# Treatment of Cheyne-Stokes Respiration Reduces Arrhythmic Events in Chronic Heart Failure

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**Cheyne-Stokes Respiration and Arrhythmias.** ***Objective:*** **This study aimed to investigate whether adequate treatment of Cheyne-Stokes respiration (CSR) reduces the risk of arrhythmic events in patients with chronic heart failure (CHF).**

***Methods:*** **A cohort of 403 registry patients with CHF (LVEF≤45%, NYHA-class≥2) and implanted cardioverter-defibrillator devices (ICD) was studied. They underwent overnight polygraphy, with 221 having mild or no CSR (apnea-hypopnea index [AHI]<15/h), and 182 having moderate to severe CSR (AHI>15/h). Latter ones were offered therapy with adaptive servoventilation (ASV), which 96 patients accepted and 86 rejected. During follow-up (21± 15 months) defibrillator therapies were recorded in addition to clinical and physiologic measures of heart failure severity.**

***Results:*** **Event-free survival from (a) appropriate cardioverter-defibrillator therapies and (b) appropriately monitored ventricular arrhythmias was shorter in the untreated CSR group compared to the treated CSR and the no CSR group. Stepwise Cox proportional hazard regression analysis showed untreated CSR (a: hazard ratio [HR] 1.99, 95% confidence interval [CI] 1.46–2.72, P < 0.001; b: HR 2.19, 95%CI 1.42–3.37, P < 0.001), but not treated CSR (a: HR 1.06, 95%CI 0.74–1.50; P = 0.77; b: HR 1.21, 95%CI 0.75–1.93, P = 0.43) was an independent risk factor. The treated CSR group showed improvements in cardiac function and respiratory stability compared to the untreated CSR group.**

***Conclusion:*** **This study demonstrates a decrease of appropriate defibrillator therapies by ASV treated CSR in patients with CHF and ICD. A reduced exposure to hyperventilation, hypoxia, and improvement in indices of CHF severity and neurohumoral disarrangements are potential causative mechanisms.** *(J Cardiovasc Electrophysiol, Vol. pp. 1-9)*

*heart failure, arrhythmia, sleep, risk factors, implantable cardioverter defibrillator, cardiac resynchronization therapy, ventricular tachycardia, Cheyne-Stokes respiration*

## Introduction

Cheyne-Stokes respiration (CSR) characterized by a waxing and waning pattern of breathing is observed in approximately one-third of CHF patients.[1,2] The mechanisms leading to CSR are not fully understood but include hemodynamic impairment and sympathetic nervous system activation with associated chemoreceptor sensitization.[3-5]

Sudden death is common in CHF, and CSR is a risk factor for mortality.[6] A possible mechanism for increased mortality is that recurrent episodes of hyperventilation and hypoxemia in CHF patients with CSR lead to an increased risk of malignant ventricular arrhythmia.[7] In addition, underlying neurohumoral disarrangements and increased sympathetic nervous system activation are major determinants of the evolution of the disease and of life-threatening events.[8,9] A recent study demonstrated that CSR is a risk factor for potentially life-threatening ventricular arrhythmias.[10]

Adaptive servoventilation (ASV) is a bi-level ventilation mode with automatic adaption of pressure support.[11] During usage, the patient's breathing pattern is continuously monitored. Whenever a significant reduction or pauses in breathing is detected, the ASV device intervenes to maintain the patient's breathing at 90% of what had been normal for that individual just prior to the decrease in breathing. Contrastingly, when the patient's breathing is stable, ASV provides just enough pressure support to help maintain airway

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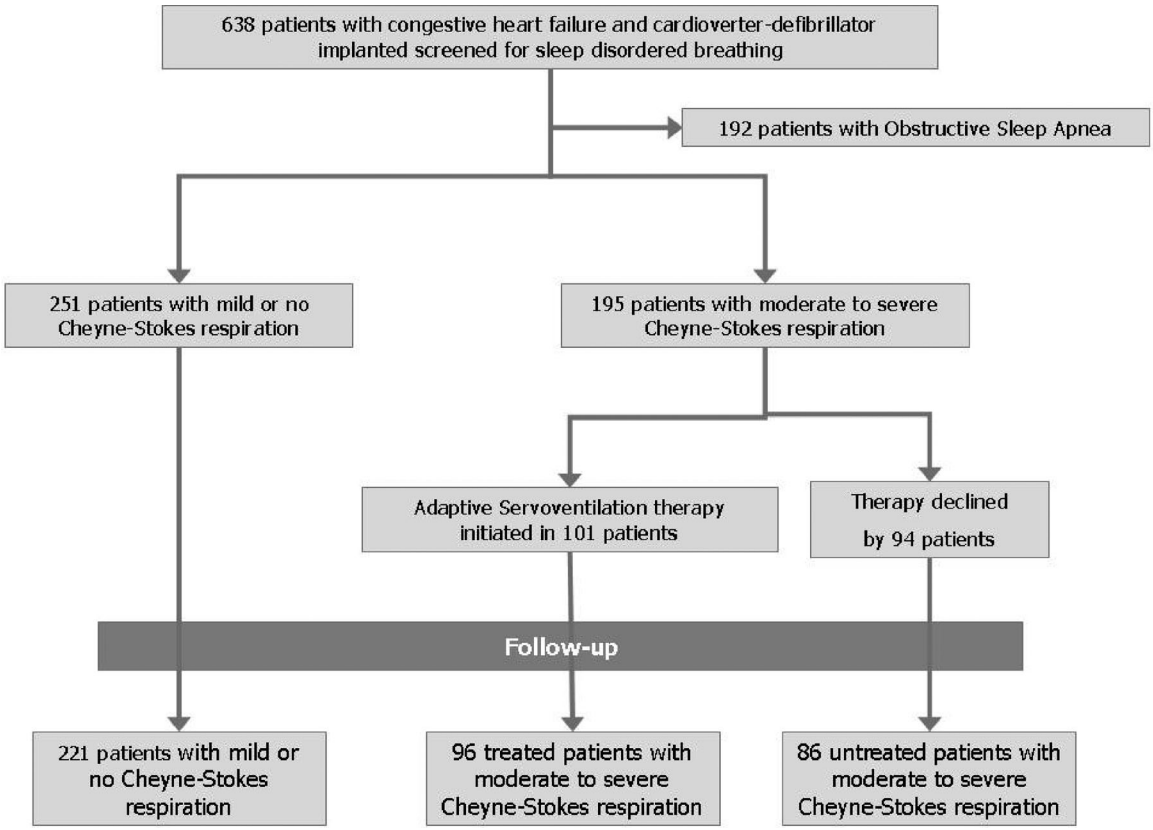



**Figure 1.** *Study flow chart. Ascertainment of the study population and flow chart of the study.*

patency. This anti-cyclic adaption of pressure support has been shown to effectively treat CSR.[12]

Its use in CHF is associated with improvements in ventricular function, sympathetic nervous system activation and respiratory stability.[13-15]

The aim of this proof-of-concept study was to determine whether treatment of CSR with ASV might reduce the risk of appropriate cardioverter-defibrillator therapies as a surrogate parameter for sudden cardiac death in patients with CHF and implanted cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) devices.

