Phenotyping of Sleep-Disordered Breathing in Patients With Chronic Heart Failure With Reduced Ejection Fraction—the SchlaHF Registry

Michael Arzt, MD; Olaf Oldenburg, MD; Andrea Graml, Dipl Stat; Erland Erdmann, MD; Helmut Teschler, MD; Karl Wegscheider, PhD; Anna Suling, PhD;* Holger Woehrle, MD;* for the SchlaHF Investigators[†]

Background—Different sleep-disordered breathing (SDB) phenotypes, including coexisting obstructive and central sleep apnea (OSA-CSA), have not yet been characterized in a large sample of patients with heart failure and reduced ejection fraction (HFrEF) receiving guideline-based therapies. Therefore, the aim of the present study was to determine the proportion of OSA, CSA, and OSA-CSA, as well as periodic breathing, in HFrEF patients with SDB.

Methods and Results—The German SchlaHF registry enrolled patients with HFrEF receiving guideline-based therapies, who underwent portable SDB monitoring. Polysomnography (n=2365) was performed in patients with suspected SDB. Type of SDB (OSA, CSA, or OSA-CSA), the occurrence of periodic breathing (proportion of Cheyne-Stokes respiration ≥20%), and blood gases were determined in 1557 HFrEF patients with confirmed SDB. OSA, OSA-CSA, and CSA were found in 29%, 40%, and 31% of patients, respectively; 41% showed periodic breathing. Characteristics differed significantly among SDB groups and in those with versus without periodic breathing. There was a relationship between greater proportions of CSA and the presence of periodic breathing. Risk factors for having CSA rather than OSA were male sex, older age, presence of atrial fibrillation, lower ejection fraction, and lower awake carbon dioxide pressure (P_{CO_2}). Periodic breathing was more likely in men, patients with atrial fibrillation, older patients, and as left ventricular ejection fraction and awake P_{CO_2} decreased, and less likely as body mass index increased and minimum oxygen saturation decreased.

Conclusions—SchlaHF data show that there is wide interindividual variability in the SDB phenotype of HFrEF patients, suggesting that individualized management is appropriate.

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Key Words: heart failure • phenotypes • sleep apnea • sleep disorders

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Heart failure (HF) is a relatively common condition, occurring in 1% to 2% of the adult population in Western countries.[1,2] There are a number of factors contributing to ongoing and projected increases in the prevalence of HF, including the aging population demographic and improved patient survival.[3,4] Despite advances in care, rates of hospitalization and readmission remain high,[5] meaning that the economic and social burden of HF is likely to increase over time.

There is an increasing focus on treatment of comorbidities and optimization of risk factors in patients with HF.[6] One such

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Clinical Perspective

What Is New?

- There are a number of different sleep-disordered breathing phenotypes in patients with heart failure and reduced ejection fraction.

What Are the Clinical Implications?

- A "one size fits all" approach to managing sleep-disordered breathing in patients with heart failure and reduced ejection fraction is unlikely to maximize clinical outcomes for each patient, and an individualized approach to therapy after definition of the sleep apnea phenotype would be more appropriate.

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comorbidity is sleep-disordered breathing (SDB), which is more common in HF patients than in the general population.[7,8] Data from the SchlaHF (Sleep-Disordered Breathing in Heart Failure) registry showed that SDB in HF is highly prevalent, with nearly half of all studied patients with HF with reduced ejection fraction (HFrEF) having moderate to severe SDB, and identifying a number of risk factors for SDB in these patients, including increasing age and body mass index (BMI), decreasing left ventricular ejection fraction (LVEF), male sex, and the presence of atrial fibrillation.[9]

However, SDB can take a number of forms, including obstructive sleep apnea (OSA), central sleep apnea (CSA) and periodic breathing (Cheyne-Stokes respiration, CSR). Many patients show a combination of different types of SDB breathing patterns that may change over the course of a night as well as over time.[10] Although both OSA and CSA/CSR have been shown to be independent predictors of worse outcome in HF patients,[11-16] the different forms of SDB are likely to have different effects on the cardiovascular system.[17] The findings of a post hoc analysis of the SERVE-HF study provided some evidence that the impact of SDB and its treatment might be different in CSA and OSA, showing effect modification when the proportion of CSR at baseline was <20%.[18] The results of a multistate model analysis of SERVE-HF also showed that patients with poor ventricular function or a high proportion of CSR at baseline randomized to adaptive servo-ventilation were at the highest risk of experiencing cardiovascular death, and that this occurred without a preceding hospital admission.[9]

Only a few studies to date have characterized different phenotypes for patients with HF and SDB.[16,19-21] Tkacova et al reported coexisting OSA and CSA in 12 of 65 patients with HFrEF.[22] However, the reliability of these and other data was limited by the sample size, and studies were conducted in predominantly male patients not being treated with the most up-to-date HF therapies. In addition, periodic breathing was often not assessed.

Therefore, the aim of the present study was to determine the proportion of OSA, CSA and coexisting OSA-CSA, as well as the proportion and extent of CSR, in a large population of optimally treated HFrEF patients with SDB referred to a sleep laboratory. In addition, the clinical phenotype of the different SDB populations and risk factors in each group were assessed.

Methods

Study Design

As described previously in the German SchlaHF registry, assessment of SDB using a 2-channel respiratory monitor (ApneaLink, ResMed, Australia, Sydney) was being performed in 256 centers (NCT01500759) with sufficient infrastructure to participate.[9,23] Between February 2008 and January 2011, type of SDB (OSA, CSA or coexisting OSA and CSA [OSA-CSA]) and the occurrence of periodic breathing (proportion of CSR ≥20%) were determined in 1557 HFrEF patients using in-lab polysomnography (Figure 1). In addition, arteriocapillary blood gases, age, body mass index (BMI), sex, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, heart rhythm, nocturnal dyspnea symptoms, nocturia, apnea-hypopnea index (AHI), HF etiology, and medication were documented. Oxygen desaturation index, average oxygen saturation (mean Sp_{O_2}), and minimum oxygen saturation (min Sp_{O_2}) were documented in 97% of patients. The SchlaHF registry received central ethics approval from the Freiburger Ethikkommission for Germany, and all participants provided written informed consent.

