Sleep-disordered breathing (SDB) with predominant obstructive or central sleep apnea (OSA/CSA) with Cheyne-Stokes respiration (CSR) is a common, but underrecognized and underappreciated, comorbidity in patients with heart failure (HF). Regardless of the type of HF (systolic or diastolic) or its etiology (ischemic, non-ischemic, valvular etc), the prevalence of SDB is remarkably high in this patient group, at 70–76%. Even more so in HF than in the general population, OSA and CSA in particular are independently associated with an impaired prognosis. This review details the pathophysiology of CSA-CSR in HF, highlights the challenges and tools available for diagnosis, explains the concept of adaptive servoventilation (ASV) therapy, and summarizes the existing literature on the use of ASV therapy in HF patients in general and HF with reduced ejection fraction in particular. (Circ J 2012; 76: 2305–2317)

Key Words: Adaptive servoventilation; Cheyne-Stokes respiration; Heart failure; Sleep-disordered breathing

Sleep-Disordered Breathing (SDB) in Heart Failure (HF)
SDB is an under-recognized but highly prevalent comorbidity in patients with HF, and has an important impact on prognosis. The prevalence of SDB (either predominantly obstructive sleep apnea [OSA] or central sleep apnea [CSA]) is up to 70% and 76% in patients with diastolic and systolic HF, respectively.1,2

OSA has been shown to be an independent risk factor for the development of HF,3 with a greater influence in men than in women.4 As the severity of HF increases and cardiac function decreases, there is an increase in the prevalence of CSA with Cheyne-Stokes respiration (CSR).1,2,5 and this may become 1 of the most important comorbidities in patients with advanced HF (Figure 1). The presence and severity of CSA-CSR is thought to mirror cardiac (dys-) function,6,7 and effective treatment of HF improves CSA-CSR.7,8 Overall for HF patients with reduced ejection fraction (EF), SDB in general,9 as well as OSA10 and, in particular, CSA11 are known to be independently associated with a worse prognosis. This is even the case for patients receiving maximum HF therapy, including cardiac resynchronization (CRT), for whom CSA-CSR and OSA can have a proven major prognostic impact.12

Definition of OSA and CSA Including Cheyne-Stokes Respiration
OSA is characterized by a partial or complete collapse within the upper airways with sustained or increasing breathing efforts, whereas absent or attenuated respiratory movements are the main feature of CSA. To be classified as an apnea, airflow has to be completely absent or reduced by ≥90% for ≥10 s. Hypopnea is defined as a ≥10-s lasting reduction in airflow amplitude of either ≥30% accompanied by oxygen desaturation of ≥4% or a ≥50% decrease in breathing amplitude with ≥3% oxygen desaturation or associated arousal.13 The apnea-
hypothesis index (AHI) describes the number of classified respiratory events per hour of sleep.

Besides these clear differences in apnea type, CSA with CSR is defined as ≥3 consecutive cyclical crescendo and decrescendo changes in breathing amplitude (Figure 2) and ≥10 consecutive minutes or ≥5 instances of central apnea or hypopnea per hour of sleep.13

**Diagnosis of SDB in HF Patients**

There are no reliable medical history questions or specific questionnaires available to exclude or diagnose OSA or CSA-CSR in HF patients.14,15 This may be, in part, because patients with HF have less subjective daytime sleepiness despite significantly reduced sleep time.14,16,17 Thus, the absence of subjective sleepiness is not a reliable means of ruling out OSA or CSA-CSR.15

To exclude SDB in HF patients, some device-based sleep apnea screening needs to be performed. Everyday cardiac signals and devices can be used to at least rule out severe SDB.18 This includes ECG and Holter ECG recordings,19-22 as well as pacemaker-derived signals.23 In addition, simple, fully-automated systems analyzing nasal airflow, respiratory efforts and/or pulse-oximetry are available.24 It must be emphasized that the latter screening tools have a proven ability to rule out sleep apnea, usually having good sensitivity but only moderate specificity.25 To date, sleep medicine and cardiac societies recommend multichannel polygraphy recordings26 or polysomnography (PSG)13,27 to definitively diagnose sleep apnea and define disease severity.

**Pathophysiology of CSR**

The appearance of CSR indicates an impaired respiratory control system (respiratory instability), a dysynchronization of the heart, the lung and the brain.28 Most HF patients with nocturnal CSA-CSR hyperventilate even while awake during the daytime.8,28,30 This hyperventilation may be a result of stimulation of pulmonary vagal irritant receptors by pulmonary congestion in combination with enhanced central and peripheral chemoreceptor sensitivity and prolonged circulation time.31,32

In HF patients with CSA-CSR, carbon dioxide (CO₂)-dependent apnea thresholds are altered,33 making them more sensitive to apnea with decreasing CO₂ partial pressure (pCO₂). Therefore, even a small additional increase in ventilation (eg, as a result of any kind of arousal) can provoke a central apnea. While the patient is apnoeic, pCO₂ rises again, until exceeding the apnea threshold again. Several mechanisms now contribute to inappropriate (crescendo) ventilation: an important one is increased receptor sensitivity to CO₂,32 and another is impaired feedback mechanisms because of prolonged circulation time in cardiac failure.34 Figure 3 shows a simplified scheme for the pathophysiology of CSA-CSR in HF patients.