## Methods

### *Patients*

All patients enrolled in the study were attending a tertiary referral hospital (Bad Oeynhausen) for the treatment of CHF between February 2005 and July 2009. A total of 638 patients with reduced left ventricular ejection fraction (LVEF) and implanted ICD or CRT-D for primary or secondary prevention of sudden cardiac death according to current guidelines[16] participated in this observational cohort study (Fig. 1). Even though all investigations and procedures are part of our daily clinical routine, patients' informed consent was obtained the day before they were screened for sleep disordered breathing (SDB). One hundred ninety-two patients had predominant obstructive sleep apnea (OSA), and were not eligible for the study. Of the remaining 446 subjects, 195 were classified as having CSR (apnea-hypopnea index [AHI] $\geq$15/h) and consecutively included into a prospective registry (ClinicalTrials.gov identifier: NCT01657188), while those with mild or no CSR (no CSR; AHI<15/h) formed the control-group. Treatment with ASV was offered to all patients with CSR and in those who accepted therapy (treated CSR) was initiated following a titration night in hospital. Inclusion criteria to this study included persistent impairment of systolic left ventricular function according to echocardiographic criteria (LVEF $\leq$ 45%), New York Heart Association (NYHA) class $\geq$ II, and an ICD or CRT-D device implanted according to current guidelines.[17] Patients with a CRT-D were not eligible for inclusion in the first 6 months after implantation. Patients were on stable heart failure medication for at least 4 weeks before enrollment. Exclusion criteria included previous or ongoing treatment of SDB, predominant OSA found on overnight polygraphy, significant valvular heart disease, significant pulmonary disease, hypercapnia ($pCO_2$ > 45 mmHg), pregnancy, and acute coronary syndrome or acute myocardial decompensation within the last 4 weeks. The study was approved by the Ethical Review Board of the Ruhr University Bochum, Bad Oeynhausen.

### *Sleep Studies*

In-hospital unattended cardiorespiratory polygraphy (PG, Embletta™, Embla, The Netherlands) was performed as the primary screening tool at baseline as described before.[1,18] SDB was defined in accordance with the 2007 American Academy of Sleep Medicine (AASM) criteria for scoring respiratory events.[19] Patients with an AHI $\geq$15/h were classified as OSA or CSR on the basis of the predominant type of SDB. If the AHI was <15/h, patients were considered to have mild or no CSR.

ASV therapy (AutoSet CS$^{TM}$2, ResMed, Australia) was introduced during wakefulness under continuous blood pressure monitoring and adjusted according to nocturnal measurements. In-hospital polysomnography (PSG, N7000/S7000, Embla, The Netherlands) was performed during therapy initiation as previously described.[14,20,21] Prior to dismissal from hospital patients that underwent ASV treatment were advised to use their device every night during sleep at home. In addition, data from the device including AHI, apnea index (AI) and compliance were downloaded and additional sleep studies were performed at 3, 6, 12, 24, 36, and 48 months of follow-up.

### *Echocardiography*

Diameter of the left atrium (LAD) and left ventricle (end diastolic, LVEDD) as well as LVEF and estimated right ventricular systolic pressure (RVsP) were measured (Vivid 7$^{TM}$, GE Healthcare, Germany) following American Society of Echocardiography guidelines[22] as previously described.[10,14]

### *Cardiopulmonary Exercise Testing*

Symptom-limited bicycle cardiopulmonary exercise testing (CPX, ZAN Ferraris, Germany) starting at 10 watts with an increase of 10 watts per minute was performed. Peak oxygen consumption ($VO_2$ peak), oxygen consumption at the individual aerobic-anaerobic threshold ($VO_2$ AT), and relationship of minute ventilation and carbon dioxide production ($VE/VCO_2$) as well as maximum workload and total exercise time were recorded. Predicted $VO_2$ peak was calculated automatically taking gender and age into account.

### *Rebreathing Test*

The hyperoxic, hypercapnic ventilatory response (HCVR) testing (ZAN Ferraris, Germany) protocol was based on the Read rebreathing testing protocol.[23] HCVR sensitivity was determined as the slope of minute ventilation (l/min) plotted against $PET_{CO2}$ (mmHg).

### *Capillary Blood Gas Analysis and Standard Laboratory*

Partial pressure of carbon dioxide ($pCO_2$), partial pressure of oxygen ($pO_2$), and capillary oxygen saturation were measured at baseline using ABL 330 (Radiometer, Copenhagen, Denmark). In addition, measurements of hemoglobin concentration, C-reactive protein (CRP), N-terminal pro – brain natriuretic peptide (NT-proBNP), sodium and creatinine were performed.

### *Follow-Up and Endpoints*

Patients were followed-up every 12 (10–14) weeks for a maximum of 48 months. Follow-up in the study continued until the first appropriate shock was delivered or an antitachycardia pacing was applied (event), the patient died, or there was a major change of therapy, defined as withdrawal from ASV therapy after more than 3 months of use, change in heart failure medication (except for dosage changes), coronary intervention/cardiothoracic surgery, initiation of SDB treatment, and replacement or explantation of the ICD/CRT-D device or electrodes for any reason (censoring criteria).

Clinical status was systematically obtained at one year follow-up for the remainder in the study that either was in the treated CSR group or rejected treatment (untreated CSR). Data included heart rate and blood pressure at rest, NYHA-functional class, echocardiographic parameters, CPX results, standard laboratory measurements and blood gas samples.

The primary study outcome was time to first appropriate ICD therapy, either by antitachycardia pacing or shock. The secondary outcome parameter was time to first ventricular tacharrhythmic event appropriately monitored by the ICD, including sustained and nonsustained ventricular tachycardia, ventricular flutter or ventricular fibrillation.

### *Implantable Cardioverter-Defibrillator Programming and Interrogations*

Because ICD as well as CRT-D devices were implanted for primary or secondary prevention, we chose a physician-tailored device programming. Thus, monitor, antitachycardia pacing and shock zones were programmed individually for each patient and remained unchanged during follow-up. ICD/CRT-D interrogations were performed at baseline and at follow-up appointments every 12 weeks by electrophysiology specialists. Arrhythmias were defined in accordance with the ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures.[24]

### *Statistical Analysis*

Statistical analysis was performed using SigmaPlot software (Version 11, Systat, Germany). Baseline data grouped by untreated CSR, treated CSR, and no CSR were checked for normal distribution using the Shapiro-Wilk test and then assessed by ANOVA with post hoc pairwise comparison (Holm-Sidak). If no normal distribution was found, ANOVA on ranks (Kruskal-Wallis) was performed followed by post hoc pairwise comparison (Dunn). Categorial data were compared using chi-square tests. Event-free survival was calculated by Kaplan-Meier analysis as the time from initial sleep study to first appropriate cardioverter-defibrillator therapy and/or first ventricular arrhythmia as stored on the CRT-D/ICD device. Log-rank test was used to assess differences in event-free survival time between groups (followed by post hoc pairwise comparison [Holm-Sidak]), and Cox proportional hazard regression model was used to identify independent predictors.

