

# Effects of Auto-Servo Ventilation on Patients with Sleep-Disordered Breathing, Stable Systolic Heart Failure and Concomitant Diastolic Dysfunction: Subanalysis of a Randomized Controlled Trial

Christoph Birner<sup>a</sup> Frederic Series<sup>d</sup> Keir Lewis<sup>e</sup> Amit Benjamin<sup>e</sup>  
Silke Wunderlich<sup>a</sup> Pierre Escourrou<sup>f</sup> Florian Zeman<sup>b</sup> Ruth Luigart<sup>a</sup>  
Michael Pfeifer<sup>a,c</sup> Michael Arzt<sup>a</sup>

<sup>a</sup>Division of Respiriology, Department of Internal Medicine II and <sup>b</sup>Center for Clinical Studies, University Hospital Regensburg, Regensburg, and <sup>c</sup>Center for Pneumology, Donaustauf Hospital, Donaustauf, Germany; <sup>d</sup>Centre de Recherche, IUCPQ, Université Laval, Québec, Canada; <sup>e</sup>Department of Respiratory Medicine, Prince Philip Hospital and Swansea College of Medicine, Llanelli, UK; <sup>f</sup>Centre de Médecine du Sommeil, Hôpital Antoine Beclère, Clamart, France

## Key Words

Auto-servo ventilation · Diastolic dysfunction · Heart failure · Sleep apnea · Sleep-disordered breathing

## Abstract

**Background:** Systolic heart failure (HF) is frequently accompanied by diastolic dysfunction and sleep-disordered breathing (SDB). **Objectives:** The objective of this subset analysis was to determine effect sizes of auto-servo ventilation (ASV and biphasic positive airway pressure ASV) on echocardiographic measures of diastolic function in patients with systolic HF and SDB. **Methods:** Thirty-two patients with stable systolic HF, concomitant diastolic dysfunction [age  $66 \pm 9$  years old, left ventricular (LV) ejection fraction:  $30 \pm 7\%$  and New York Heart Association class II: 72] and SDB (apnea-hypopnea index, AHI:  $48 \pm 19/h$ ; 53% had predominantly obstructive sleep apnea) receiving either ASV ( $n = 19$ ) or optimal medical treatment (control,  $n = 13$ ) were analyzed in a randomized controlled clinical trial. Polysomnographic and echocardiographic measurements were obtained at baseline and after 12 weeks. **Results:** AHI significantly im-

proved in the ASV group compared to the control group ( $-39 \pm 18$  vs.  $-0.2 \pm 13.2/h$ ,  $p < 0.001$ ). At baseline, 24 (75%) patients had impaired LV relaxation, and 8 (25%) had a pseudo-normalized filling pattern. At the 12-week control visit, diastolic function assessed by the isovolumetric relaxation time ( $-10.3 \pm 26.1$  vs.  $9.3 \pm 49.1$ ,  $p = 0.48$ ) and deceleration time ( $-43.9 \pm 88.8$  vs.  $12.4 \pm 68.8$ ,  $p = 0.40$ ) tended to improve after ASV treatment, but did not reach statistical significance. Likewise, the proportion of patients whose diastolic dysfunction improved was nonsignificantly higher in the ASV than in the control group, respectively (37 vs. 15%,  $p = 0.25$ ). **Conclusions:** ASV treatment efficiently abolishes SDB in patients with stable systolic HF and concomitant diastolic dysfunction, and was associated with a statistically nonsignificant improvement in measures of diastolic dysfunction. Thus, these data provide estimates of effect size and justify the evaluation of the effects of ASV on diastolic function in larger randomized controlled trials.

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This paper contains parts of the MD thesis of S. Wunderlich.

## Introduction

Heart failure (HF), affecting about 1–2% of individuals in the Western World with increasing prevalence with increasing age, is still associated with high morbidity and mortality [1]. Systolic left ventricular (LV) impairment, a hallmark of HF with reduced ejection fraction (HFREF), is often accompanied by diastolic dysfunction, which has been shown to represent an independent prognostic factor for a worse outcome – even in patients with concomitant systolic dysfunction [2–4]. Beyond that, accumulating evidence links HFREF to sleep-disordered breathing (SDB) as further concomitant entity, affecting about 51–76% of patients with HFREF [5–7].