Many other factors can contribute to and influence this pathophysiologic pathway. However, the key elements are low pCO₂ and hyperventilation, which differentiate CSA-CSR from OSA and influence the choice of therapeutic strategies (Figure 4). To stabilize respiration in CSA-CSR, reduced or low-normal pCO₂ should be raised or stabilized to mid-normal values. In contrast, in OSA with elevated or high-normal pCO₂, therapeutic interventions are designed to decrease or prevent a sleep-associated inappropriate increase in pCO₂.

**Adaptive Servoventilation Therapy (ASV)**

The concept of ASV was introduced by Teschler et al.35 The
Cheyne-Stokes Respiration in HF

**Figure 3.** Simplified pathophysiology pathway of Cheyne-Stokes respiration (CSR). Chronic hyperventilation characterizes CSR. Arousals from sleep may further exaggerate ventilation leading to a drop in pCO$_2$ below the apneic threshold. This CO$_2$-dependent apnea threshold is altered in chronic heart failure (CHF) patients with CSA-CSR; essentially, there is only a small range between eupnea and apnea during sleep. As soon as the pCO$_2$ falls below this threshold, a central apnea occurs until CO$_2$ accumulates and exceeds the threshold again. An increased sensitivity of central CO$_2$ receptors now leads to an overshoot in ventilation (crescendo) until ventilation decreases (decrescendo) again with falling pCO$_2$. Many factors such as age, sex, sympathetic nervous tone etc. are influencing the respiratory control center and respiration itself. In heart failure, an impaired feedback control because of delayed circulation time might contribute significantly as well. Recent studies propose that a potential overnight fluid shift from the periphery towards the lungs might deteriorate pulmonary congestion, exaggerating J-receptor stimulation and ventilation. PCWP, pulmonary capillary wedge pressure.

**Figure 4.** Simplified scheme of the differences in pathophysiology, clinical appearance, therapeutic strategies and goals in obstructive (OSA) and central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR). Often heart failure (HF) patients with OSA present with high-normal or slightly elevated pCO$_2$, whereas HF patients with CSA-CSR show low-normal (<38mmHg) or even decreased pCO$_2$. In OSA that may be a trend towards a risk of hypercapnia because of a decrease in ventilation, for HF patients with CSA-CSR that indicates chronic hyperventilation.
Acute Effects of ASV in Congestive HF

Use of PAP treatment in patients with HF can cause an unexpected drop in blood pressure (BP). At least a transient drop in mean arterial pressure (to ≤70 mmHg) has been documented in approximately 10% of HF patients starting PAP therapy. A major risk factor for this hypotensive effect is low baseline BP. However, it remains to be determined whether this drop in BP is sustained and/or this hypotensive reaction has a negative effect on patients’ compliance with PAP therapy.

Haruki et al investigated the effects of 30 min of ASV treatment in HF patients. There were clear reductions in heart rate and BP. In addition, echocardiography documented an increase in stroke volume and cardiac output, leading to decreased systemic vascular resistance. The authors hypothesized that ASV reduces left ventricular (LV) afterload by increasing intrathoracic pressure and reducing LV transmural pressure. However, their results are based on a small number of patients (n=30), and some showed no relevant change in cardiac output and 2 even showed a small decrease. As previously reported for continuous PAP (CPAP), an increase in cardiac output during ASV might be dependent on LV filling pressures. HF patients with elevated filling pressures might show a beneficial increase in cardiac output during ASV, whereas no appreciable changes in cardiac output may be seen in those with low filling pressures.

To date, most studies investigating the acute hemodynamic effects of PAP therapy used low and fixed levels of end-expiratory pressure (EEP). However, new generations of ASV devices use algorithms that allow automatic adjustments of EEP over a wide range. Therefore, it is recommended that symptoms and hemodynamic data (heart rate and BP) should be monitored during the initiation of any PAP therapy in HF patients.

Long-Term Effects of ASV in HF Patients

Previous studies looking at SDB in patients with HF have largely focused on reversal of sleep apnea and associated neurological, respiratory and sleep medicine findings only. Although important, these parameters are really only surrogate endpoints in patients with HF, and the most important outcomes are actually cardiovascular parameters. Thus, when investigating SDB in HF patients it is important to use a combination of endpoints, because an improvement in SDB does not necessarily equate with beneficial effects on HF symptoms, quality of life (QOL) or cardiac function.

A post-hoc analysis of the CANPAP (Canadian Continuous Positive Airway Pressure) Trial suggested that effective suppression of nocturnal respiratory events was required to improve the prognosis of HF patients with CSA-CSR. A residual AHI of more than 15/h did not appear to be sufficient to improve outcome. Therefore, at our institution we recommend reducing the AHI to <10/h during ASV.