Demographic and clinical data from baseline analyses, which are associated with a negative or positive impact on prognosis in patients with chronic heart failure (CHF), were included into univariate Cox proportional hazard regression models for primary and secondary endpoints. To determine if untreated and/or treated CSR increased the risk of events, multivariate Cox proportional hazard models were performed for case a (appropriate cardioverter-defibrillator therapies) and case b (monitored ventricular tachyarrhythmias). SDB-type (untreated CSR, treated CSR, no CSR) as well as age, sex, ischemic cause, BMI, preexisting atrial fibrillation, implantation for primary/secondary porphylaxis, LVEF, $VO_2$peak, and NYHA-class as pre-specified potential confounders were included in two different multivariate Cox proportional hazard models. The models were performed without interaction. To select the best model, backward selection in accordance with the Akaike Information Criterion (AIC) was used. The p-to-enter value had to be lower than 0.1 and the p-to-remove value greater than 0.1.

Changes of sleep study results from baseline to follow-up within the treatment group were analyzed using paired

*t*-test. Changes in NYHA-functional class, nocturia as well as results from echocardiography, cardiopulmonary exercise testing, and laboratory measurements (NT-proBNP, blood gas analysis) were checked for normal distribution using the Shapiro-Wilk test and then assessed by ANOVA with repeated measures with post hoc pairwise comparison (Holm-Sidak). If data were not normally distributed ANOVA with repeated measures on ranks was performed followed by post hoc pairwise comparison (Tukey). A value of $P < 0.05$ was considered significant for all comparisons. Data are given as mean ± SD unless stated otherwise.

## Results

### *Basic Data*

There were 446 patients enrolled in the study (Fig. 1). In 43 patients (9.6%) no follow-up data were available: 15 (3.4%) had a major change of therapy before the first follow-up investigations, 8 (1.4%) died before the first follow-up, and 20 (6.3%) were lost to follow-up. There were no differences in baseline characteristics between this group and the remainder of the cohort. During follow-up 70/446 patients (15.7%) died, 14 (3.1%) underwent heart transplantation, and 9 (2.0%) received an assist-device. Mean follow-up duration was 21±15 months.

Baseline characteristics of the 403 participants on whom follow-up data are available are shown in Table 1. A total number of 307 patients had a CRT-D device implanted, while 96 patients were provided with an ICD device. Device programming data are shown in Table 1. At study inclusion 129 patients (32.0%) were on class-III-antiarrhythmic drug treatment. Of those, 118 were on amiodarone, while 11 patients were treated with sotalol. In addition, 3 patients were on additive phenytoin or mexiletine medication. Indication to antiarrhythmic drug treatment was made individually by their treating physicians.

ASV was successfully initiated in 101 patients and was declined in 94 patients who were either unwilling to use the device or stopped using it before the first follow-up investigation at 3 months.

### *Cardioverter-Defibrillator Therapies*

In total, 126 out of 403 (31.2%) patients were affected by appropriate cardioverter-defibrillator therapies (CRT-D 76 out of 289 patients (26.2%), ICD 50 out of 114 patients (43.5%, $P < 0.01$). Those included 61 out of 221 (27.6%) patients with no CSR, 40 out of 86 (46.5%) patients with untreated CSR, and 25 out of 96 (26.0%) patients with treated CSR, respectively. Mean event-free survival time (Fig. 2) was 37.2 ± 1.2 months in the no CSR group, 26.4 ± 2.4 months in the untreated CSR group, and 34.8 ± 2.2 months in the treated CSR group, respectively (no CSR vs untreated CSR: $P < 0.001$; treated CSR vs untreated CSR: $P = 0.01$, no CSR vs treated CSR: $P = 0.38$). Comparing patients with a device-usage above average (>5:56 hours per day and usage on >60% of all days, $n = 39$, adherent) to patients with a usage below average ($n = 57$, nonadherent), mean event-free survival time (Fig. 3) was 37.8 ± 3.7 months in the adherent group and 32.2 ± 2.9 months in the nonadherent group (adherent vs untreated: $P < 0.001$; nonadherent vs untreated: $P = 0.10$; adherent vs nonadherent: $P = 0.16$). Univariate Cox proportional hazards results are given in Table 2. Multivariate Cox proportional hazards with backward selection, adjusted for age, sex, ischemic cause, BMI, preexisting afib, implantation for primary/secondary porphylaxis, LVEF, $VO_2$peak, and NYHA-class revealed untreated CSR (hazard ratio [HR] 2.65, 95% confidence interval [CI] 1.78 to 3.96, $P < 0.001$) as a significant risk factor. Treated CSR as well as no CSR were eliminated by P-value method.

### *Stored Ventricular Tachyarrhythmias*

During follow-up, 210 patients (52.1%) were affected by ventricular tachyarrhythmia. Initial arrhythmia was nonsustained ventricular tachycardia, seen in 156 patients (38.7%), while 54 (13.4%) were primarily affected by sustained ventricular tachycardia or ventricular flutter. Ventricular tachyarrhythmias were documented in 112 out of 221 (50.7%) patients with no CSR, 55 out of 86 (64.0%) patients with untreated CSR, and 43 out of 96 (44.8%) patients with treated CSR. Mean event-free survival time was 28.1 ± 1.3 months in the no CSR group, 19.5 ± 2.3 months in the untreated CSR group, and 26.2 ± 2.2 months in the treated CSR group ($P < 0.001$ no CSR vs untreated CSR; $P < 0.01$ treated CSR vs untreated CSR, and $P = 0.63$ no CSR vs treated CSR). Univariate Cox proportional hazards are shown in Table 2. Multivariate Cox proportional hazards with backward selection, adjusted for age, sex, ischemic cause, BMI, preexisting afib, implantation for primary/secondary porphylaxis, LVEF, $VO_2$peak, and NYHA-class revealed untreated CSR (HR 2.40, 95% CI 1.70 to 3.40, $P < 0.001$) as a significant risk factor. Treated CSR as well as no CSR were eliminated by P-value method.

### *Changes in Cardiopulmonary Functional Parameters and Sleep Study Results*

Changes in cardiopulmonary functional parameters were recorded on a regular basis during follow-up visits in the treated CSR and untreated CSR group. Of 104 patients at risk in these groups we were able to obtain complete datasets for 82 (79%, 51 treated CSR, 31 untreated CSR) at one year follow-up. Results are displayed in Table 3.

Sleep studies showed that ASV effectively treated CSR with a reduction of AHI (median (quartiles)) from 32/h (23/h, 40/h) at baseline to 1/h (1/h, 4/h; $P < 0.001$), and improvements in mean oxygen saturation (92.7 ± 2.2% to 94.4 ± 2.2%, $P < 0.001$), maximum oxygen desaturation (81% (77%, 84%) to 89% (86%, 91%), $P < 0.001$), mean desaturation (6.6 ± 2.6% to 3.8 ± 2.3%, $P < 0.001$), longest apnea period (41.5 ± 17.7s to 16.6 ± 19.7s, $P < 0.001$), and longest hypopnea (49.0 ± 21.3s to 37.0 ± 23.0s, $P < 0.001$). Data from therapy devices demonstrated a mean AHI of 4.3 ± 4.0/h with a mean apnea index (AI) of 0.5 ± 1.1/h. Average usage was 60 ± 34% of all days with a mean daily usage of 5:57 ± 1:53h (usage days only).