Participants

The inclusion criteria were as follows: chronic HF diagnosed according to the European Society of Cardiology (ESC) guidelines[24] ≤12 weeks before enrollment; moderate to severe left ventricular systolic dysfunction (LVEF ≤45% by an imaging method such as echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging) documented <12 weeks before enrollment; NYHA class III or IV at the time of inclusion, or NYHA class II with ≥1 hospitalization for HF in the past 12 months; patient able to fully understand study information and give written informed consent. Patients were excluded if they had any of the following: current use of positive airway pressure therapy; life expectancy <1 year for diseases unrelated to chronic HFREF; cardiac surgery, percutaneous coronary intervention, myocardial infarction, or unstable angina within 6 months before randomization; cardiac resynchronization therapy implantation scheduled or performed within 6 months before randomization; transient ischemic attack or stroke within
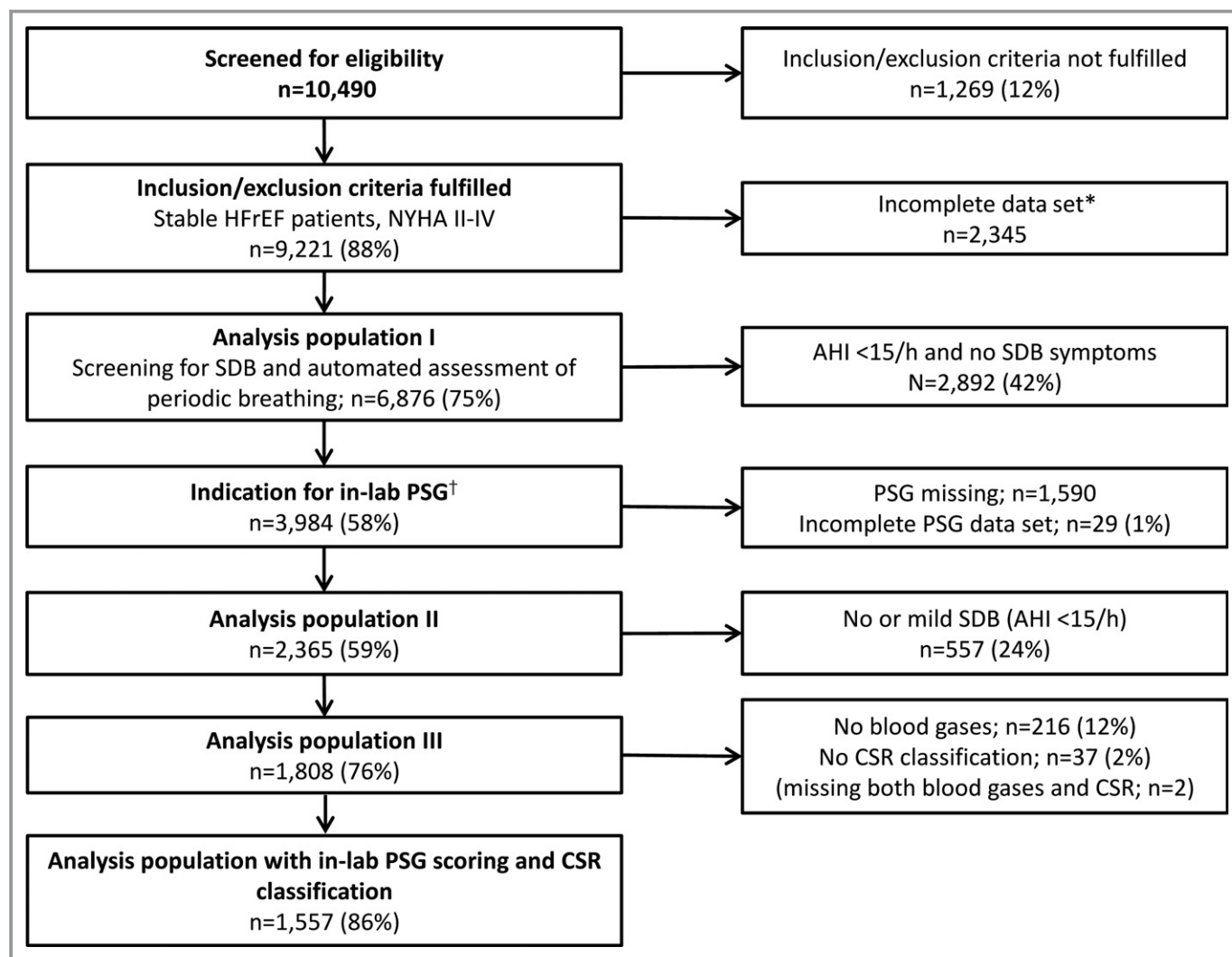
Figure 1. Patient populations and flow in the SchlaHF registry. AHI indicates apnea-hypopnea index; CSR, Cheyne-Stokes respiration; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; PSG, polysomnography; SDB, sleep-disordered breathing. †SDB or typical clinical symptoms indicative of SDB. *Incomplete data included patients with no data on SDB screening (n=390), age (n=1), body mass index (BMI; n=1), left ventricular ejection fraction (LVEF; n=1946), NYHA class (n=1957), atrial fibrillation (n=1977), and etiology of HFrEF (patients could have more than 1 piece of data missing). The high number of missing values for BMI, LVEF, and NYHA was due to recording of these variables being introduced to the registry after a protocol change.

3 months before enrollment; primary hemodynamically significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease expected to require surgery; acute myocarditis/pericarditis within 6 months before enrollment.

Assessment of SDB

Diagnosis of OSA or CSA With Polysomnography

As described previously,[23] patients with positive SDB monitoring (AHI ≥15/h) and/or suspicious clinical symptoms were referred to a sleep laboratory, where polysomnography (PSG) was performed to make a definite diagnosis of SDB. A

standardized qualification process was used to ensure comparability among centers in the scoring of respiratory events. Prior to participation, every center had to send at least 3 diagnostic respiratory scorings to a central lab that validated whether these scorings were performed according to a detailed operating manual for technical requirements of PSG and respiratory scoring. If quality was not acceptable, specific training was provided, followed by another quality assessment. A key element of the PSG scoring was the differentiation of apneas and hypopneas as central or obstructive using flattening of the inspiratory airflow curve, paradoxical breathing, arousal position, sleep stages, and breathing pattern at the end of the hypopnea.[25,26]

PSG included brain activity (electroencephalogram), eye movement (electro-oculogram), muscle activity or skeletal muscle activation (electromyogram), heart rhythm (ECG), breathing and respiratory effort measures during sleep, as well as the recording of body position. Flow measurement was performed by nasal cannula and thermistor during diagnostic procedures.