Current pathophysiological concepts indicate that both HFREF and SDB stand in a reciprocal relationship with each other. While impaired cardiac function can cause and aggravate SDB [8], SDB may contribute to worsening of HFREF by increasing cardiac afterload, causing hypertension and myocardial hypertrophy [6, 9–14].

In this context, facing the somehow stagnating therapeutic options in HFREF treatment [15], it has been hypothesized that an SDB-specific therapy might also be effective in improving parameters of cardiac dysfunction. In HF patients with impaired systolic function, there is robust evidence that continuous positive airway pressure (CPAP) modestly increases LV ejection fraction (LVEF). However, current evidence in such patients is conflicting with studies of auto-servo ventilation (ASV) showing a modest improvement in LVEF [16], whereas others did not [17, 18].

Furthermore, the effects of positive airway pressure treatment on diastolic dysfunction have not been studied in detail. A randomized crossover study in patients with SDB without evidence of HF showed that CPAP modestly improves echocardiographic parameters of diastolic dysfunction [19]. Another trial investigating ASV therapy in patients with SDB and concomitant HF with normal EF likewise found a moderate improvement in echocardiographic diastolic parameters [20]. However, there is no randomized controlled study evaluating the extent to which an SDB-specific therapy might influence diastolic dysfunction in patients with HFREF.

We therefore tested in a subset of patients with HFREF and SDB with concomitant diastolic dysfunction from a multicenter, randomized, rater-blinded, open label, parallel group trial [21] to which extent an SDB-specific therapy (ASV, biphasic PAP ASV, Philips Respironics) influences echocardiographic measures of LV structure and diastolic function compared to an optimal medical therapy alone.

## Patients and Methods

### Patients

The patient population analyzed is a subset of the multicenter, randomized, rater-blinded, open label, parallel group trial ‘Treatment of Sleep-Disordered Breathing with Auto-Servo Ventilation in Congestive Heart Failure’, which has been registered at <http://www.clinicaltrials.gov/> (ISRCTN04353156) [21].

Individuals were eligible to be part of the present analysis if they were 18–80 years old, had chronic HF due to ischemic or nonischemic cardiomyopathy, had a LVEF  $\leq 40\%$  on echocardiography, were in a stable clinical status (New York Heart Association class II or III) with optimal medical treatment according to the guidelines of the European Society of Cardiology [22] for at least 4 weeks and had an apnea-hypopnea index (AHI)  $\geq 20/h$  sleep as assessed by in-laboratory polysomnography. Subjects were excluded if they had evidence of an unstable clinical status (unstable angina, myocardial infarction, cardiac surgery or hospital admission within the previous 3 months), had contraindications to PAP therapy, were on oxygen therapy, or had severe restrictive or obstructive airway disease. All patients gave written informed consent, and the protocol was approved by the local ethics boards of the participating institutions.

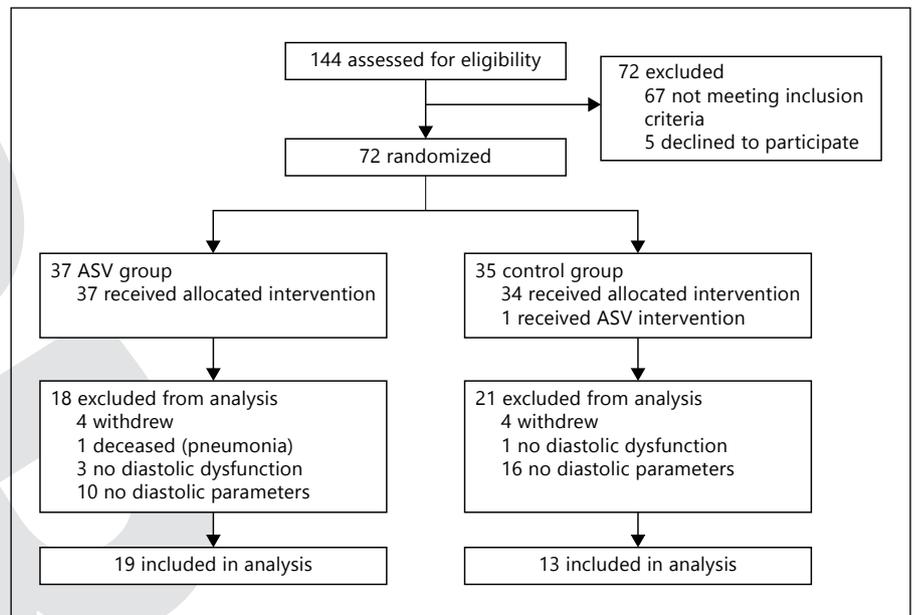
Eligible patients meeting all inclusion criteria were then assigned to either an ASV-treated group receiving ASV in addition to an optimal medical treatment for HF or a control group with optimal medical treatment alone. Echocardiographic (evaluation of systolic/diastolic function and LV diameters), hemodynamic (systolic and diastolic blood pressure, BP), neurohumoral [N-terminal (NT)-pro-B-type natriuretic peptide (BNP)] and SDB parameters (AHI) were determined at baseline and after 12 weeks, respectively.