## Discussion

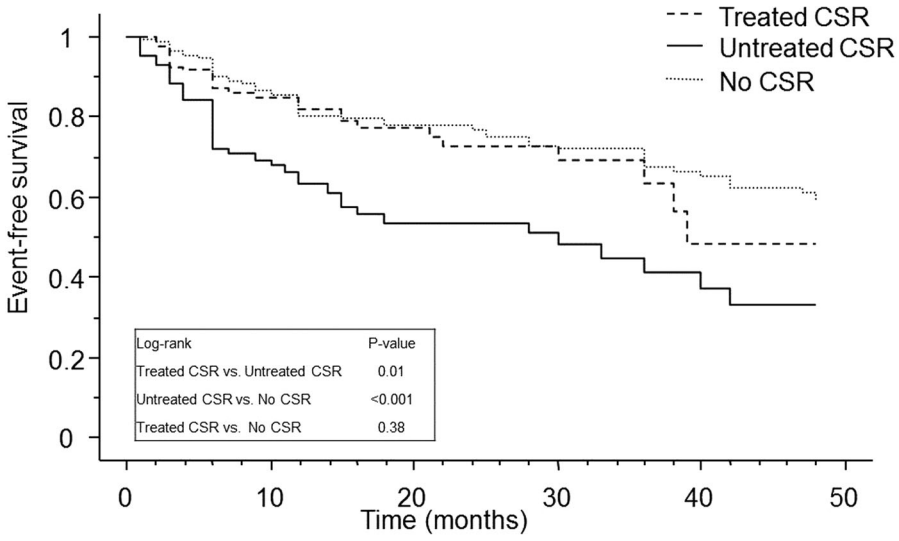
As a proof-of-concept this study aimed to investigate beneficial effects of adequate treatment of CSR on the incidence of potentially life threatening ventricular arrhythmias in a CHF population. Results confirm CSR to be associated with adequate cardioverter-defibrillator therapies and suggest that effective treatment may reduce the risk to a similar level to those without CSR. Positive effects on ventricular function,

**TABLE 1**

Baseline Data of the Study Population

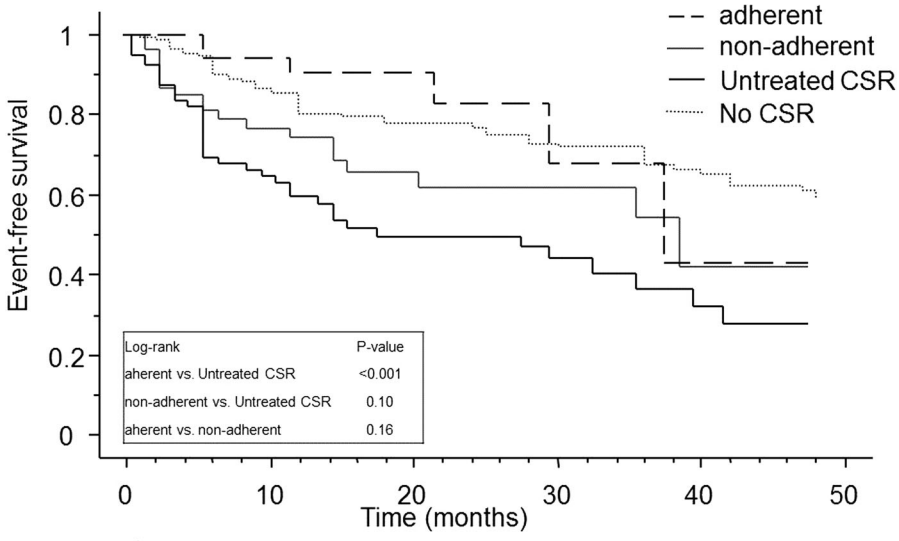
| | Treated CSR | Untreated CSR | No CSR |
|---|---|---|---|
| **Demographic data** | | | |
| N | 96 | 86 | 221 |
| Male, n (%) | 83 (86.5) | 73 (84.9) | 146 (66.0)*† |
| Age, years; median (quartiles) | 69 (62, 72) | 68 (61, 73) | 65 (53, 70)*† |
| Body-mass-index, kg/m$^2$; median (quartiles) | 27 (24, 29) | 26 (23, 29) | 25 (23, 28)* |
| Nocturia; median (quartiles) | 1 (0, 2) | 1 (0, 2) | 0 (0, 2) |
| NYHA-class III or IV, n (%) | 51 (53.1) | 47 (54.6) | 89 (40.3)*† |
| CRT implanted, n (%) | 61 (63.5) | 56 (65.1) | 172 (77.8)*† |
| Systolic blood pressure, mmHg; median (quartiles) | 110 (96, 123) | 110 (98, 120) | 115 (100, 125)*† |
| Diastolic blood pressure, mmHg; median (quartiles) | 69 (60, 79) | 70 (61, 78) | 70 (63, 80) |
| Atrial fibrillation, n (%) | 29 (30.2) | 17 (19.8) | 31 (14.0)* |
| Heart rate, min$^{-1}$; median (quartiles) | 70 (60, 76) | 70 (60, 77) | 66 (60, 75) |
| Ischemic cause, n (%) | 54 (56.3) | 43 (50.0) | 88 (39.8)* |
| Defibrillator for secondary prophylaxis, n (%) | 25 (26.0) | 18 (20.9) | 69 (31.2) |
| History of diabetes, n (%) | 30 (31.3) | 26 (30.2) | 63 (28.5) |
| **Medication, n (%)** | | | |
| Beta blockers | 93 (96.9) | 80 (93.0) | 214 (96.8) |
| ACE/AT1-inhibitors | 94 (97.9) | 85 (98.8) | 221 (100)* |
| Aldosterone blockers | 75 (78.1) | 67 (77.9) | 163 (73.8) |
| Class III antiarrhythmic drugs | 41 (42.7) | 33 (38.4) | 55 (24.9)*† |
| Digitalis glycosides | 44 (45.8) | 40 (46.5) | 111 (50.2) |
| Diuretics | 93 (96.9) | 86 (100) | 212 (95.9) |
| **Blood gas analysis and sleep studies** | | | |
| pH; median (quartiles) | 7.445 (7.428, 7.459) | 7.440 (7.418, 7.471) | 7.438 (7.418, 7.456) |
| $pO_2$, mmHg; median (quartiles) | 76.9 (69.5, 83.3) | 67.7 (69.6, 82.4) | 77.6 (70.2, 84.2) |
| $pCO_2$, mmHg; median (quartiles) | 36.1 (33.7, 38.7) | 35.4 (32.5, 38.5) | 37.1 (35.1, 40.4)*† |
| Base excess; median (quartiles) | 1.3 (0.2, 2.7) | 0.5 (−0.8, 2.5) | 1.2 (0.1, 2.7) |
| AHI, h$^{-1}$; median (quartiles) | 32 (23, 40) | 33 (24, 44) | 3 (2, 7)*† |
| Mean oxygen saturation (%); median (quartiles) | 93 (91, 95) | 93 (92, 95) | 95 (93, 97)*† |
| Maximum oxygen desaturation (%); median (quartiles) | 81 (77, 84) | 83 (79, 85) | 88 (85, 90)*† |
| Average oxygen desaturation (%); median (quartiles) | 6 (5, 8) | 6 (5, 7) | 4 (3, 5)*† |
| Longest apnea duration, s; median (quartiles) | 38 (29, 52) | 37 (28, 53) | 15 (10, 27)*† |
| Longest hypopnea duration, s; median (quartiles) | 43 (37, 54)‡ | 41 (33, 50) | 30 (24, 38)*† |
| **Echocardiography** | | | |
| LVEF (%); median (quartiles) | 25 (25, 30) | 26 (24, 32) | 30 (25, 35)*† |
| LVEDD, mm; median (quartiles) | 69 (65, 71) | 71 (65, 74) | 67 (62, 74)† |
| LAD, mm; median (quartiles) | 50 (46, 57) | 50 (46, 55) | 48 (43, 52)*† |
| RVsP; median (quartiles) | 40 (27, 49) | 42 (33, 50) | 33 (25, 46) |
| **Rebreathing test** | | | |
| HCVR (L/min/mmHg); median (quartiles) | 3.500 (2.330, 5.645) | 3.807 (3.059, 5.174) | 2.302 (1.802, 3.030)*† |
| **Cardiopulmonary exercise testing** | | | |
| Duration, min; median (quartiles) | 7 (5, 9) | 7 (5, 9) | 7 (5, 9) |
| Maximum workload, watts; median (quartiles) | 70 (52, 88) | 73 (54, 99) | 74 (58, 94) |
| $VO_2$ AT, mL/min/kg; median (quartiles) | 11.6 (9.0, 14.2) | 12.4 (10.0, 14.3) | 12.2 (10.3, 15.1) |
| $VO_2$ peak, mL/min/kg; median (quartiles) | 13.4 (11.0, 15.7) | 14.6 (12.4, 16.5) | 14.3 (11.7, 17.4) |
| $VO_2$ predicted,%; median (quartiles) | 55 (46, 67) | 56 (46, 66) | 59 (56, 78) |
| $VE/VCO_2$; median (quartiles) | 34 (30, 42) | 34 (32, 38) | 31 (27, 35)*† |
| **Laboratory measurement** | | | |
| NT-proBNP overall, pg/mL; median (quartiles) | 1593 (887, 3855)* | 1300 (645, 3140) | 968 (318, 1984) |
| - Sinus rhythm | 1583 (579, 3693)* | 1104 (584, 2804) | 964 (314, 1990) |
| - Atrial fibrillation | 1593 (977, 3959) | 1679 (1200, 4670) | 1110 (557, 1890) |
| Hb, g/dL; median (quartiles) | 14.4 (13.0, 15.0) | 13.7 (12.5, 14.9) | 13.6 (12.4, 14.7) |
| Sodium, mmol/L; median (quartiles) | 139 (137, 142) | 139 (137, 141) | 139 (137, 141) |
| Creatinine, mg/dL; median (quartiles) | 1.4 (1.1, 1.7) | 1.4 (1.2, 1.7) | 1.1 (0.9, 1.5) |
| high-sensitivity CRP, mg/dL; median (quartiles) | 0.31 (0.17, 0.57) | 0.37 (0.12, 0.78) | 0.28 (0.11, 0.63) |
| **Device programming** | | | |
| Charge time, s; median (quartiles) | 8.7 (8.0, 10.6) | 9.5 (7.9, 10.6) | 9.0 (7.8, 10.5) |
| Zones, n; median (quartiles) | 2 (2,2) | 2 (2,2) | 2 (2,2) |
| VT-Zone, min$^{-1}$; median (quartiles) | 170 (167, 171) | 171 (170, 171) | 171 (170, 171) |
| Bursts, n; median (quartiles) | 3 (3, 4) | 3 (3, 4) | 3 (3, 4) |
| Ramp, n; median (quartiles) | 3 (3, 4) | 3 (3, 4) | 3 (3, 4) |
| - Shock, n; median (quartiles) | 5 (4, 5) | 4 (4, 5) | 4 (4, 5) |
| VF-Zone, min$^{-1}$; median (quartiles) | 200 (200, 200) | 200 (200, 200) | 200 (200, 200) |
| Shock, n; median (quartiles) | 6 (6, 8) | 6 (6, 8) | 6 (6, 8) |
| Impedance RA, Ohm; median (quartiles) | 463 (412, 508) | 468 (417, 515) | 473 (420, 520) |
| Impedance RV, Ohm; median (quartiles) | 511 (449, 623) | 508 (427, 623) | 515 (451, 637) |
| Impedance LV, Ohm; median (quartiles) | 634 (504, 757) | 620 (494, 741) | 641 (513, 768) |
| Sensing RA, mv; median (quartiles) | 3.2 (2.5, 4.5) | 3.0 (2.3, 4.4) | 3.1 (2.3, 4.5) |
| Sensing RV, mv; median (quartiles) | 12.4 (8.8, 17.2) | 12.4 (8.7, 17.2) | 12.6 (8.9, 17.5) |