Definitions for respiratory events were the same as those used in the SERVE-HF study.[18] Apnea was defined as >90% reduction from baseline in peak amplitude of the signal from nasal cannula and oral thermistor, lasting ≥10 seconds. Hypopnea was defined as a ≥30% reduction in flow and a ≥3% desaturation from baseline for ≥10 seconds or as a ≥50% reduction in flow from the preevent baseline for ≥10 seconds.

A central apnea was defined in the absence of thoracoabdominal excursions. If the central component of an apnea already satisfied the definition of a central apnea (ie, ≥10 seconds), 3 consecutive obstructive breaths were needed to classify that as an obstructive apnea. Just 1 or 2 obstructed breaths at the end of an apnea did not change the classification to a central event. Obstructive versus central hypopneas were determined based on the presence/absence of inspiratory flow limitation and/or paradoxical abdominal/thoracic movements on respiratory inductance plethysmography if available.[25,26]

In contrast to SERVE-HF,[18] for this analysis the number of (central) apnea and hypopnea episodes per hour of sleep (AHI and cAHI [central apnea-hypopnea index], respectively) was determined and reported for total sleep time. SDB was defined as an AHI ≥15 per hour of sleep. Patients with SDB were stratified into 3 groups according to the proportion of central apneas and hypopneas in relation to total apnea and hypopneas: OSA (defined as cAHI/AHI 0% to 19.9%), coexisting obstructive sleep apnea+central sleep apnea (OSA-CSA, defined as cAHI/AHI ≥20.0% and <80%), and CSA (defined as cAHI/AHI ≥80.0%).

Polysomnographic Visual Assessment of CSR

CSR was defined as ≥3 episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apneas or hypopneas. It was visually quantified by the presence or absence, and if present by the percentage of the recording time: <20%, ≥20% and <50%, ≥50%.[18] A subgroup analysis of the SERVE-HF trial indicated that adaptive servo-ventilation use in patients with HFrEF and CSA without CSR was associated with a lower risk of the primary end point (all-cause death or life-saving cardiovascular intervention plus unplanned hospitalization for worsening chronic heart failure).[18]

Blood Gases

Blood gases were determined in arterialized earlobe capillary blood taken during the day when patients were at rest.

Statistical Analysis

Descriptive statistics were absolute and relative frequency or mean±SD (whichever was appropriate). Because prevalences varied considerably among centers (cardiology practices or departments), presumably reflecting differences in patient populations, all inferential statistics were calculated with centers as a random term.

A linear mixed model with percentage AHI/AHI as a continuous response variable was applied for the SDB severity analysis. A random effects logistic regression model with CSR ≥20% versus CSR <20% as the dichotomous response variable was applied to determine risk factors for CSR. Potential risk factors for both disorders analyzed were age, BMI, sex, LVEF, NYHA class, atrial fibrillation, ischemic origin, minimum Sao_2, and Pco_2. To study sex differences, interaction terms with all determined risk factors were added to the model and selected by backward elimination based on likelihood ratio tests. Results are visualized by forest plots showing adjusted regression coefficients or odds ratios together with 95% confidence intervals. A *P*-value of <0.05 was considered to be statistically significant. Statistical analysis was performed with STATA 14.1 (STATA Corporation, College Station, TX).

Results

A total of 9221 patients had stable HFrEF (NYHA class II-IV) and were screened for SDB. Of these, 1557 had certified scoring of laboratory PSG results and CSR classification and were included in this analysis (Figure 1).

Patient Characteristics

Type of SDB: OSA, OSA-CSA, and CSA

In this population of SchlaHF registry participants, the most common form of SDB was coexisting OSA-CSA (624 patients, 40%); OSA and CSA were found in 452 (29%) and 481 (31%) patients, respectively. There were a number of statistically significant differences among patients with different types of SDB (Table 1). Patients with OSA were younger than those with OSA-CSA, had a higher body mass index, LVEF, and NYHA class, were more likely to be female, less likely to have atrial fibrillation, be receiving ß-blockers, diuretics, and digitalis, and had lower oxygen levels and higher carbon dioxide levels (Table 1). Other significant interpatient differences included a significantly higher proportion of men in the CSA versus OSA group, lower LVEF in those with CSA versus OSA-CSA or OSA-CSA versus OSA, and an increased prevalence of atrial fibrillation when the proportion of CSA was higher (Table 1). Baseline data by sex are shown in Table S1 and Table S2.

Table 1. Patient Demographic Data and Characteristics at Baseline Based on Type of Sleep–Disordered Breathing

	OSA	OSA-CSA	CSA
N (%)	452 (29)	624 (40)	481 (31)
Age, y	66±11*	69±10	69±10[†]
Female, n (%)	94 (21)*	67 (11)	43 (9)[†]
Body mass index, kg/m^2	31±6*	29±5[‡]	28±4[†]
LVEF, %	35±8*	34±8[‡]	32±8[†]
NYHA class III+IV, n (%)	334 (74)*	422 (68)[‡]	356 (74)
Ischemic cardiomyopathy, n (%)	226 (50)	343 (55)	279 (58)[†]
Atrial fibrillation, n (%)	103 (23)*	203 (33)	174 (36)[†]
Medication, n (%)			
ACE inhibitors and/or ARBs	394 (87)	572 (92)	431 (90)
β-Blockers	391 (87)*	571 (92)	436 (91)[†]
Diuretics	349 (77)*	519 (83)	398 (83)[†]
Digitalis	64 (14)*	126 (20)	101 (21)[†]
Aldosterone antagonists	195 (43)	282 (45)	237 (49)
Polysomnography			
AHI, per h	37±19	36±16	38±15[†]
cAHI, per h	2±3*	20±11[‡]	35±14[†]
AI, per h	19±19*	21±16	24±18[†]
cAHI/AHI, %	6±6*	54±17[‡]	92±6[†]
Mean Sa_{O_2}, %[§]	92±3*	93±2	93±3[†]
Minimum Sa_{O_2}, %[§]	78±9*	80±8[‡]	81±7[†]
Time with Sa_{O_2}<90%, min[‖]	62±78	51±69[‡]	50±70[†]
Awake P_{CO_2}, mm Hg	39±5*	37±4[‡]	37±5[†]

Values are mean±SD or number of patients (%). *P*-values from ANOVA for metric variables and logistic regression for dichotomous variables; groupwise comparisons only in case of global significance (*P*<0.05). ACE indicates angiotensin-converting enzyme; AHI, apnea-hypopnea index; AI, apnea index; ARB, angiotensin receptor blocker; cAHI, central AHI; CSA, central sleep apnea (defined as cAHI/AHI ≥80.0%); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnea (defined as cAHI/AHI 0-19.9%); OSA-CSA, obstructive sleep apnea+central sleep apnea (defined as cAHI/AHI ≥20.0% and <80%); P_{CO_2}, partial pressure of carbon dioxide; Sa_{O_2}, oxygen saturation.
*P<0.05 OSA vs OSA-CSA.
[†]P<0.05 CSA vs OSA.
[‡]P<0.05 OSA-CSA vs CSA.
[§]Values missing for 1 patient with OSA.
[‖]Values missing for 4 patients with OSA, 4 with OSA-CSA, and 4 with CSA.