In the first study of ASV, patients preferred ASV to all other types of PAP treatment. In addition, better compliance with ASV than with CPAP has been documented after 6 months of treatment. In the latter study, QOL improved with either mode of nocturnal ventilation, but was better in ASV-treated patients and there was a positive correlation between compliance and

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Figure 5. Concept of adaptive servoventilation (ASV). Low levels of (continuous) end-expiratory positive airway pressure (EPAP) provide positive hemodynamic effects on the failing heart, avoid potential passive airway narrowing or closure at the end of a central apnea. Spontaneous ventilation is supported with varying amounts of inspiratory pressure support (IPAP). If spontaneous ventilation ceases, ASV will increase inspiratory support (pressure) or provide back-up ventilation using an adjusted back-up respiration rate. If spontaneous ventilation then increases, support will gradually reduce again. Although the details of available ASV algorithms are not known, target ventilation is lower than the long-term averaged spontaneous ventilation. This reduces nocturnal hyperventilation as documented by normalization in pCO₂.
improvement in QOL.53

Improvements in HF symptoms and QOL have been reported in several other studies (Table 1). The first observational studies on long-term ASV treatment of CSA-CSR in HF patients demonstrated important beneficial effects on QOL, HF symptoms (NYHA functional class), natriuretic peptide concentrations, LVEF, 6-min walk test and cardiopulmonary exercise test results.30,53-64 In one trial, a sustained and important reduction nocturnal respiratory events in patients compliant with ASV was documented. The AHI was reduced from 37.4±9.4/ h to 3.9±4.1/ h (P<0.001), N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations decreased from 2,285±2,192 pg/ml to 1,061±1,293 pg/ml (P=0.01) and LVEF increased from 28.2±7% to 35.2±11% (P=0.001). At the same time, mean NYHA functional class improved from 2.43±0.50 to 1.93±0.75 (P<0.001) and workload and oxygen consumption improved (eg, predicted VO2 peak increased from 58±12% to 69±17%; P=0.007).64 A non-randomized controlled trial confirmed the findings of the observational study and also documented beneficial effects on cardiac remodeling (eg, a decrease in LV end-diastolic diameter) and improved respiratory control.30 The acute effects of ASV in HF therefore appear to include a decrease in LV afterload and an increase in forward stroke volume. During chronic therapy, reversal of cardiac remodeling is accompanied by a reduction in (functional) mitral regurgitation.43,64 This might include a decrease in LV filling pressures and less activation of pulmonary irritant J-receptors, a key element in the pathophysiology of hyperventilation in CSA-CSR. Thus, the final result might be more stable respiratory control with improved respiratory control.30

OSA and CSA-CSR, in particular, are associated with increased sympathetic drive,66 which is independently associated with poor prognosis in HF.57,68 In combination with other contributing factors such as oxygen desaturation, increased LV wall tension and afterload, and BP changes, this may lead to malignant ventricular arrhythmias, which have been documented in these patients.69 Treatment with ASV may reduce the risk of life-threatening arrhythmias,70 at least in part secondary to a decrease in sympathetic nervous tone.71 This may contribute to the improved survival of HF patients seen in the first studies investigating PAP therapy in general,92 and ASV treatment in particular.65-73

Although the aforementioned results are promising, there are no published randomized controlled trials (RCTs) on the potential beneficial effects of ASV treatment with respect to important outcome endpoints such as rehospitalization for HF decompensation or death. However, a number of RCTs are currently underway to help answer this question. One is the “Treatment of Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (Serve-HF)” study (ClinicalTrials.gov Identifier: NCT00733343). An associated substudy (ClinicalTrials.gov Identifier: NCT011464592) is using echocardiography and/or cardiac MRI effects to investigate potential mechanisms for clinical benefits. Another RCT (ADVENT-HF) is investigating the “Effects of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admission in Heart Failure” independently of a predominance of central or obstructive respiratory events (ClinicalTrials.gov Identifier: NCT01128816).

Although all ASV devices look the same, their underlying technology and algorithms vary substantially and they can not be used interchangeably. Thus, comparative studies are warranted to specify short- and long-term efficacy, advantages and disadvantages.74

SDB in Diastolic HF

More than 50% of all HF patients have diastolic disease.75 Diastolic HF affects more women than men, and is associated with a substantially impaired prognosis.76,77 The prevalence of SDB in diastolic HF is comparable to that in systolic HF, with approximately 70% of patients having ≥2 AHI episodes/h and approximately 30% showing CSA-CSR respiratory patterns. As for systolic HF, the occurrence of CSA-CSR in particular seems to be related to the degree of impaired diastolic function: the greater the impairment of LV filling, the higher the prevalence and severity of CSA-CSR.1 However, there is a lack of convincing evidence of the prognostic effect of SDB in general, and OSA and CSA in particular, for patients with diastolic HF.

In the past 2 years, several published studies evaluated the effect of ASV in HF patients independent of impaired or preserved EF (Table 2). Because of the heterogenic group of HF patients investigated, the results need to be interpreted with caution and cardiac parameters are even harder to follow. However, at least hints towards an improvement in cardiac function are provided: symptoms, BNP concentrations and, in some studies, exercise capacity improved.30,49,51,65

In a first study on ASV treatment of CSA-CSR in a group of pure and, according to ESC guidelines, defined diastolic HF patients, treatment was associated with significant improvements in symptoms, exercise capacity, and NT-proBNP concentrations.78 Although being non-randomized, this study was controlled and the first in this field. However, in the end, it represents a pilot study and a RCT is clearly warranted to confirm these results.