*$P < 0.05$ treated CSR versus no CSR,
†$P < 0.05$ untreated CSR versus no CSR,
‡$P < 0.05$ treated CSR versus untreated CSR.




| Number at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|---|---|---|---|---|---|---|---|---|---|
| Treated CSR | 96 | 86 | 62 | 48 | 30 | 20 | 12 | 7 | 7 |
| Untreated CSR | 86 | 63 | 42 | 29 | 25 | 19 | 12 | 9 | 9 |
| No CSR | 221 | 196 | 159 | 125 | 109 | 92 | 79 | 48 | 39 |

**Figure 2.** *Kaplan-Meier plot on appropriate cardioverter-defibrillator therapies (primary study endpoint), arranged according to treated Cheyne-Stokes respiration (Treated CSR), untreated Cheyne-Stokes respiration (Untreated CSR), and no Cheyne-Stokes respiration (No CSR).*




| Number at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|---|---|---|---|---|---|---|---|---|---|
| ahderent | 39 | 38 | 27 | 22 | 10 | 7 | 3 | 2 | 2 |
| non-adherent | 57 | 48 | 35 | 26 | 20 | 13 | 9 | 5 | 5 |
| Untreated CSR | 221 | 196 | 159 | 125 | 109 | 92 | 79 | 48 | 39 |
| No CSR | 221 | 196 | 159 | 125 | 109 | 92 | 79 | 48 | 39 |

**Figure 3.** *Kaplan-Meier plot on appropriate cardioverter-defibrillator therapies arranged according to device adherence. Kaplan-Meier plot on appropriate cardioverter-defibrillator therapies (primary study endpoint), arranged according to treatment device-usage above average (adherent), treatment device-usage below average (nonadherent), untreated Cheyne-Stokes respiration (Untreated CSR), and no Cheyne-Stokes respiration (No CSR).*

neurohumoral disarrangements, respiratory stability, and hypoxia are potential causative mechanisms.

In total, 126 patients (32.3%) were affected by appropriate defibrillator therapies. Compared with current CRT-D trials this number appears quite high.[25] However, in 112 patients (27.8%) devices were implanted for secondary prevention. These patients in specific are known to face a higher risk for defibrillator therapies.[26,27] Consequently, we also identified implantation for secondary prevention as the most important risk factor.