Type of Breathing Pattern: CSR

The majority of patients (59%) showed <20% CSR on PSG; the proportions of patients with ≥20% to <50% CSR and ≥50% CSR on PSG were similar (22% and 19%, respectively). Patients with less periodic breathing were significantly younger, significantly more likely to be female, had a significantly higher LVEF, and were significantly less likely to have atrial fibrillation in comparison to patients with CSR ≥50% (Table 2). Patients with ≥50% CSR on PSG had a significantly higher AHI, cAHI, and apnea index than patients with lower proportions of CSR on

Table 2. Baseline Characteristics in Patients With and Without Periodic Breathing

	CSR-PSG		
	<20%	≥20% to <50%	≥50%
N (%)	915 (59)	349 (22)	293 (19)
Age, y	67±11*	69±10	70±9[†]
Female, n (%)	154 (17)*	33 (9)	17 (6)[†]
Body mass index, kg/m^2	30±5*	28±4	29±5[†]
LVEF, %	34±8*	33±8	33±8[†]
NYHA class III+IV, n (%)	656 (72)	249 (71)	207 (71)
Ischemic cardiomyopathy, n (%)	484 (53)	193 (55)	171 (58)
Atrial fibrillation, n (%)	250 (27)*	126 (36)	104 (35)[†]
Medication, n (%)			
ACE inhibitors and/or ARBs	817 (89)	313 (90)	267 (91)
β-Blockers	805 (88)	320 (92)[†]	273 (93)
Diuretics	733 (80)	296 (85)	237 (81)
Digitalis	156 (17)	74 (21)	61 (21)
Aldosterone antagonists	413 (45)	172 (49)	129 (44)
Polysomnography			
AHI, per h	35±18*	36±14[‡]	43±14[†]
cAHI, per h	11±13*	26±14[‡]	35±13[†]
AI, per h	19±17*	20±15[‡]	30±17[†]
cAHI/AHI, %	34±33*	73±22[‡]	82±15[†]
Mean Sa_{O_2}, %[§]	93±3	93±2	92±3
Minimum Sa_{O_2}, %[§]	79±8*	81±6[‡]	79±9
Time with Sa_{O_2}<90%, min[‖]	52±72	49±64[‡]	68±79[†]
Awake P_{CO_2}, mm Hg	38±5*	37±4	36±5[†]

Values are mean±SD or number of patients (%). *P*-values from ANOVA for metric variables and logistic regression for dichotomous variables; groupwise comparisons only in case of global significance (*P*<0.05). ACE indicates angiotensin-converting enzyme; AHI, apnea-hypopnea index; AI, apnea index; ARB, angiotensin receptor blocker; cAHI, central AHI; CSR-PSG, Cheyne-Stokes respiration on polysomnography; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; P_{CO_2}, partial pressure of carbon dioxide; Sa_{O_2}, oxygen saturation.
*P<0.05 <20% CSR-PSG vs ≥20% to <50% CSR-PSG.
[†]P<0.05 ≥50% CSR-PSG vs <20% CSR-PSG.
[‡]P<0.05 ≥20% to <50% CSR-PSG vs ≥50% CSR-PSG.
[§]Values missing for 1 patient with OSA.
[‖]Values missing for 6 patients with OSA, 1 patient with OSA-CSA, and 5 patients with CSA.

PSG, and also spend more time with oxygen saturation at <90%; use of cardiac medication did not vary by the proportion of CSR on PSG (Table 2).

Influence of Sex

OSA was markedly more common in female heart failure patients compared with male patients with HFrEF, whereas
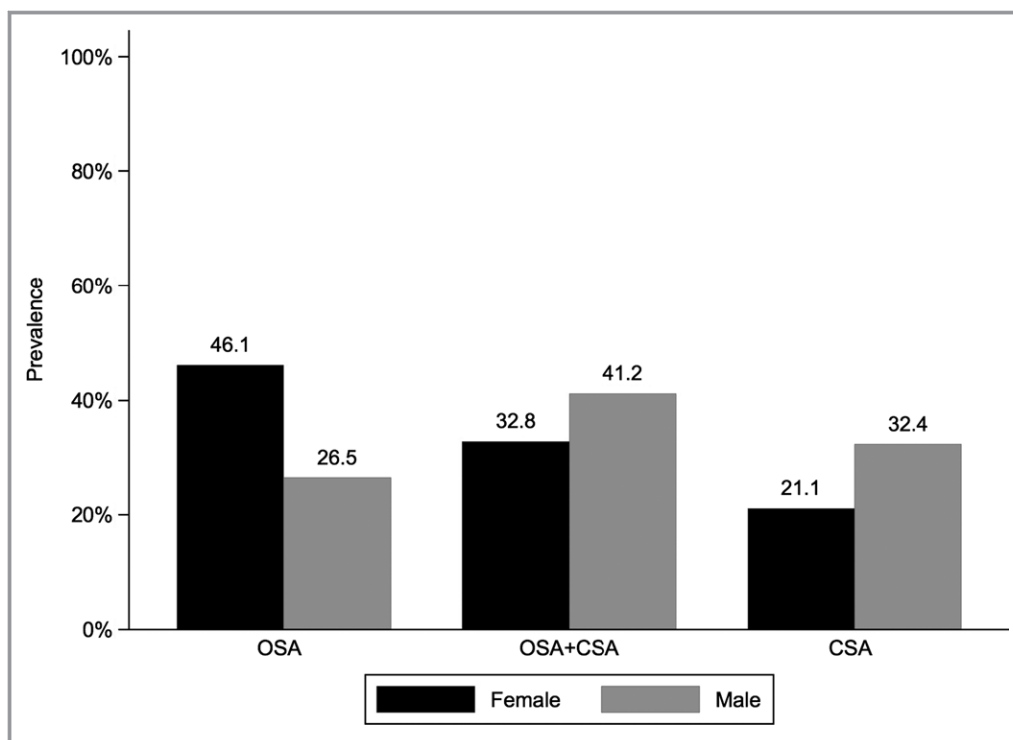
Figure 2. Prevalence of obstructive and central sleep apnea by sex. CSA indicates central sleep apnea (defined as cAHI/AHI ≥80%); OSA, obstructive sleep apnea (defined as cAHI/AHI 0% to 19.9%); OSA+CSA, obstructive sleep apnea+central sleep apnea (defined as cAHI/AHI 20% to 79.9%). AHI indicates apnea-hypopnea index; cAHI, central AHI.

men were more likely to have OSA-CSA or CSA (Figure 2). There were no important differences between male and female patients in the proportion of periodic breathing within different types of SDB (Figure 3).

