heart disease is the leading cause of death in the United States, with 1 in 4 deaths having heart failure as a contributing cause. All total, about 610,000 people die of heart disease in the United States each year.¹⁸

US adults living with diagnosed heart disease now number 28.2 million, which is more than 10% of the population.¹⁹ Treating all of these patients is costly. In 2011, the American Heart Association estimated medical expenditures related to heart disease were growing at a rate of about 6% per year and that by 2030 direct medical costs related to heart failure will reach \$92.6 billion (adjusted to 2019 dollars).²⁰

There is evidence that addressing sleep-disordered breathing in heart failure could be part of

the broad range of solutions needed to tackle the cost problem. Researchers have recently noted a link between treatment of sleep-disordered breathing in heart failure patients and a reduced rate of hospitalizations,^{14,15} which in turn may mean lower healthcare costs.

Indeed, a 2016 independent analysis commissioned by the American Academy of Sleep Medicine noted that about 3.1 million patients have both sleep apnea and heart disease and they collectively contribute \$6.7 billion to healthcare costs.²¹

Since there is a known link between these conditions, management of sleep-disordered breathing in patients with heart failure could reduce costs related to the care of these very medically complex patients.

can share research articles with them and say, 'You know, this is why, or this is why not.' Just having that transparency and conversation, I think makes it so much easier to take care of patients. And that's what I would recommend to everybody, because even though we are physicians and we're supposed to know everything in medicine, there's a lot of unknowns."

NOT THE END OF THE STORY

New research will continue to expand on the ASV story. Indeed, a large multi-center study enrolling up to 800 patients is currently examining whether ASV improves cardiovascular outcomes in heart failure patients with sleep apnea. Results from the ADVENT-HF trial are expected in June 2020, and although the study results are blinded from both participants and the investigators until the end of the study to avoid bias, so far compliance rates in this study are better than in previous similar studies, according to lead investigator T. Douglas Bradley, MD, at the

University of Toronto. Furthermore, the study's data safety monitoring board has reviewed the results five times since 2015 when the SERVE-HF study came out and not found any safety concerns that would stop the study.

Parthasarathy and Patel are retrospectively and prospectively investigating the possible physiologic impacts of ASV in patients with and without heart failure and are eager to share the findings of their studies, when available.

When you look at how much the practice of sleep medicine has changed over the years, it is evident that it will continue changing, shifting, and evolving, notes Lee-Chiong.

"When somebody comes in with a problem falling asleep, we gave them barbiturates," he says. "Or 20 years ago, we gave them benzodiazepines. Now we rarely do that stuff because we have become better over time. What used to be accepted care is now no longer part of the regimen of solutions we give our patients, and I can almost guarantee that

what we think is the best practice today will in the next five or 10 years no longer be so because science is progressive. We will abandon certain therapies and pick up new ones."

For now, what clinicians should do is monitor patients on ASV closely for both benefits and harms, talk with patients about what is important to them in both quality of life and length of life, realize that there is no one-size-fits-all approach (as devices and patients vary), and finally keep up with new research, Lee-Chiong advises.

"Every clinician who is using ASV or planning to use ASV for periodic breathing in heart failure should be aware of SERVE-HF and should join the discussions regarding SERVE-HF," he says. "But they should also understand that the story of ASV did not end with SERVE-HF." **SR**

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