Additional inclusion criteria for the present analysis were that echocardiographic parameters of diastolic dysfunction were available and that individuals fulfilled echocardiographic criteria for diastolic dysfunction (classified as either impaired relaxation, or pseudo-normal or restrictive filling pattern). These additional criteria applied to 44% of the initially included study cohort representing all subjects with a complete echocardiographic evaluation of diastolic dysfunction, which has been performed in two of four study centers (see fig. 1 for patient flow).

### Initiation of ASV

By protocol, nighttime pressure settings had to be within the range of tolerated pressure settings during an attended daytime titration with monitoring of BP and heart rate (HR). During the first night, CPAP was titrated under polysomnographic monitoring from 4 cm H<sub>2</sub>O in 1-cm H<sub>2</sub>O increments to the point where any sign of flow limitation was eliminated or the maximum level the patient could tolerate ( $\leq 10$  cm H<sub>2</sub>O).

Before initiating ASV at night, a daytime titration with bilevel PAP was performed in order to avoid long-term application of ASV with pressure settings that may lead to hemodynamic compromise. First baseline BP and HR were recorded as described. Expiratory PAP was set at the optimal CPAP level suppressing upper airway obstruction determined by polysomnography. Inspiratory pressure support was titrated starting from 1 cm H<sub>2</sub>O and increased by 1-cm H<sub>2</sub>O up to the maximum of 10 cm H<sub>2</sub>O every 5 min after BP and HR reading was taken. Attended daytime inspiratory pressure support titration was stopped when a pressure



**Fig. 1.** Study protocol.

of 10 cm H<sub>2</sub>O was reached or if mean BP <60 mm Hg or a drop of >15 mm Hg occurred or the patient did not tolerate inspiratory pressure support.

At the ASV initiation night, the expiratory PAP of the ASV device was set to the CPAP determined during the titration night. The minimum inspiratory PAP was set to the expiratory PAP level, and the maximum inspiratory PAP to a maximum of 10 cm H<sub>2</sub>O above the expiratory PAP level, or not higher than the maximum the patient could tolerate during the daytime test. The default backup rate of the machine was used. Assessment of hours of ASV use over this period were obtained from the downloadable SmartCard located in the device.

#### Echocardiography

Transthoracic echocardiography was performed with patients in the supine and left-lateral positions using high-quality echocardiographs. Images were obtained in the parasternal long- and short-axis, apical 2- and 4-chamber, and subcostal views with 2D, M-mode and Doppler echocardiography. Investigators were experienced echocardiographers, and each echocardiogram was centralized to two blinded analysts. Left atrial diameter, LV end-diastolic and end-systolic diameters, as well as interventricular septum thickness and LV posterior wall thickness were determined in accordance with the recommendations of the American Society of Echocardiography [23]. LV systolic function was assessed by LVEF obtained by the Simpson's method (LV end-diastolic volume minus LV end-systolic volume divided by end-diastolic volume). LV mass (LVM) was calculated from M-mode echocardiograms according to the formula described by Devereux et al. [24], and LVM index (LVMI) was obtained by indexing LVM to body surface area. Relative wall thickness was determined by the formula  $(2 \times \text{PWTd})/\text{LVIDD}$ , where PWTd is posterior wall thickness at end-diastole and LVIDD is end-diastolic ventricular internal dimension at end-diastole [23].