Complex Sleep Apnea Syndromes (complSA)

complSA is defined as the emergence of CSA during CPAP treatment under initial diagnostic PSG in patients with predominantly mixed sleep apnea and OSA.79 One study documented respiratory control instability in these patients, comparable to that seen in those with HF and primarily CSA-CSR.80 It seems likely that patients with complSA have undiagnosed HF, kidney disease or stroke. In a well-defined group of 192 HF patients with moderate to severe OSA, 34 (18%) went on to develop complSA.80 In terms of suppression of nocturnal respiratory events, ASV has been shown to be more effective than CPAP.81,82 Regarding HF symptoms and cardiac performance, ASV has been shown to improve NYHA functional class, NT-proBNP concentrations and oxygen uptake during cardiopulmonary exercise testing. Moreover, as in HF patients with CSA-CSR, there is a parallel improvement in respiratory control.80

Alternatives to ASV in the Treatment of CSA-CSR in HF Patients

This review focuses on the treatment of CSA-CSR in HF patients using ASV. A systematic review and comparison of all supposed alternative treatments goes well beyond this review, but a recent review and 2 up-to-date meta-analyses are available, providing an overview of alternative treatment options.83-85

In summary, medical treatment is not recommended as a standard intervention. The medications used include acetazolamide and theophylline.86-89 Small studies using these drugs have shown some beneficial effect in terms of reduced central respiratory events, but no effect on HF parameters. Because of
### Table 1. Studies of ASV in Stable HF Patients With Reduced EF and SDB