Different SDB Phenotypes

There was a clear relationship between greater proportions of central apneas and the presence of periodic breathing. Periodic breathing was seen infrequently in patients with OSA (both male and female) and was much higher (≈50%) in patients with OSA-CSA or CSA, irrespective of sex (Figure 3).

Clinical Risk Factors for Different SDB Phenotypes in HFrEF Patients With SDB

Central Sleep Apnea

The likelihood of having CSA (higher cAHI/AHI) rather than OSA (lower cAHI/AHI) was significantly higher in male versus female heart failure patients and those with versus without atrial fibrillation (Figure 4). In addition, there was a significant increase in the risk for higher cAHI/AHI as age increased and as awake P_{CO_2} and LVEF decreased. Conversely, the risk of CSA decreased significantly as BMI increased and minimum

oxygen saturation decreased (Figure 4). None of the interaction terms with sex was statistically significant.

Cheyne-Stokes Respiration

Male sex was significantly associated with the presence of periodic breathing, as were increasing age, the presence of atrial fibrillation, worsening left ventricular function, and decreasing awake P_{CO_2} (Figure 5). The risk of having periodic breathing decreased significantly as BMI increased (Figure 5). Again, none of the interaction terms with sex was statistically significant.

Discussion

This analysis of the SchlaHF registry has identified several major novel findings. The first is that a large proportion (40%) of a population with chronic HFrEF and SDB present with coexisting OSA and CSA. Clearly predominant OSA or CSA (≥80% obstructive or central events, respectively) was diagnosed in 29% and 31% of HFrEF patients with SDB. Second, although the proportion of patients with coexisting OSA and CSA was greater than the frequency of predominant OSA or CSA in men, the most common type of SDB in women was predominant OSA. Third, male sex, older age, lower BMI and
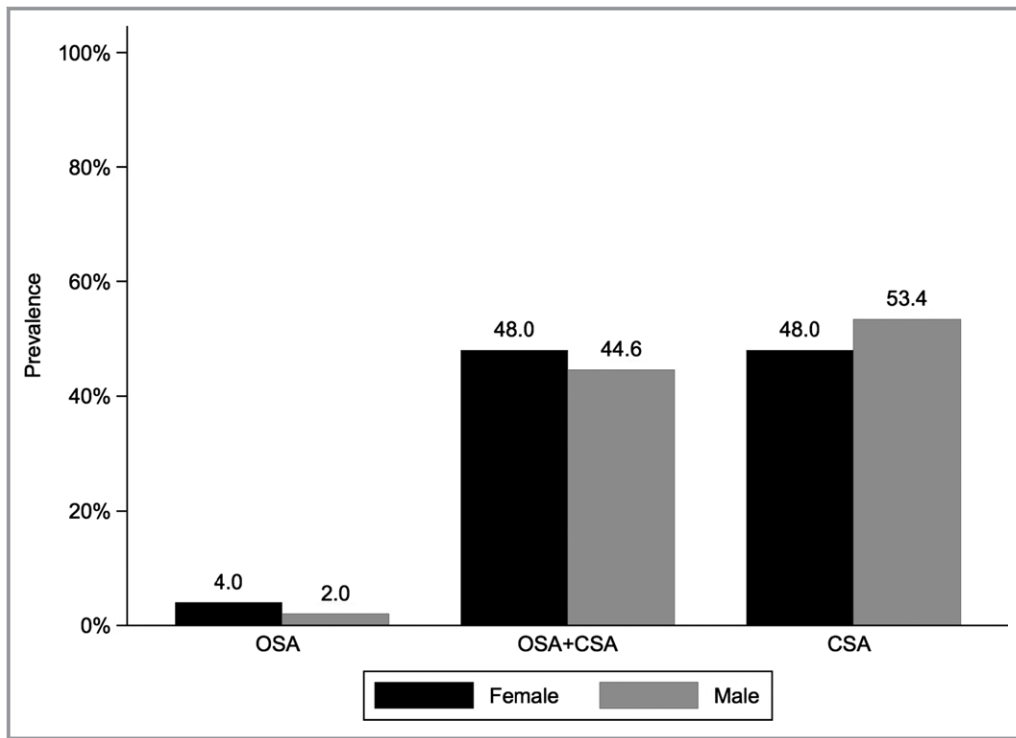
Figure 3. Prevalence of periodic breathing (defined as Cheyne–Stokes respiration [CSR] ≥20%) according to sleep apnea type. CSA indicates central sleep apnea (defined as cAHI/AHI ≥80.0%); OSA, obstructive sleep apnea (defined as cAHI/AHI 0% to 19.9%); OSA+CSA, obstructive sleep apnea+central sleep apnea (defined as cAHI/AHI 20% to 79.9%). AHI indicates apnea-hypopnea index; cAHI, central AHI.