LV diastolic function was assessed by measuring the mitral inflow pattern (with the sample volume placed between the leaflet tips using pulsed-wave Doppler technique), the deceleration time (DT) and the isovolumetric relaxation time (IVRT). Peak flow velocity in early diastole (E wave) was divided by the peak velocity at atrial contraction (A wave) resulting in the E/A ratio. LV filling patterns were then classified as normal, impaired relaxation, pseudo-normal or restrictive. A normal pattern was defined by E/A ratio >1, and normal DT (<220 ms) and IVRT (<100 ms). Impaired relaxation was identified by E/A ratio <1, DT >220 ms and IVRT >100 ms. A pseudo-normal pattern was determined by E/A ratio ranging from 1 to 1.5, DT <150 ms and IVRT <60 ms, and a restrictive pattern was defined by E/A ratio >1.5, DT <150 ms and IVRT <60 ms [25].

#### Statistical Analysis

Values are expressed as means  $\pm$  SD or percentages. Baseline characteristics of the patients in the two groups were compared using the nonparametric Wilcoxon-Mann-Whitney test. To take into account potential differences in baseline rates between the two groups, we used a generalized linear model based on ranks (nonparametric) with the respective baseline value as covariate. All statistical tests were two sided with a significance level of 5%. All statistical tests were performed with SPSS 20.0.

## Results

#### Patient Characteristics

In the initial study cohort (participating patients with complete assessment of diastolic function; fig. 1), the prevalence of diastolic dysfunction was very high (86 and 93% in the treatment and control group, respectively).

**Table 1.** Baseline characteristics of the study patients

	ASV	Control	p value
Patients, n	19	13	
Age, years	66±9	66±11	0.73
Males, n (%)	18 (95)	11 (85)	0.55
Body mass index, kg/m <sup>2</sup>	29.9±4.0	30.7±3.6	0.58
Smokers, n (%)	2 (11)	3 (23)	0.16
BP, mm Hg			
Systolic	120±18	128±24	0.40
Diastolic	70±14	75±11	0.37
Heart rate, b.p.m.	70±10	71±12	0.64
New York Heart Association class, n (%) <sup>1</sup>			0.35
II	12 (63)	11 (85)	
III	5 (26)	1 (8)	
LVEF, %	30±8	29±7	0.66
NT-pro-BNP, ng/ml	1,046±1,195	997±1,344	0.33
Cause of HF, n (%)			0.47
Ischemic	9 (47)	6 (46)	
Nonischemic	10 (53)	7 (54)	
Sleep apnea, n (%)			1.00
Obstructive	10 (53)	7 (54)	
Central	9 (47)	6 (46)	
AHI, events/h	51.7±18.9	43.1±18.4	0.33
Medication, n (%)			
Diuretic	11 (58)	11 (85)	0.14
Spironolactone	9 (47)	8 (62)	0.49
ACEI	15 (79)	9 (69)	0.68
ARB	4 (21)	5 (38)	0.43
β-Blocker	16 (84)	13 (100)	0.25

ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

<sup>1</sup> Data of 2 and 1 patients are missing in the ASV and control group, respectively.

Patients with diastolic dysfunction were predominantly normotensive males with both ischemic and nonischemic systolic HF (mainly New York Heart Association class II congestive HF severity) and concomitant obstructive or central sleep apnea indicated by a pathological AHI. Medical therapy was sufficient according to current guidelines with a high percentage of patients treated with β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone. Table 1 shows the proportion of patients using cardiac medication, which did not change significantly during the follow-up period: in 1 patient from the control group, a β-blocker was added, and in 2 patients from the ASV group spironolactone was discontinued.

There were no statistically significant differences between both groups in demographic, hemodynamic, echocardiographic or SDB parameters.

### SDB Parameters

At baseline, AHI was 51.7 ± 18.9 events/h in the ASV-allocated group and 43.1 ± 18.4 events/h in the control group (p = 0.33). After 12 weeks of ASV treatment, AHI was significantly reduced to 11.2 ± 7.2 events/h, whereas it remained unchanged in the control group (p < 0.001 ASV vs. control; table 2). The average daily ASV use during the study period was 4.2 ± 2.7 h.

### Hemodynamic, Neurohumoral and Functional LV Parameters

Individuals of both groups were normotensive at baseline, and neither systolic nor diastolic BP did vary significantly after 12 weeks (table 2). Likewise, NT-pro-BNP levels were similar in both groups at baseline, showing no significant difference after 12 weeks (table 2). Baseline LV systolic function measured by LVEF was 30 ± 8% in the ASV group and 29 ± 7% in the control group (p = 0.66). After 12 weeks, the change in LVEF was similar in the ASV-treated and control groups (p = 0.75, table 2).