<table>
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<tr>
<th>Study</th>
<th>Device</th>
<th>Study design</th>
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<th>SDB inclusion criteria</th>
<th>HF inclusion criteria</th>
<th>Follow-up</th>
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<tr>
<td>Teschner et al (2001)⁹⁵</td>
<td>AutoSet CS³, ResMed</td>
<td>Single-night, randomized, cross-over</td>
<td>Oxygen, CPAP, BiLevel vs. ASV (n=14)</td>
<td>ODI3% &gt;15/h; predominant CSA-CMR; &lt;10 obstructive events/h</td>
<td>Stable HF outpatients, dilated hearts, reduced fractional shortening</td>
<td>Single night</td>
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<td>Peppenell et al (2003)⁹²</td>
<td>AutoSet CS³, ResMed</td>
<td>Prospective, parallel, randomized, double-blind</td>
<td>Therapeutic vs. Subtherapeutic ASV (n=30)</td>
<td>ODI3% &gt;10/h; CSA-CMR</td>
<td>NYHA II – IV*</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Schädicl et al (2004)⁷⁴</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>ASV group (n=20)</td>
<td>cAHI &gt;15/h</td>
<td>NYHA II+III, stable HF and EF 20–50%</td>
<td>3 and 12 months</td>
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<td>Töpfer et al (2004)³⁷</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>ASV group (n=11)</td>
<td>CSR with AHI &gt;20/h</td>
<td>NYHA II – IV, stable HF and EF &lt;40%</td>
<td>6 weeks</td>
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<tr>
<td>Philippe et al (2006)³³</td>
<td>AutoSet CS³, ResMed</td>
<td>Prospective, parallel, parallel, multicenter</td>
<td>ASV (n=12) vs. CPAP (n=13)</td>
<td>AHI &gt;15/h; CSA-CMR (&gt;80% central events)</td>
<td>NYHA II – IV; stable congestive HF, EF ≤45%</td>
<td>3 months and 6 months</td>
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<tr>
<td>Szollosi et al (2006)⁸⁵</td>
<td>AutoSet CS³, ResMed</td>
<td>Single-night, randomized, cross-over</td>
<td>Control night vs. DS vs. ASV</td>
<td>CSA with AHI &gt;5/h and &lt;10% obstructive events</td>
<td>NYHA II+III, EF &lt;50% and MVO₂ in CPX testing &lt;30 ml·kg⁻¹·min⁻¹</td>
<td>Single night</td>
</tr>
<tr>
<td>Oldenburg et al (2008)³⁹</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>ASV group (n=29)</td>
<td>AHI ≥15/h with &gt;80% central events</td>
<td>NYHA ≥ II stable HF and EF ≤40%</td>
<td>5.8±3.5 months</td>
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<td>Fietze et al (2008)³¹</td>
<td>AutoSet CS³, ResMed</td>
<td>Randomized</td>
<td>BiLevel-ST (n=20) vs. ASV (n=17)</td>
<td>CSR with RDI &gt;15/h, &lt;20% obstructive events, &lt;10% snoring sounds</td>
<td>NYHA II – III, stable HF, EF &lt;45%</td>
<td>6 weeks</td>
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<td>Hastings et al (2010)³⁵</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>Patients declining ASV treatment (n=8) vs. ASV treated (n=11)</td>
<td>OSA and CSA with AHI &gt;15/h</td>
<td>NYHA II +III, stable HF, EF &lt;45%</td>
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<td>Kasai et al (2010)¹¹²</td>
<td>HeartPAP, Respironics</td>
<td>Prospective, randomized, multicenter</td>
<td>CPAP (n=15) vs. ASV (n=15)</td>
<td>AHI ≥15/h with coexisting OSA (obstructive AHI ≥5/h) and CSA-CMR</td>
<td>NYHA ≥ II, stable HF, EF &lt;50%</td>
<td>3 months</td>
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<tr>
<td>Koyama et al (2010)³¹</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>Non-ASV (not tolerating; n=7) vs. ASV- tolerating patients (n=10)</td>
<td>AHI≥15/h with majority of central events or symptoms related to sleep apnea</td>
<td>NYHA II or III; history of worsening of HF or EF &lt;55%</td>
<td>4 weeks</td>
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<tr>
<td>Campbell et al (2011)⁴¹</td>
<td>AutoSet CS³, ResMed</td>
<td>Randomized, cross-over</td>
<td>ASV vs. overnight oxygen (2 L/min) (n=7)</td>
<td>AHI &gt;15/h with predominant CSA-CMR (&gt;50%)</td>
<td>Clinically stable, EF &lt;50%</td>
<td>8 weeks for each treatment with 3-week washout between the next page.</td>
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<tr>
<td>Oldenburg et al (2011)³⁸</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>Control group (includes non-ASV-treated, non-ASV-tolerated and non-ASV-compliant patients, n=59) vs. ASV-tolerant and -compliant patients (n=56)</td>
<td>AHI≥15/h with majority of central events (&gt;80%)</td>
<td>NYHA ≥ II stable HF and EF ≤40%</td>
<td>6.7±3.2 for ASV and 6.2±3.1 months for control group</td>
</tr>
<tr>
<td>Hakuri et al (2011)⁴¹</td>
<td>AutoSet CS³, ResMed</td>
<td>Observational</td>
<td>Non-ASV (not tolerating; n=15) vs. ASV-tolerating patients (n=15)</td>
<td>AHI ≥15 and oAl ≤5/h</td>
<td>NYHA ≥ II stable HF with EF &lt;50%</td>
<td>Mean: 24 weeks</td>
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<tr>
<td>Hetland et al (2011)³⁸</td>
<td>AutoSet CS³, ResMed</td>
<td>Randomized, controlled</td>
<td>Non-ASV (n=15) vs. ASV (n=15)</td>
<td>Sleep in CSA-CMR &gt;25%</td>
<td>NYHA III + IV, stable HF, EF &lt;40%</td>
<td>3 months</td>
</tr>
<tr>
<td>Miyata et al (2012)³³</td>
<td>HeartPAP or BiPAP autoSV, Respironics</td>
<td>Randomized, controlled</td>
<td>Non-ASV (n=11) vs. ASV (n=11)</td>
<td>CSA-CMR with AHI &gt;15/h at 12 month of CRT-D</td>
<td>NYHA ≥ II, stable HF, CRT-D*</td>
<td>3 and 6 months</td>
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(Table 1 continued the next page.)
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<th>Study</th>
<th>Adherence</th>
<th>Main results of ASV on SDB parameters</th>
<th>Respiratory stability</th>
<th>Main results on HF parameters</th>