LVEF, atrial fibrillation, and lower P_{CO_2} were identified as significant and independent clinical predictors for the presence of predominant CSA rather than OSA in patients with chronic HFrEF and SDB. Furthermore, periodic breathing (CSR for >20% of recording time) was present in 41% of HFrEF patients with SDB. Although only 3% of HFrEF patients with
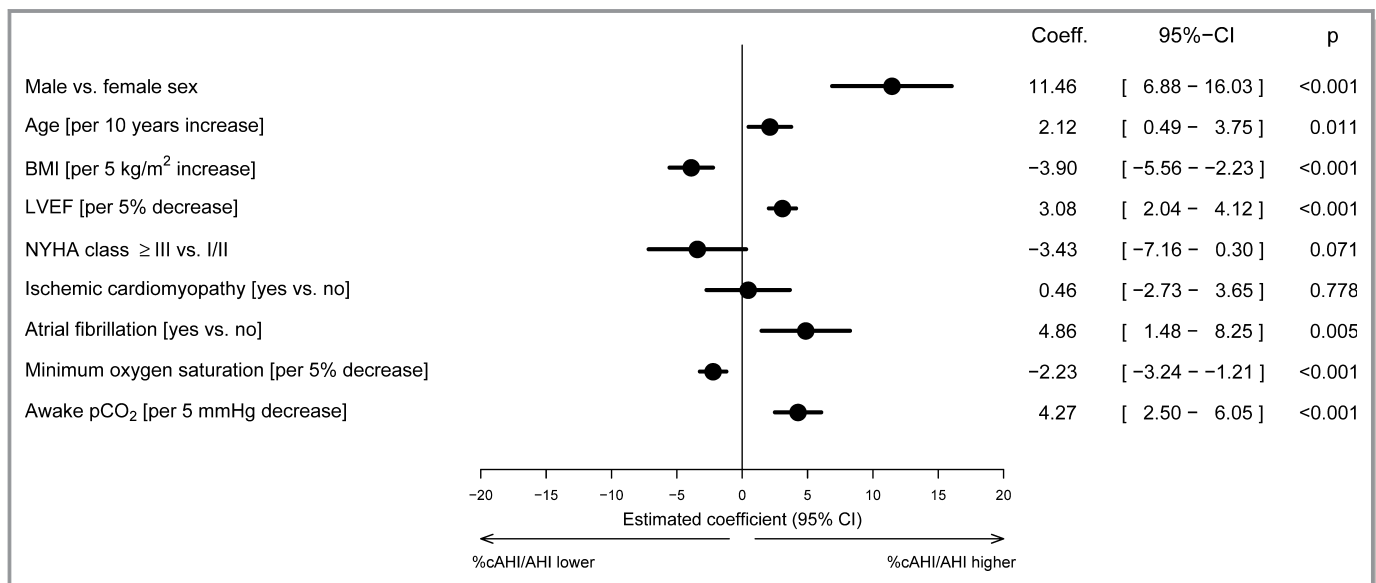
Figure 4. Forest plot of risk factors for central sleep apnea (higher cAHI/AHI percentage) and obstructive sleep apnea (lower cAHI/AHI percentage). AHI indicates apnea-hypopnea index; BMI, body mass index; cAHI, central AHI; CI, confidence interval; LVEF, left ventricular ejection fraction; min, minimum; NYHA, New York Heart Association; P_{CO_2}, partial pressure of carbon dioxide; Sa_{O_2}, oxygen saturation.
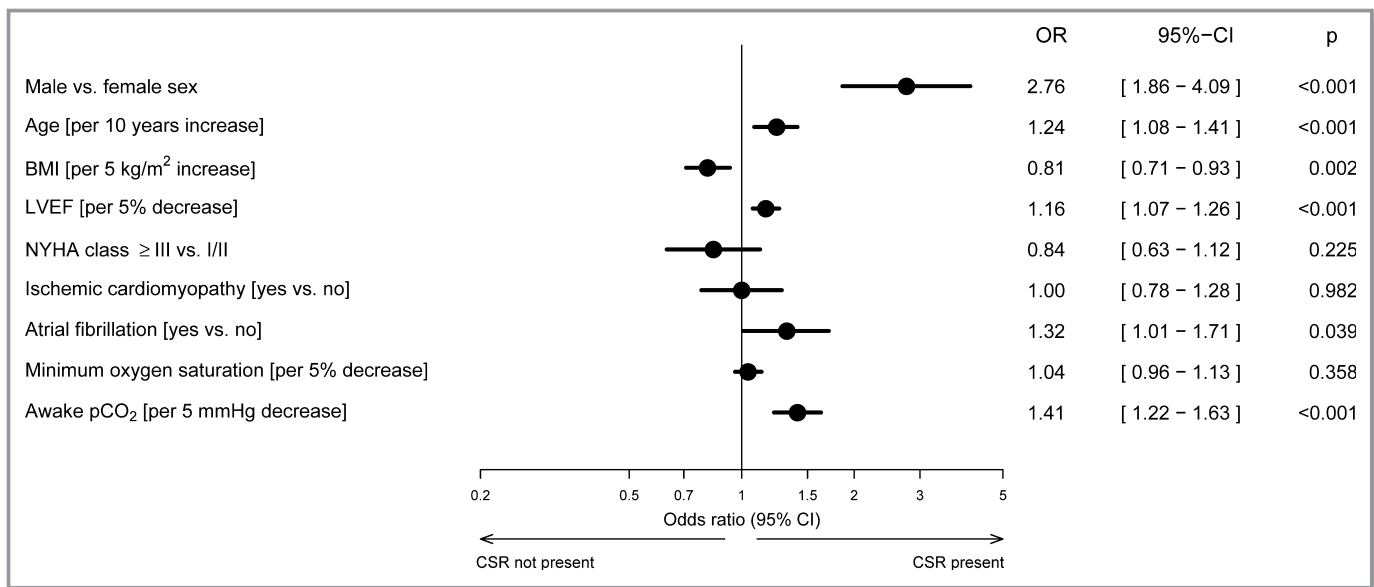
Figure 5. Forest plot of risk factors for periodic breathing (defined as Cheyne-Stokes respiration [CSR] ≥20%). AHI indicates apnea-hypopnea index; BMI, body mass index; cAHI, central AHI; CI, confidence interval; LVEF, left ventricular ejection fraction; min, minimum; NYHA, New York Heart Association; P_{CO_2}, partial pressure of carbon dioxide; Sa_{O_2}, oxygen saturation.

OSA had underlying CSR, a significant proportion of those with CSA (71%) had periodic breathing. Across all types of SDB, the frequency of periodic breathing was similar in men and women. Thus, significant and independent clinical predictors for the presence of periodic breathing were male sex, older age, lower BMI and LVEF, atrial fibrillation, and lower P_{CO_2}.

The finding that the most common form of SDB in our population of HFrEF patients was coexisting OSA and CSA is new—there are few published data reporting the rate of coexisting OSA and CSA in HF patients.[22] In terms of OSA in HFrEF patients, our rate of 29% is higher than values reported previously, which range from 11% to 26%.[16,19,20] Conversely, our CSA prevalence rate of 31% was somewhat lower than in some studies (37% to 40%)[19,20] but higher than in another (26%).[16] None of these other studies reported data on the prevalence of coexisting OSA-CSA.