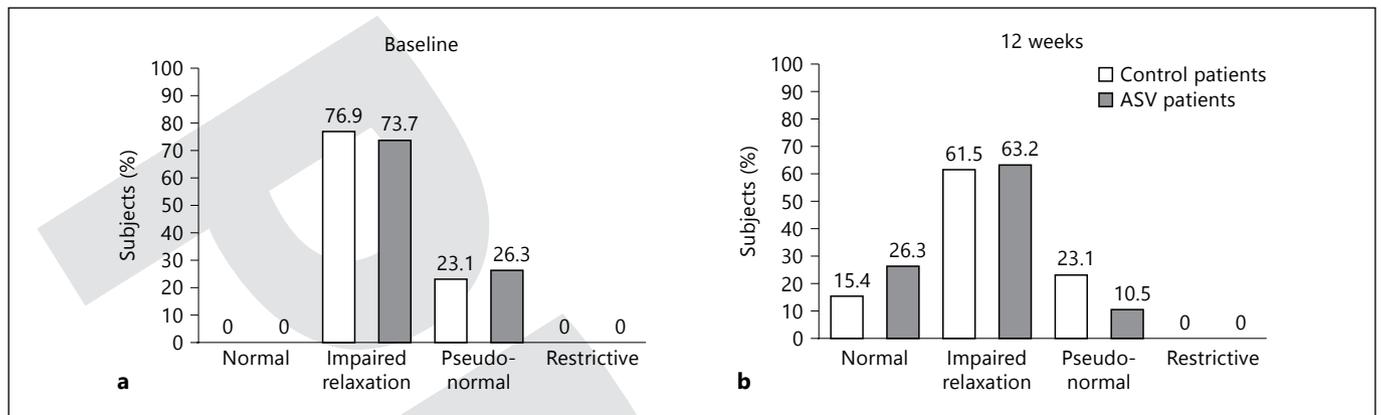
### LV Structural Parameters

LV structural parameters were largely unchanged during the 12-week follow-up of both the ASV and the control group. Relative wall thickness was unchanged in the treatment group but tended to increase in control subjects.

### Parameters of Diastolic LV Dysfunction

Severity of diastolic dysfunction was graded according to echocardiographic measurements of the E/A ratio, DT and IVRT. At baseline, most patients had impaired LV relaxation (i.e. grade 1 diastolic dysfunction), and about one quarter revealed a pseudo-normal filling pattern (fig. 2a). After 12 weeks, more ASV than control patients improved to a normal filling pattern (26 vs. 15%), and less ASV than control patients remained in the pseudo-normal state (11 vs. 23%), even though neither of these ASV-mediated improvements reached statistical significance (p = 0.55; fig. 2b). Regarding the individual parameters of diastolic dysfunction, the E/A ratio slightly increased in both study groups (fig. 3a).

In the ASV group, DT and IVRT were reduced, indicating improvement in diastolic function, while in the control group DT remained similar within the follow-up period. Between-group differences comparing the change in DT and IVRT within 12 weeks were statistically not significant (p = 0.40 and p = 0.48, respectively; table 2; figure 3b, c).



**Fig. 2.** Grade of diastolic dysfunction at baseline (a) and after 12 weeks (b) in ASV (gray bars) and control subjects (white bars).

**Table 2.** Sleep, neurohumoral and echocardiographic parameters and blood pressure in ASV versus control patients at baseline and after 12 weeks