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</thead>
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<tr>
<td>Teschler et al (2001)</td>
<td>Patients preference to ASV compared with CPAP or BiLevel</td>
<td>Not exclusively but mostly pronounced improvements with ASV for AHI, cAI, cAII, SWS and REM sleep</td>
<td>pCO2: 32.1±0.7 mmHg to 34.2±0.7 mmHg (NS)</td>
<td>NA</td>
</tr>
<tr>
<td>Pepperell et al (2003)</td>
<td>Improvement in daytime sleepiness (Osler test)</td>
<td></td>
<td>pCO2: 4.9kPa to 5.4kPa (P=0.002)</td>
<td>Significant decrease in BNP and metadrenaline excretion in therapeutic ASV group</td>
</tr>
<tr>
<td>Schädlich et al (2004)</td>
<td>Average use after 12 months: 4.3±2.1 h</td>
<td>Normalization of AHI and Arl. Improvement in oxygen saturations and SWS, but not in REM or sleep efficacy</td>
<td>No change in pCO2</td>
<td>Significant improvement in EF und 6min walking distance after 3 and 12 months</td>
</tr>
<tr>
<td>Töpfer et al (2004)</td>
<td>Average use: 5.8±2.1 h</td>
<td>Significant decrease in AHI and Arl</td>
<td>NA</td>
<td>Increase in QOL (MLwHFQ)</td>
</tr>
<tr>
<td>Philippe et al (2006)</td>
<td>Compliance after 6 months better with ASV</td>
<td>Greater decrease in AHI after 3 and 6 months with ASV</td>
<td>NA</td>
<td>Significant increase in EF in ASV-treated patients only (n=7)</td>
</tr>
<tr>
<td>Szollosi et al (2006)</td>
<td>NA</td>
<td>ASV and DS with significant improvement in respiratory parameters (AHI, AI) and oxygen saturation. Increase in AHI and decrease of total sleep time with DS</td>
<td>Increase/normalization of eupneic sleep PetCO2 with DS but not with ASV</td>
<td>NA</td>
</tr>
<tr>
<td>Zhang et al (2006)</td>
<td>NA (patients with poor compliance with ASV were excluded)</td>
<td>AHI and Arl significantly decreased by oxygen, but further decreased by ASV; improvement SWS with ASV only</td>
<td>NA</td>
<td>Significant increase in 6-min walking distance with both interventions, but significantly higher in ASV; increase in EF in ASV-treated patients only</td>
</tr>
<tr>
<td>Oldenburg et al (2008)</td>
<td>AHI and AI normalized and oxygenation improved with ASV treatment</td>
<td>pCO2: increased from 36.5±4.6 mmHg to 37.5±5.3 mmHg (P=0.028)</td>
<td>Improvement in NYHA class, NT-proBNP, EF, and CPX: VO2-AT, VO2peak, predicted VO2peak</td>
<td>NA</td>
</tr>
<tr>
<td>Fietze et al (2008)</td>
<td>Average use: 4.8 h</td>
<td>Decrease in central respiratory events, RDI and ODI with both treatment modalities, no difference between both groups. No change in sleep quality, improvement in RERAs only</td>
<td>No change in respiratory drive</td>
<td>Significant increase in EF with BiLevel, but not with ASV</td>
</tr>
<tr>
<td>Hastings et al (2010)</td>
<td>Average nightly use: 4.5±2.6/h</td>
<td>Significant decrease in AHI, Arl, ODI%, sleep efficacy and sleep architecture with ASV</td>
<td>No change in VE/VO2-slope</td>
<td>Significant increase in EF in ASV-treated patients; no change in BNP or peakVO2</td>
</tr>
<tr>
<td>Kasai et al (2010)</td>
<td>Better compliance with ASV than CPAP (5.2±0.9 h vs. 4.4±1.1 h)</td>
<td>Significant decrease in AHI in both groups, but greater with ASV than with CPAP</td>
<td>Significant increase in pCO2 with ASV only</td>
<td>Improvement in EF better in ASV than CPAP; significant improvement in urinary norepinephrine, BNP, 6-min walking distance and LVESD in ASV-treated patients only</td>
</tr>
<tr>
<td>Koyama et al (2010)</td>
<td>Significant improvement in AHI, AI and Arl in ASV-treated patients; greater improvement in mean SaO2 in ASV-treated patients</td>
<td>NA</td>
<td></td>
<td>Improvement in NYHA class, EF and BNP in ASV-treated patients only</td>
</tr>
<tr>
<td>Campbell et al (2011)</td>
<td>Average use of ASV during the study 5.2±2 h, but only 1 patient was willing to continue ASV after the study</td>
<td>Significant reduction in AHI with oxygen, but in &lt;30% of patients an AHI &lt;10/h was achieved. Significant and, compared with oxygen, better reduction in AHI with almost normalization of AHI. In 86% of patients an AHI &lt;10/h was achieved. Improvement in sleep quality with both treatment modalities</td>
<td>NA</td>
<td>No change in EF with oxygen, non-significant trend towards an increase with ASV. No change in LV diameters, urinary noradrenaline concentrations or exercise capacity with either treatment</td>
</tr>
<tr>
<td>Oldenburg et al (2011)</td>
<td>Average use in ASV group: 6.4±1:07 (h:min)</td>
<td>Significant improvement in AHI, cAI, cAII, mAI, HI and oxygen saturation parameters in ASV group</td>
<td>pCO2: increased and HCVR and VE/VO2-slope decreased in ASV group exclusively</td>
<td>NYHA class, EF and end-diastolic LV diameter, and CPX: workload, VO2-AT, VO2 peak and predicted VO2 peak; 6-min walking distance and NT-proBNP concentrations improved in ASV group only</td>
</tr>
<tr>
<td>Hakuri et al (2011)</td>
<td>NA</td>
<td>Significant reduction in AHI</td>
<td>NA</td>
<td>Improvement in NYHA class, systolic and diastolic LV function; decrease in LV and LA volumes; increase in SV, CO and SVR in ASV-treated (tolerating) patients</td>
</tr>
<tr>
<td>Hetland et al (2011)</td>
<td>NA</td>
<td>Not reported, only abstract available yet</td>
<td>NA</td>
<td>Significant improvement in EF (primary endpoint); 6-min walking distance and NYHA class (secondary endpoints)</td>
</tr>
<tr>
<td>Miyata et al (2012)</td>
<td>NA</td>
<td>Improvement of respiratory events (AHI, cAI, cAII), Arl, oxygen concentration and SWS</td>
<td>NA</td>
<td>Increase in EF and decrease in LV dimensions seen in both groups. Decrease in BNP after 3 and 6 months in ASV-treated patients only</td>
</tr>
</tbody>
</table>