Although OSA-CSA was the most common type of SDB overall, there were significant variations by sex, with predominant OSA being the most common type of SDB in women (46.1%) and predominant CSA being relatively less common (21.1%); the most common type of SDB in men was OSA-CSA (41.2%), similar to the overall result. Although there is growing interest in sex differences in SDB,[27] women are often underrepresented in clinical trials. In fact, some previous studies of SDB in HF patients have included only male subjects,[19,20] making comparisons with the current data impossible. In 1 study of HFrEF patients with moderate to severe SDB, the prevalence of both OSA and CSA was significantly higher (by about 2.5-fold) in men than in women.

The rate of CSA in our study was about 1.5 times higher in men compared with women, but the opposite was the case for OSA, where the rate in women was 1.7 times higher than in men.

In terms of risk factors for predominant CSA, we identified male sex, older age, lower BMI and LVEF, atrial fibrillation, and lower P_{CO_2} as significant and independent clinical predictors for the presence of predominant CSA (versus predominant OSA) in our large population of patients with chronic HFrEF and SDB. These are largely consistent with existing data on CSA risk factors, which have been reported to include atrial fibrillation, ventricular arrhythmias, lower LVEF, low P_{CO_2}, older age, and male sex.[16,19,20] In our study, OSA was more common when BMI was high and NYHA class and oxygen saturation were lower. Interestingly, this analysis did not identify male sex and age as risk factors for OSA, in contrast to what has been reported previously.[16]

In the SchlaHF registry population, almost half (41%) had CSR for >20% of the PSG recording time (defined as periodic breathing). This subgroup of HFrEF patients with SDB was shown to be at higher risk of experiencing a primary end-point event during treatment with adaptive servo-ventilation in a subgroup analysis of the SERVE-HF trial.[18] Therefore, these patients might represent 1 specific SDB phenotype in HF, with specific data available on which to define treatment options. In contrast to the sex differences we identified in the different types of SDB, the frequency of periodic breathing in the SchlaHF population was similar in men and women. This is a novel finding because sex comparisons were not possible in previous studies.[19,20]

This is the first large study to look at different SDB phenotypes in patients with HF. Its strengths include the inclusion of a large population of male and female patients being treated with up-to-date, guideline-based medical and device therapy. Therefore, the results should be widely applicable to patients with HFrEF, but they cannot be generalized to those with HF and preserved ejection fraction, which were not included in the SchlaHF registry. Other limitations include its design as a registry analysis, meaning that data were not prospectively collected, and there is therefore a potential for bias. Of the HFrEF patients with an indication to undergo PSG, only 59% ultimately underwent PSG for a variety of reasons, such as long waiting periods in German sleep laboratories and possible insufficient subjective priority for a sleep study as defined by the referring cardiologist and the patient. In addition, there may be limitations on the amount of data available (eg, echocardiographic data other than LVEF), and information on confounding factors may be lacking.

Conclusions

These data from a large number of patients enrolled in the SchlaHF registry show that there is marked interindividual variability in the SDB phenotype of HFrEF patients, with many showing coexisting OSA-CSA. Taken together with data from recent large, randomized clinical trials,[18,28] our findings suggest that all HF patients with SDB are not alike, and therefore, management strategies need to be tailored on an individual basis in order to optimize patient outcomes.

Acknowledgments

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Disclosures

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Supplemental Material

Table S1. Patient demographic data and characteristics at baseline based on type of sleep-disordered breathing and sex

	OSA		OSA-CSA		CSA	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
N (%)	94 (46)	358 (26)	67 (33)	557 (41)	43 (21)	438 (32)
Age, years	68±10	65±11	70±8	69±11	68±12	69±10
Body mass index, kg/m²	33±6	31±6	29±6	29±5	29±5	28±4
LVEF, %	36±8	35±8	34±8	34±8	32±8	32±8
NYHA class III+IV	76 (81)	258 (72)	50 (75)	372 (67)	34 (79)	322 (74)
Ischemic cardiomyopathy, n (%)	28 (30)	198 (55)	33 (49)	310 (56)	20 (47)	259 (59)
Atrial fibrillation, n (%)	24 (26)	79 (22)	22 (33)	181 (32)	16 (37)	158 (36)
Medication, n (%)						
ACE inhibitors and/or ARBs	78 (83)	316 (88)	60 (90)	512 (92)	40 (93)	391 (89)
β-blockers	73 (78)	318 (89)	62 (93)	509 (91)	38 (88)	398 (91)
Diuretics	75 (80)	274 (77)	50 (75)	469 (84)	32 (74)	366 (84)
Digitalis	12 (13)	52 (15)	15 (22)	111 (20)	10 (23)	91 (21)
Aldosterone antagonists	37 (39)	158 (44)	33 (49)	249 (45)	22 (51)	215 (49)
Polysomnography						
AHI, /h	33±17	38±20	34±16	36±16	34±14	38±15
cAHI, /h	2±3	2±3	18±11	20±11	32±14	35±14
AI, /h	14±14	20±19	14±12	22±16	19±15	24±18
%cAHI/AHI	5±6	6±6	53±16	55±18	92±7	92±6
Mean SaO_2, %*	92±3	92±3	92±2	93±2	93±2	93±3
Minimum SaO_2, %*	77±9	78±9	80±7	80±8	81±6	81±7
Time with SaO_2 <90%, min†	64±83	61±77	57±77	50±68	52±54	50±71
Awake pCO_2, mmHg	40±4	39±4	37±4	37±4	37±4	36±5

Values are mean ± standard deviation, or number of patients (percentage).
*Values missing for 1 patient with OSA; †Values missing for 4 patients with OSA, 4 with OSA-CSA and 4 with CSA.

ACE indicates angiotensin converting enzyme; AHI, apnea-hypopnea-index; AI, apnea index; ARB, angiotensin receptor blocker; cAHI, central AHI; CSA, central sleep apnea (defined as %cAHI/AHI ≥80.0%); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnea (defined as %cAHI/AHI 0-19.9%); OSA-CSA, obstructive sleep apnea + central sleep apnea (defined as %cAHI/AHI ≥20.0% and <80%); pCO_2, partial pressure of carbon dioxide; SaO_2, oxygen saturation.