CSR has been associated with ventricular ectopy and arrhythmias in community and CHF populations. Mehra *et al*. reported that in a community cohort of 2911 men (6% with heart failure) CSR was an independent risk factor for complex ventricular ectopy (OR 1.55, 95%CI 1.2 to 2.0).[28] Lanfranchi *et al*. investigated 47 patients with CHF and found a higher incidence of nonsustained ventricular arrhythmias in those with CSR.[29] Although these studies as well as our data suggest a higher incidence of arrhythmias with CSR, ventricular ectopy, and nonsustained ventricular tachycardia are of little predictive value with respect to life-threatening arrhythmias.[30]

Staniforth *et al*. demonstrated an increased risk for life-threatening arrhythmias in 101 heart failure patients with suspected CSR after an average follow-up period of 6 months.[31] Our group has previously reported on a cohort of 255 patients with implanted CRT-D devices followed for up to 48 months. Both OSA and CSR were independently associated with

**TABLE 2**

Univariate Analysis of Risk Factors for Ventricular Arrhythmias and Therapy Events Stored by CRT-D or ICD Devices

| Risk factor | Hazard ratio | 95% Lower | 95% Upper | P-Value |
|---|---|---|---|---|
| **Stored ventricular arrhythmias** | | | | |
| Male gender | 1.298 | 0.940 | 1.794 | 0.113 |
| Age > 70 years | 0.934 | 0.687 | 1.271 | 0.666 |
| BMI < 20 | 2.850 | 1.400 | 5.801 | **0.004** |
| Ischemic cause of CHF | 1.067 | 0.813 | 1.401 | 0.651 |
| Secondary prophylaxis | 2.087 | 1.584 | 2.754 | **<0.001** |
| NYHA-class III or IV | 1.059 | 0.806 | 1.391 | 0.97 |
| Systolic blood pressure <100 mmHg | 1.127 | 0.816 | 1.555 | 0.468 |
| Diastolic blood pressure < 60 mmHg | 0.815 | 0.502 | 1.323 | 0.408 |
| Atrial fibrillation | 1.085 | 0.766 | 1.537 | 0.65 |
| Heart rate >75/min | 1.068 | 0.792 | 1.440 | 0.666 |
| Evident diabetes | 1.205 | 0.897 | 1.620 | 0.216 |
| Class III antiarrhythmics | 1.060 | 0.793 | 1.418 | 0.69 |
| LVEF (per −1%) | 1.007 | 0.988 | 1.027 | 0.45 |
| LVEDD (per +1 mm) | 1.013 | 0.998 | 1.027 | 0.09 |
| LAD (per +1 mm) | 1.024 | 1.007 | 1.041 | **<0.01** |
| HCVR (per +1L/min/mmHg) | 1.026 | 0.979 | 1.074 | 0.29 |
| $VO_2$ peak (per −1 mL/min/kg) | 1.001 | 0.974 | 1.028 | 0.920 |
| Predicted $VO_2$ (per −1%) | 1.005 | 0.997 | 1.012 | 0.240 |
| $VE/VCO_2$ (per +1) | 1.009 | 0.986 | 1.032 | 0.464 |
| NT-proBNP>2000 | 1.228 | 0.897 | 1.680 | 0.198 |
| Anemia (Hb< 13 g/dL) | 1.016 | 0.750 | 1.375 | 0.920 |
| Hyponatremia ($Na^+$< 137 mmol/L) | 1.360 | 0.929 | 2.000 | 0.119 |
| Renal failure (Creatinine> 1.2 mg/dL) | 1.030 | 0.782 | 1.357 | 0.832 |
| Untreated Cheyne-Stokes respiration | 1.890 | 1.366 | 2.614 | **<0.001** |
| Treated Cheyne-Stokes respiration | 1.055 | 0.740 | 1.504 | 0.77 |
| **Cardioverter-defibrillator therapies** | | | | |
| Male gender | 1.621 | 1.044 | 2.517 | **0.031** |
| Age > 70 years | 1.259 | 0.862 | 1.839 | 0.233 |
| BMI < 20 kg/m$^2$ | 2.867 | 1.255 | 6.548 | **0.012** |
| Ischaemic cause | 1.412 | 0.995 | 2.003 | 0.054 |
| ICD for secondary prohylaxis | 3.268 | 2.300 | 4.651 | **<0.001** |
| NYHA-class III or IV | 1.529 | 1.076 | 2.169 | **0.012** |
| Systolic blood pressure <100 mmHg | 1.582 | 1.070 | 2.336 | **0.021** |
| Diastolic blood pressure <60 mmHg | 1.957 | 1.140 | 3.367 | **0.015** |
| Atrial fibrillation | 1.469 | 0.964 | 2.239 | 0.074 |
| Heart rate >75/min | 0.880 | 0.591 | 1.310 | 0.529 |
| Evident diabetes | 0.994 | 0.670 | 1.474 | 0.97 |
| LVEF (per −1%) | 1.043 | 1.016 | 1.070 | **<0.01** |
| LVEDD (per +1 mm) | 1.025 | 1.007 | 1.044 | **<0.01** |
| LAD (per +1 mm) | 1.043 | 1.023 | 1.063 | **<0.001** |
| HCVR (per +1 L/min/mmHg) | 1.063 | 1.013 | 1.114 | **0.034** |
| $VO_2$ peak (per −1 mL/min/kg) | 0.958 | 0.920 | 0.998 | **0.04** |
| Predicted $VO_2$ (per −1%) | 0.985 | 0.974 | 0.995 | **0.003** |
| $VE/VCO_2$ (per +1) | 1.039 | 1.009 | 1.069 | **0.009** |
| NT-proBNP > 2000 | 1.447 | 0.974 | 2.150 | 0.067 |
| Anemia (Hb < 13 g/dL) | 0.701 | 0.486 | 1.011 | 0.057 |
| Hyponatremia ($Na^+$< 137 mmol/L) | 1.132 | 0.702 | 1.824 | 0.611 |
| Renal failure (Creatinine> 1.2 mg/dL) | 1.330 | 0.935 | 1.892 | 0.112 |
| Untreated Cheyne-Stokes respiration | 2.416 | 1.617 | 3.609 | **<0.001** |
| Treated Cheyne-Stokes respiration | 1.207 | 0.754 | 1.932 | 0.43 |

appropriate ICD therapies.[10] In this study, which investigated a larger group of patients, similar results were found although the hazard ratio was lower than in our previous study (2.7 vs 3.4). These results confirm that untreated CSR is a significant risk factor for the development of potentially life threatening ventricular arrhythmias.