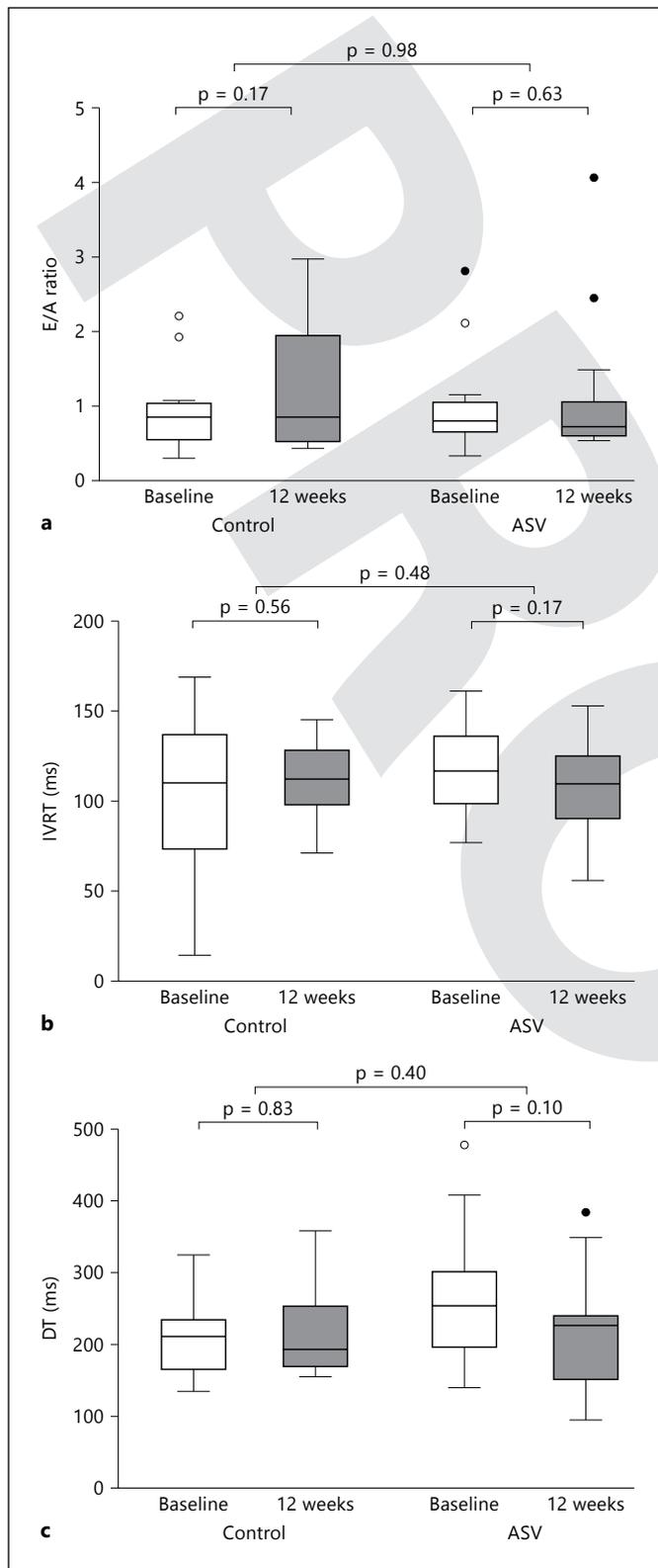
	ASV		Control		p value
	baseline	12 weeks	baseline	12 weeks	
Parameter of SDB severity					
AHI, events/h	52±19	11±7	43±18	43±19	<0.001
Hemodynamic, neurohumoral and functional LV parameters					
Systolic BP, mm Hg	119±18	110±18	128±24	125±19	0.22
Diastolic BP, mm Hg	70±14	70±17	75±11	74±14	0.80
NT-pro-BNP, ng/ml	1,046±1,195	1,163±1,498	997±1,344	1,042±1,312	0.92
LVEF, %	30±8	31±10	29±7	32±9	0.75
LV structural parameters					
LVEDD, mm	67±9	67±9	66±7	65±7	0.32
LVESD, mm	55±11	55±12	52±10	50±8	0.31
IVS, mm	11±2	11±2	10±2	10±2	0.41
LVPW, mm	10±2	10±2	10±2	11±2	0.21
Left atrial diameter, mm	48±8	49±7	46±7	50±10	0.37
RWT, %	0.30±0.08	0.30±0.06	0.31±0.06	0.33±0.07	0.09
LVM, g	378±111	371±106	351±96	364±135	0.91
LVMI, g/m <sup>2</sup>	188±58	183±52	174±42	179±57	0.66
LV diastolic parameters					
E wave, m/s	0.63±0.21	0.69±0.30	0.59±0.21	0.63±0.20	0.66
A wave, m/s	0.73±0.27	0.70±0.25	0.73±0.25	0.66±0.28	0.48
E/A ratio	0.99±0.61	1.20±0.99	0.94±0.55	1.25±0.89	0.98
DT, ms	259.0±86.6	212.3±82.4	207.5±55.5	217.7±68.1	0.40
IVRT, ms	117.4±25.8	106.2±25.2	102.9±43.3	107.9±23.1	0.48

LVEDD = LV end-diastolic diameter; LVESD = LV end-systolic diameter; IVS = interventricular septum thickness; LVPW = LV posterior wall thickness; RWT = relative wall thickness. To be able to take potential differences in baseline rates between the two groups into account, a generalized linear model based on ranks (nonparametric) with the respective baseline value as covariate was used.