(Table 1’s footnote is on the next page.)
potential side effects, including cardiac arrhythmias, these medications should be used with caution in HF patients, if used at all.

Carbon dioxide or deadspace administration was studied to eliminate hypocapnic CSA in HF patients as well.\(^{90,96}\) However, the studies are small and show divergent results in terms of sleep quality. In addition, long-term HF follow-up studies are missing, leading to the conclusion that carbon dioxide is not a recommended treatment option.\(^{85}\)

Nocturnal nasal oxygen supplementation has been used for a long time to treat HF-related CSA-CSR. To date, the underlying mechanisms of improved respiration and potentially cardiac function are not fully understood. A recent meta-analysis recommends oxygen (besides CPAP and ASV) as a standard therapy for CSA-CSR.\(^{85}\) Although included studies report different results,\(^{90,97–105}\) and 1 small study reported no difference in cumulative incidence rate of cardiac events between an oxygen and a control group,\(^{101}\) the overall direction in terms of reducing the AHI and improving EF seems to be positive.\(^{85}\) In addition, the universal availability of oxygen influenced the recommendation as a standard therapy.\(^{85}\)

A new and very different therapeutic strategy uses unilateral

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**Table 2. Studies of ASV in Stable HF Patients Independent of EF and With SDB**

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>Study design</th>
<th>Control group</th>
<th>SDB inclusion criteria</th>
<th>HF inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westhoff et al (2010)</td>
<td>AutoSet CS, ResMed</td>
<td>Observational</td>
<td>ASV-compliant patients (n=15; mean usage &gt;4h/day)</td>
<td>CSA-CSR (cA1&gt;5/h, cAHI &gt;15/h) not effectively treated by CPAP (AHI with CPAP &gt;15h)</td>
<td>Stable HF, NYHA I–III, elevated BNP (&gt;100pg/ml)</td>
</tr>
<tr>
<td>Yoshishita et al (2011)</td>
<td>Heart PAP, Respironics</td>
<td>Observational</td>
<td>Non-ASV (not tried or tolerating; n=37) vs. ASV-tolerating patients (n=23)</td>
<td>AHI &gt;15/h with &gt;50% central events</td>
<td>Symptomatic, stable HF and NYHA II*</td>
</tr>
<tr>
<td>Randerath et al (2012)</td>
<td>BiPAP AutoSV, Respironics</td>
<td>Randomized, parallel</td>
<td>ASV (ITT: n=36, PP: n=26) vs. CPAP (ITT: n=34, PP: n=25)</td>
<td>AHI &gt;15/h with coexisting obstructive (20–50%) and central (&lt;80%) events</td>
<td>Clinically diagnosed HF, EF ≥20%*</td>
</tr>
<tr>
<td>Oldenburg et al (2012)</td>
<td>Somnovent CR, Weinmann</td>
<td>Observational</td>
<td>ASV-compliant patients (n=23)</td>
<td>Combined central and mixed SDB with AHI ≥15/h</td>
<td>Stable HF because of diastolic or systolic dysfunction, NYHA II, elevated NT-proBNP</td>
</tr>
</tbody>
</table>

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**Table 3. Follow-up, Adherence, Main results of ASV on SDB parameters, Respiratory stability, Main results on HF parameters**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Adherence</th>
<th>Main results of ASV on SDB parameters</th>
<th>Respiratory stability</th>
<th>Main results on HF parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westhoff et al (2010)</td>
<td>6 weeks</td>
<td>5.5±1.0h/day</td>
<td>Normalization of AHI and ArI, improvement in oxygen saturations, no significant effect on sleep stages</td>
<td>NA</td>
<td>Significant decrease in BNP, more pronounced in CSA-CSR with accompanying OSA</td>
</tr>
<tr>
<td>Yoshishita et al (2011)</td>
<td>3 and 6 months</td>
<td>378±167min/day</td>
<td>Improvement in AHI, cA1, ODI2%, oxygen saturations, sleep efficacy</td>
<td>NA</td>
<td>Improvement in NYHA class, BNP, systolic and diastolic LV function in ASV-treated patients only. Improved event free survival (rehospitalization, death) with ASV</td>
</tr>
<tr>
<td>Randerath et al (2012)</td>
<td>3 and 12 months</td>
<td>ASV: 5.2±2.0h/day, CPAP: 4.3±2.3 (P=NS)</td>
<td>Both modes improved AHI, but ASV improved central and mixed events significantly better than CPAP; both modes improved obstructive events, oxygen saturation and Ar; no difference in sleep stages</td>
<td>NA</td>
<td>BNP improved with ASV in PP analysis; no change in CPX parameters with either treatment</td>
</tr>
<tr>
<td>Oldenburg et al (2012)</td>
<td>3.6±1.2 months</td>
<td>NA</td>
<td>Improvement in AHI, cA1, oAI, mAI, HI and oxygen saturations; no difference in sleep stages or sleep efficacy</td>
<td>Significant increase in pCO2 in ASV-treated patients only (35.3±4.8mmHg to 39.8±4.5mmHg)</td>
<td>Improvement in NYHA class, VO2AT, VO2peak and predicted VO2peak</td>
</tr>
</tbody>
</table>

*No specific upper EF inclusion criteria was stated, but baseline EF values prove inclusion of patients with preserved and reduced EF.