Data on effects of therapy of CSR on ventricular arrhythmias are scarce. Javaheri *et al*. reported that treatment with continuous positive airway pressure (CPAP) reduced ventricular irritability in CHF patients with CSR.[32]

The CANPAP trial investigated the influence of CPAP on transplant-free survival in 258 heart failure patients with

**TABLE 3**

Changes in Clinical Status, Echocardiographic Parameters, and Cardiopulmonary Exercise Testing From Baseline to 12 Months Follow-Up

| | Treated CSR | Untreated CSR | P-value |
|---|---|---|---|
| **Clinical status** | | | |
| NYHA-class | − 0.5 ± 0.8 | 0.1 ± 0.6 | <0.001 |
| Heart rate (min$^{-1}$) | −2 ± 10 | 0 ± 16 | 0.69 |
| Systolic blood pressure (mmHg) | −1 ± 21 | 0 ± 20 | 0.87 |
| Diastolic blood pressure (mmHg) | −2 ± 13 | −1 ± 17 | 0.94 |
| **Echocardiography** | | | |
| LVEF (%) | 2.5 ± 6.9 | − 1.0 ± 6.1 | 0.03 |
| LVEDD (mm) | − 1.6 ± 7.6 | 0.8 ± 9.5 | 0.16 |
| LAD (mm) | − 0.3 ± 6.0 | 1.6 ± 6.0 | 0.14 |
| **Cardiopulmonary exercise testing** | | | |
| Workload (watts) | 5.4 ± 20.9 | − 2.9 ± 20.6 | 0.06 |
| $VO_2$ AT (mL/min/kg) | 0.2 ± 5.2 | − 1.8 ± 2.7 | 0.10 |
| $VO_2$ peak (mL/min/kg) | 1.5 ± 3.3 | − 2.1 ± 3.2 | <0.01 |
| Predicted $VO_2$ peak (%) | 5.8 ± 14.5 | − 5.8 ± 18.0 | 0.02 |
| $VE/VCO_2$ | − 1.8 ± 3.5 | 0.6 ± 3.4 | 0.07 |
| **Blood gas samples and laboratory** | | | |
| pH | − 0.011 ± 0.037 | 0.002 ± 0.054 | 0.35 |
| $pO_2$ (mmHg) | 1.5 ± 8.6 | − 1.6 ± 4.5 | 0.08 |
| $pCO_2$ (mmHg) | 1.2 ± 3.8 | 0.1 ± 3.9 | 0.16 |
| Creatinine (mg/dL) | − 0.1 ± 0.7 | 0.2 ± 0.8 | 0.28 |

CSR.[33] No overall mortality differences were found, but CPAP was only partially successful at eliminating CSR with a mean residual AHI of 19 events per hour. A subgroup analysis of patients who responded to CPAP (AHI<15/h) showed a significant improvement in mortality.[34] ASV is a more reliable treatment than CPAP and it normally eliminates CSR.[12] In this study the mean AHI on ASV therapy at follow-up was 1/h, confirming that treatment was efficacious. Moreover, our results also suggest that if CSR is successfully treated with ASV the risk of appropriate cardiverter-defibrillator therapies is reduced and that therapy compliance is of substantial importance.

We assume multiple mechanisms involved in a risk reduction from potentially life threatening ventricular arrhythmias due to ventilation therapy. ASV may reduce the burden of tachyarrhythmic events by inducing positive remodelling, which was shown in this study (Table 3) as well as in several other investigations.[13,14] Second, patients with CSR are exposed to intermittent hypoxemias and especially hyperventilation periods occurring with alterations in sympathetic and parasympathetic nervous system activity.[35] This provokes ventricular ectopy as well as T-wave alternans, which likely is reduced with abolishing hyperventilation periods under ASV therapy.[36,37] Third, CSR per se functions as a biomarker of neurohumoral disarrangements. As mentioned before, CSR is caused by haemodynamic alterations and increased sympathetic activity that leads to an abnormal cardiorespiratory reflex control and is associated with blunted baroreflex sensitivity, daytime hyperventilation, and enhanced ventilatory response to exercise.[4,5,38,39] These markers per se stand in line with CSR to have a crucial prognostic impact in patients with CHF.[9,40-43] We previously confirmed higher HCVR an independent risk factor for malignant cardiac arrhythmias.[10] Possibly, ASV therapy not only modulates CSR but moreover has a direct and/or an indirect impact via positive remodelling on these neurohumoral disarrangements. As HCVR was not measured at follow-up in our cohort, evidence for chemoreceptor desensitization and a reduction of sympathetic activity can be derived from a decrease of $VE/VCO_2$ during CPX as

well as from an increase in $pCO_2$ in capillary blood gas analysis at one year follow-up by trend in the treated CSR group compared to the untreated CSR cohort, which has also been reported before.[14]

## Limitations

This was an observational cohort study, and treatment allocation was not randomized, but rather determined by patients' decision to accept ASV therapy. With 101 out of 195 patients accepting the therapy and only 39 of the 96 analyzed demonstrating an adherence >60%, less than a quarter of patients with CSR accepted and were compliant with therapy. This may have posed a bias as patients declining ASV therapy, although having very similar baseline characteristics to those who accepted ASV therapy, may have been less compliant with other aspects of their therapy. Initial evaluation of SDB was done with cardiorespiratory polygraphy rather than PSG, the gold standard. This may have led to minor inaccuracies in the determination of AHI, even though an extremely close correlation between the results obtained by PG and PSG has been reported.[44] As defibrillator devices were implanted for primary or secondary prevention, we chose a physician-tailored device programming. Even though data were not different between groups, this may have influenced the validity regarding truly life-threatening arrhythmias. Previous studies suggested programming strategies that prolong detection duration or increase heart rate threshold to reduce the number of tachyarrhythmias subjected to shock therapy without any increase of syncope or death.[45,46]

## Conclusions

This proof-of-concept study is the first to suggest a reduction of adequate cardiverter-defibrillator therapies by ASV treated CSR in patients with CHF and ICD/CRT-D therapy. Several mechanisms can be involved in the reduction of arrhythmia burden: patients using ASV had reduced exposure to hyperventilation, hypoxemia, cyclical changes in autonomic tone, and a global improvement in indices of CHF severity compared to untreated patients. The influence of CSR on the risk of ventricular tachyarrhythmia may be an explanation for the impaired prognosis associated with CSR in CHF. If CSR really is a therapeutic target for patients with CHF at risk of ventricular arrhythmias needs to be addressed by forthcoming randomized, controlled trials.