## Discussion

The main findings of this study evaluating ASV therapy in patients with HFREF, diastolic dysfunction and SDB are that (1) prevalence of diastolic dysfunction is

very high in patients with HFREF and SDB; (2) ASV therapy effectively suppresses SDB, and (3) ASV therapy does not significantly alter echocardiographic measures of LV structure and diastolic dysfunction in this study cohort.



**Fig. 3.** E/A ratio (a), IVRT (b) and DT (c) in ASV-treated (right) versus control subjects (left) at baseline (white bars) and after 12 weeks (gray bars).

### Prevalence of LV Diastolic Dysfunction

Diastolic dysfunction was detected in a total of 89% of patients with HFREF in the current analysis, which is similar to the 82% prevalence reported in larger samples of HFREF patients from the community [26]. A previous study in patients with normal EF observed a close relationship between SDB and diastolic dysfunction affecting 23 [27] to 56% [19] of subjects under investigation with a stepwise further increase as severity of SDB rises, ultimately reaching a prevalence of approximately 70% [28]. Even though this link between SDB and diastolic dysfunction is evident, the underlying pathophysiological mechanisms are still not well characterized. It has been hypothesized that both elevations in nocturnal BP and activation of the sympathetic nervous system might contribute to this effect [29–31] by increasing LV afterload [32]. Furthermore, futile inspiratory efforts hallmarking obstructive sleep apnea might increase LV transmural pressure and hence afterload by inducing negative intrathoracic pressures [32], ultimately provoking diastolic dysfunction. Even though each of these concepts could plausibly explain the impact of SDB on diastolic dysfunction on its own, any deterioration in diastolic filling in patients with advanced complex disease, such as severely impaired cardiac function, might most likely be caused polyetiologically.

### Effectiveness of ASV Therapy on SDB Severity and LV Systolic Dysfunction

In accordance with previous studies, ASV therapy was highly efficient in suppressing apnea and hypopnea in patients with SDB and HF [16, 17, 33–38].

In contrast, LV systolic function determined by EF did not significantly improve in ASV-treated patients. On the one hand, this is congruent with previous findings, which also did not reveal a significant effect of an SDB-specific therapy on LVEF in HF patients [17, 39] but, on the other hand, it contrasts with studies reporting a positive effect on systolic function [16, 36, 38, 40–43]. For instance, Bradley et al. [40] described a rather moderate but significant gain of systolic function (LVEF  $2.2 \pm 5.4$  vs.  $0.4 \pm 5.3\%$ ,  $p = 0.02$ ) in their study evaluating CPAP versus no CPAP in 258 HF patients with central sleep apnea. This discrepancy between trials showing positive effects of an SDB-specific therapy on LVEF and studies, e.g. ours, which could not find such a relationship, could have two main reasons. First, improvements in LVEF might depend on the duration of SDB-specific therapy. This is supported by the finding that trials with a treatment du-

ration  $\leq 6$  weeks could not show a significant effect of ASV on LVEF [17, 18], whereas studies with a treatment duration  $> 6$  weeks did [36, 38]. This time dependency was also found in trials evaluating acute versus chronic effects of an SDB-specific therapy: so LVEF was even significantly reduced after acute initiation of CPAP treatment and only improved with ongoing therapy eventually leading to a significant gain of LVEF in the longer term [44, 45]. Secondly, since treatment effects on LVEF are generally rather low (as seen by a  $2.2 \pm 5.4\%$  improvement in LVEF in the 258 patients evaluated by Bradley et al. [40]), the cohort size under investigation might also be of relevance, and larger cohorts need to be evaluated to finally judge the impact of ASV therapy on LVEF.