ITT, intention to treat analysis; PP, per protocol analysis. Other abbreviations as in Table 1.
Cheyne-Stokes Respiration in HF

eral phrenic nerve stimulation to treat CSA-CSR in HF patients. A first feasibility study is published, showing a significant reduction in respiratory events, improvement in oxygen saturation, and improvement in acute circulatory delay without affecting sleep quality or efficacy. Results of a first pilot study are pending and long-term effects on HF need to be determined.

In general, ASV has been shown to suppress respiratory events within 1 night of treatment more effectively than oxygen, CPAP or bilevel PAP. These superior effects of ASV were confirmed after 3, 6 and 12 months by other studies using different devices.

Two meta-analyses show an overall beneficial effect of ASV in terms of suppression of respiratory events (Figure 6) and improvement in EF (Figure 7). Although the study of Sharma et al includes at least 1 study based on HF patients with reduced and preserved EF (Table 2), ASV was more efficacious in reducing SDB severity and improving cardiac function in HF patients with CSA-CSR compared with control conditions (subtherapeutic ASV, CPAP, BiPAP, oxygen or no treatment).

It needs to be emphasized that long-term treatment of HF patients should be based on current guidelines, which should include medical and evidence-based device therapy such as CRT. If CSA-CSR persists, special treatment of this comorbidly is recommended. In this context, national guidelines vary on the preferred mode of therapy, but the most recent include ASV.

**Perspectives**

**Benefits of ASV Treatment for Chronic HF Independent of Pre-Existing SDB**

In a pilot study, Takama and Kurabayashi documented a beneficial effect of 6-months’ ASV treatment, independent of SDB type and severity. They found a significant and comparable improvement in BNP levels and LVEF in HF patients with mild, moderate or severe SDB. Koyama et al confirmed the beneficial effect of ASV on BNP and LVEF after a follow-up of 12 months, again independent of SDB severity. In addition, there was a reduction in rehospitalization and an improvement in short-term prognosis.

**ASV Treatment of Acute Decompensated HF**

Current HF guidelines recommend noninvasive ventilation with positive EEP (PEEP) as early as possible in all patients with acute pulmonary edema and hypertensive acute HF. In clinical practice, intermittent CPAP is most often used and recommended. Whether ASV offers any advantages in terms of tolerability, reversal of pulmonary edema or outcome remains to be determined.

Figure 6. Two recent meta-analyses showing an overall impressive reduction in the apnea-hypopnea index with adaptive servoventilation (ASV) therapy in patients with heart failure. (A) Aurora et al., (B) Sharma et al. Both reprinted with permission. CI, confidence interval.
be determined.

**Pathways for SDB Diagnosis and Treatment**

Clinical pathways for the diagnosis and treatment of SDB vary considerably between countries and continents. An in-hospital, attended PSG study is the gold standard in sleep medicine. However, in terms of SDB and the emerging need for effective diagnosis and treatment, the most appropriate options involve several medical disciplines. In particular, cardiologists need to be involved or may even lead the discussion.

As soon as there is enough convincing evidence that ASV leads to improved QOL, improved survival and/or less hospital admissions, guidelines will include this therapy into standard medical care. As a consequence, diagnostic and therapeutic pathways need to be simplified, because the devices will require more self-adjusting modalities, compliance and therapeutic efficacy surveillance, as well as HF status monitoring features.

**Conclusion**

Studies of the treatment of CSA-CSR in well-defined HF patients are limited. To date, ASV seems to be the most efficient and promising treatment available. Endpoints of further studies need to be cardiovascular rather than sleep-medicine specific only.

Based on the current literature, the AHI needs to be lowered below a certain threshold (at least <15/h), which seems to be achieved with ASV most reliably and efficiently. It needs to be emphasized that this theoretical and still unproven threshold applies to CPAP therapy only. It may be hypothesized that, because of a potential beneficial effect of PAP ventilation itself, it might valid for other PAP therapies, including ASV, as well. At least for non-PAP-therapies, including medication, oxygen, deadspace, CO₂, or other devices (phrenic nerve stimulation), other thresholds might exist and need to be explored.

For ASV, 2 large RCTs will clarify its role in the long-term treatment of stable HF patients with reduced EF, but it can only be speculated about many other indications such as acute decompensated HF, HF with preserved EF or even for prevention of HF, arrhythmia or stroke.

As pointed out by Shiomi et al, it is important to diagnose SDB in HF and to differentiate between OSA and CSA-CSR, to consider the potential side effects of therapy and choose the right ASV device and algorithm.

**Disclosures**

The author has received travel grants and speaker’s honoraria from ResMed and Weinmann.

**References**

1. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal ejection frac-

The text continues with various references and citations, covering topics such as sleep apnea, its effects on heart failure, and the use of various interventions and technologies to manage these conditions. The references are presented in a consistent format, providing a comprehensive overview of the field as of 2012.