## References


1. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V: Sleep-disordered breathing in patients with symptomatic heart failure: A contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251-257.
2. Javaheri S: Sleep disorders in systolic heart failure: A prospective study of 100 male patients. The final report. Int J Cardiol 2006 2006;106:21-28.
3. Javaheri S: A mechanism of central sleep apnoea in patients with heart failure. N Engl J Med 1999;341:949-954.
4. Oldenburg O, Bitter T, Wiemer M, Langer C, Horstkotte D, Piper C: Pulmonary capillary wedge pressure and pulmonary arterial pressure in heart failure patients with sleep-disordered breathing. Sleep Med 2009;10:726-730.
5. Yumino D, Redolfi S, Ruttanaumpawan P: Nocturnal rostral fluid shift: A unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation 2010;13:1598-1605.
6. Javaheri S, Shukla R, Zeigler H, Wexler L: Central sleep apnoea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007;49:2028-2034.
7. Ryan CM, Juvet S, Leung R, Bradley TD: Timing of nocturnal ventricular ectopy in heart failure patients with sleep apnea. Chest 2008;133:934-940.
8. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD: Adverse consequences of high sympathetic nervous activation in the failing human heart. J Am Coll Cardiol 1995;26:1257-1263.
9. Giannoni A, Emdin M, Bramanti F, Iudice G, Francis DP, Barsotti A, Piepoli MF, Passino C: Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. J Am Coll Cardiol 2009;53:1975-1980.
10. Bitter T, Westerheide N, Prinz C, Hossain MS, Vogt J, Langer C, Horstkotte D, Oldenburg O: Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J 2011;32:61-74.
11. Oldenburg O: Cheyne-Stokes respiration in chronic heart failure. Circ J 2012;76:2305-2317.
12. Teschler H, Döhring J, Wang YM, Berthon-Jones M: Adaptive pressure support servo-ventilation: A novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 2001;164:614-619.
13. Kasai T, Usui Y, Yoshioka T, Yanagisawa N, Takata Y, Narui K, Yamaguchi T, Yamaguchi A, Momomura S: Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. Circ Heart Fail 2010;3:140-148.
14. Oldenburg O, Bitter T, Lehmann R, Korte S, Dimitriadis Z, Faber L, Schmidt A, Westerheide N, Horstkotte D: Adaptive servoventilation improves cardiac function and respiratory stability. Clin Res Cardiol 2011;100:107-116.
15. Harada D, Joho S, Oda Y, Hirai T, Asanoi H, Inoue H: Short term effect of adaptive servo-ventilation on muscle sympathetic nerve activity in patients with heart failure. Auton Neurosci 2011;161:95-102.
16. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Europace 2006;8:746-837.
17. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, van Veldhuisen DJ; Committee for Practice Guidelines of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG): 2010 Focused Update of ESC guidelines on device therapy in heart failure: An update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac resynchronisation therapy developed with the special contribution of the Heart Failure Assocation and the European Heart Rhythm Association (abstr). Eur J Heart Fail 2010;12:1143-1153.
18. Bitter T, Prinz C, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O: Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail 2009;11:602-608.
19. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF: The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications. In: *AASM Manual for Scoring Sleep*. American Academy of Sleep Medicine: Westchester, IL; 2007.
20. Bitter T, Westerheide N, Faber L, Hering D, Prinz C, Langer C, Horstkotte D, Oldenburg O: Adaptive servoventilation in diastolic heart failure and Cheyne-Stokes respiration. Eur Respir J 2010;36:385-392.
21. Bitter T, Westerheide N, Hossain MS, Lehmann R, Prinz C, Kleemeyer A, Horstkotte D, Oldenburg O: Complex sleep apnoea in congestive heart failure. Thorax 2011;66:402-407.
22. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK; American College of

Cardiology; American Heart Association; American Society of Echocardiography: Guideline Update for the Clinical Application of Echocardiography: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003;16:1091-1110.
23. Read DJ: A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med 1967;16:20-32.
24. Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Greene HL, Haines DE, Hayes DL, Heidenreich PA, Miller JM, Poppas A, Prystowsky EN, Schoenfeld MH, Zimetbaum PJ, Goff DC, Grover FL, Malenka DJ, Peterson ED, Radford MJ, Redberg RF: ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation 2006;114:2534-2570.
25. Saxon LA, Hayes DL, Gilliam FR: Long-term outcome after ICD and CRT-D implantation and influence of remote device follow-up: The ALTITUDE survival study. Circulation 2010;122:2359-2367.
26. Germano JJ, Reynolds M, Essbag V, Josephson ME: Frequency and causes of implantable cardioverter-defibrillator therapies: Is device-therapy proarrhythmic? Am J Cardiol 2006;97:1255-1261.
27. The antiarrhythmic versus implantable defibrillators (AVID) investigators: A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
28. Mehra R, Stone KL, Varosy PD, Hoffman AR, Marcus GM, Blackwell T, Ibrahim OA, Salem R, Redline S: Nocturnal arrhythmias across a sprectrum of obstructive and central sleep disordered breathing in older men: Outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med 2009;169:1147-1155.
29. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P: Central sleep apnoea in left ventricular dysfunction: Prevalence and implications for arrhythmic risk. Circulation 2003;107:727-732.
30. Teerlink JR, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G, Packer M, Massie BM: Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. Circulation 2000;101:40-46.
31. Staniforth AD, Sporton SC, Early MJ, Wedzicha JA, Nathan AW, Schilling RJ: Ventricular arrhythmia, Cheyne-Stokes respiration, and death: Observations from patients with defibrillators. Heart 2005;91:1418-1422.
32. Javaheri S: Effects of continuous positive airway pressure on sleep apnoea and ventricular irritability in patients with heart failure. Circulation 2000;101:392-397.
33. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrieson D, Ferguesson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS; CANPAP Investigators: Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025-2033.
34. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD; CANPAP Investigators: Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: A post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial (CANPAP). Circulation 2007;115:3173-3180.
35. Van De Borne P, Mezzetti S, Montano N, Narkiewicz K, Degaute JP, Somers VK: Hyperventilation alters arterial baroreflex control of heart rate and muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol 2000;279:536-541.
36. Leung RS, Diep TM, Bowman ME, Lorenzi-Filho G, Bradley TD: Provocation of ventricular ectopy by Cheyne-Stokes respiration in patients with heart failure. Sleep 2004;27:1337-1343.
37. Takasugi N, Nishigaki K, Kubota T, Tsuchiya K, Natsuyama K, Takasugi M, Nawa T, Ojio S, Aoyama T, Kawasaki M, Takemura G, Minatoguchi S: Sleep apnoea induces cardiac electrical instability assessed by T-wave alternans in patients with congestive heart failure. Eur J Heart Fail 2009;11:1063-1070.
38. Van De Borne P, Mezzetti S, Montano N, Narkiewicz K, Degaute JP, Somers VK: Hyperventilation alters arterial baroreflex control of heart rate and muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol 2000;279:536-541.
39. Arzt M, Harth M, Luchner A, Mulders F, Holmer SR, Blumberg FC, Riegger GA, Pfeifer M: Enhanced ventilator response to exercise in patients with chronic heart failure and central sleep apnea. Circulation 2003;107:1998-2003.
40. Javaheri S, Shukla R, Zeigler H, Wexler L: Central sleep apnoea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007;49:2028-2034.
41. Javaheri S, Corbett WS: Association of low PaCO2 with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 1998;128:204-207.
42. Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, Pozzoli M, Opasich C, Tavazzi L: Arterial baroreflex modulation of heart rate in chronic heart failure: Clinical and haemodynamic correlates and prognostic implications. Circulation 1997;96:3450-3458.
43. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, Florea V, Banasiak W, Poole-Wilson PA, Coats AJS, Anker SD: Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: Marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 2001;103:967-972.
44. Dingli K, Coleman EL, Vennelle M, Finch SP, Wraith PK, Mackay TW, Douglas NJ: Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. Eur Respir J 2003;21:253-259.
45. Wilkoff B, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW, Birgersdotter-Green UM, Wathen MS, Van Gelder IC, Heubner BM, Brown ML, Holloman KK; PREPARE Study Investigators: Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients. J Am Coll Cardiol 2008;52:541-550.
46. Gasparini M, Menozzi C, Proclemer A, Landolina M, Iacopino S, Carboni A, Lombardo E, Regoli F, Biffi M, Burrone V, Denaro A, Boriani G: A simplified biventricular defibrillator with fixed long detection intervals reduces implantable cardioverter defibrillator (ICD) interventions and heart failure hospitalizations in patients with non-ischaemic cardiomyopathy implatend for primary prevention: The RELEVANT study. Eur Heart J 2009;30:2758-2767.