#### *Impact of ASV Therapy on Diastolic Dysfunction and LV Geometry*

Our study was the largest one to evaluate echocardiographic parameters of LV diastolic dysfunction in a collective of HFREF patients with concomitant sleep apnea. Even though there was no significant overall change in diastolic dysfunction, we nevertheless found a modest decrease in both DT and IVRT in the ASV-treated group with opposite changes in the control group. These moderate alterations translated into more patients in the ASV-treated group reaching a normal diastolic function with less patients remaining in the state of a pseudo-normal filling pattern than control patients, respectively. As for the systolic LV function, treatment duration might again be a determinant of effect size, which means that longer treatment periods could eventually unveil more distinct changes in LV diastolic function. This is supported by Bitter et al. [20], who evaluated ASV treatment in patients with HF and normal EF. In this trial, echocardiographic parameters of diastolic dysfunction improved after a time period of  $11.6 \pm 3$  months. In contrast, Arias et al. [19], investigating the impact of ASV treatment on diastolic function in individuals with obstructive sleep apnea, but no concomitant cardiac disease, found an improvement in echocardiographic parameters already after a mean of  $104 \pm 31$  days, with effect sizes which were rather similar to the ones found in our study. This in mind, it seems plausible that ASV treatment needs to be executed the longer the more severely cardiac function is impaired to eventually improve also diastolic dysfunction.

Patients included in the current analysis displayed a pronounced eccentric LV hypertrophy indicated by a relatively low LV wall thickness and a high LVMI. Even though it did not reach statistical significance, LVMI

tended to decrease in the ASV treatment group and to further increase in the control group after 12 weeks, respectively.

Interestingly, it has been shown that LVMI is positively correlated with the severity of sleep apnea in patients with both normal [46] and impaired systolic LV function [47]. Furthermore, CPAP therapy proved to be efficient in reducing LVM in a cohort of patients with normal EF [48]. Sleep apnea seems to further aggravate structural LV anomaly even in HFREF patients, and an SDB-specific therapy has the potential to reverse pathological LV remodeling. Against this background, it seems plausible that subjects suffering from severely impaired cardiac function, as the ones included in the current analysis, might need SDB therapy for a longer period than 12 weeks to more explicitly exhibit reverse cardiac remodeling. This is also supported by the work from Colish et al. [48], who found an ongoing decrease in LVMI even after 12 months of CPAP therapy in patients without LV systolic dysfunction.

Regarding other measures of LV geometry, Kaneko et al. [49] observed in a single-center randomized controlled trial of similar sample size in patients with congestive HF and obstructive sleep apnea a significant reduction of LV end-systolic diameter after 4 weeks of CPAP treatment versus control. In the present multicenter study in patients with congestive HF on contemporary HF therapy with both obstructive and central sleep apnea, ASV therapy had no significant effects on LV diameters.

#### *Limitations*

The number of study patients was limited, since this subset analysis was conceptually intended as pilot trial to provide estimates of effect size to be expected. Otherwise, this investigation is the largest one to date which analyzed effects of ASV therapy on diastolic dysfunction in HFREF patients.

Furthermore, since randomization of the initial study cohort was stratified by study center and type of SDB (i.e. central and obstructive sleep apnea), every subset analysis might alter this initial randomization and stratification scheme. However, the proportion of patients from each center included in the present analysis was similar in the ASV and control groups, respectively, and the proportion of patients with predominantly obstructive sleep apnea was similar in the primary analysis [50] and in the present analysis (ASV group: 47 vs. 53%; control group: 52 vs. 54%). Thus, it is unlikely that the present subgroup analysis of ASV and control patients significantly altered the

original randomization or stratification scheme, leading to a false-positive result.

Finally, there might have been additional confounders influencing the effects of ASV therapy on diastolic function, such as a change in medication or compliance to use ASV during the study period. We therefore additionally adjusted for these parameters, which resulted in a significant decrease in NT-pro-BNP in the ASV group after 12 weeks compared to control patients ( $p = 0.009$ ), whereas there was no significant alteration in any structural or functional (systolic and diastolic) LV parameter (data not shown).

## Conclusion

The current study revealed a high prevalence of diastolic dysfunction in patients with HFREF and concomitant sleep apnea. It furthermore confirmed the efficiency of ASV in reducing apnea-hypopnea events in SDB patients. Whereas neither systolic nor diastolic parameters significantly changed after ASV therapy, there were nevertheless trends towards an improvement in both diastolic function and cardiac remodeling. Thus, these data pro-

vide estimates of effect size and justify the evaluation of the effects of ASV on diastolic function in larger randomized controlled trials.

## Financial Disclosure and Conflict of Interest

This work was supported by a grant from Philips Home Healthcare Solutions (Murrysville, Pa., USA). The sponsor played no role in the design, conduct of the study as well as analysis and interpretation of the data. The sponsor played no role in the preparation, review and approval of the paper.

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