Table S2. Patient demographic data and characteristics at baseline for patients with versus without in-lab PSG and CSR classification (included versus excluded from the current analysis)

	Included patients		Excluded patients		Total	
	Values	Missing, n (%)	Values	Missing, n (%)	Values	Missing, n (%)
N (%)	1557 (23)		5319 (77)		6876 (100)	
Age, years	68±10	0 (0)	66±12	0 (0)	67±11	0 (0)
Female, n (%)	204 (13)	0 (0)	1244 (23)	0 (0)	1448 (21)	0 (0)
Body mass index, kg/m²	29±5	0 (0)	28±5	0 (0)	28±5	0 (0)
LVEF, %	34±8	0 (0)	33±8	0 (0)	33±8	0 (0)
NYHA class III+IV	1112 (71)	0 (0)	3795 (71)	0 (0)	4907 (71)	0 (0)
Ischemic cardiomyopathy, n (%)	848 (54)	0 (0)	2855 (54)	0 (0)	3703 (54)	0 (0)
Atrial fibrillation, n (%)	480 (31)	0 (0)	1384 (26)	0 (0)	1864 (27)	0 (0)
Medication, n (%)						
ACE inhibitors and/or ARBs	1397 (90)	0 (0)	4684 (88)	0 (0)	6081 (88)	0 (0)
β-blockers	1398 (90)	0 (0)	4710 (89)	0 (0)	6108 (89)	0 (0)
Diuretics	1266 (81)	0 (0)	4156 (78)	0 (0)	5422 (79)	0 (0)
Digitalis	291 (19)	0 (0)	1025 (19)	0 (0)	1316 (19)	0 (0)
Aldosterone antagonists	714 (46)	0 (0)	2548 (48)	0 (0)	3262 (47)	0 (0)
Polysomnography						
AHI, /h	37±17	0 (0)	17±17	4495 (85)	30±19	4495 (65)
cAHI, /h	19±16	0 (0)	7±12	4509 (85)	15±16	4509 (66)
AI, /h	21±17	0 (0)	9±13	4495 (85)	17±17	4495 (65)
%cAHI/AHI	52±35	0 (0)	37±36	4518 (85)	47±36	4481 (66)
Mean SaO_2, %	93±3	1 (0)	93±2	4497 (85)	93±3	4498 (65)
Minimum SaO_2, %	80±8	1 (0)	83±7	4498 (85)	81±8	4499 (65)
Time with SaO_2 <90%, min	54±72	12 (1)	34±66	4500 (85)	47±71	4512 (66)
Awake pCO_2, mmHg	38±5	0 (0)	38±4	4804 (90)	38±5	4804 (70)

Values are mean ± standard deviation, or number of patients (percentage).
ACE indicates angiotensin converting enzyme; AHI, apnea-hypopnea-index; AI, apnea index; ARB, angiotensin receptor blocker; cAHI, central AHI; CSA, central sleep apnea (defined as %cAHI/AHI ≥80.0%); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnea (defined as %cAHI/AHI 0-19.9%); OSA-CSA, obstructive sleep apnea + central sleep apnea (defined as %cAHI/AHI ≥20.0% and <80%); pCO_2, partial pressure of carbon dioxide; SaO_2, oxygen saturation.

Appendix

SchlaHF investigators (all from Germany)

Site	Investigator(s)	City
Ambulantes Cardiovasculäres Centrum Ravensburg	Dr. K Schlotterbeck	Ravensburg
Ambulantes Herzzentrum Kassel	Dr. A Utech	Kassel
Ärztezentrum Holthausen-Biene	Dr. L Stauff	Lingen
Asklepios Klinik Barmbek	Dr. G Grönefeld, Prof. H Becker	Hamburg
Augusta Krankenanstalten Bochum	Dr. W Lucanus	Bochum
Augusta-Kranken-Anstalt gGmbH Thoraxzentrum Ruhrgebiet	Dr. M Neddermann	Herne
Cardio-Praxis Herne Dr. Furche	Dr. K-G Furche	Herne
Cardiopraxis Ingelheim	Dr. M Speth-Nitschke	Ingelheim
Charité Campus Mitte	Prof. G Baumann	Berlin
Charité Campus Mitte CCM	Prof. I Fietze	Berlin
Charité Campus Virchow-Klinikum	Dr. H-D Düngen	Berlin
Charité Campus Virchow-Klinikum II	Dr. M Rauchhaus	Berlin

Site	Investigator(s)	City
Deutsches Zentrum für Herzinsuffizienz, CHFC, Universitätsklinikum Würzburg	Prof. C Angermann	Würzburg
DRK Krankenhaus	Dr. O Laakmann	Alzey
DRK Krankenhaus Mölln-Ratzeburg	Dr. S Kuster	Ratzeburg
Elisabeth-Krankenhaus Essen	Prof. GV Sabin	Essen
Evangelische Lungenfachklinik Buch	Prof. C Grohe	Berlin
Evangelisches Krankenhaus	Prof. E Vester	Düsseldorf
Evangelisches Krankenhaus Mülheim	Dr. P Kekes	Mülheim an der Ruhr
Facharztzentrum Dresden-Neustadt GbR	Dr. B Krosse	Dresden
Facharztzentrum Sonneberg	Dr. C Franke	Sonneberg
Fachkliniken Wangen	Dr. H Knape	Wangen
Fachkrankenhaus Coswig	Prof. G Höffken	Coswig
Florence Nightingale Krankenhaus	Dr. U Heidland, Dr. M Neddermann	Düsseldorf
Gemeinschaftspraxis Weiß/Dr. Heesing	Dr. B Heesing	Arnsberg
Gemeinschaftspraxis Dres Böhmeke/Schmidt	Dr. T Böhmeke	Gladbeck

Site	Investigator(s)	City
Gemeinschaftspraxis Dres Leischik/Littwitz	Dr. R Leischik	Hagen
Gemeinschaftspraxis Dres. Brandt/Jakobs	Dr. C Jakobs	Mannheim
Gemeinschaftspraxis Dres. Guckenbiehl	Dr. M Guckenbiehl	Flonheim
Gemeinschaftspraxis Dres. Gysan/Heinzler/May	Dr. E May	Köln
Gemeinschaftspraxis Dres. Heifer/Loster/Schernus	Dr. U Loster	Mannheim
Gemeinschaftspraxis Dres. Schmidt/Gronke	Dr. K Gronke	Dresden
Gemeinschaftspraxis Dres. Subin/Lutter	Dr. B Subin	Hamburg
Gemeinschaftspraxis Dres. Wauer/ Windstetter	Dr. B Wauer	München
Gemeinschaftspraxis Groß-Ziethener Chaussee	Dr. K Laskos	Berlin
Gemeinschaftspraxis Kardiologie	Dr. G Kerkhoff	Bottrop
Gemeinschaftspraxis Kardiologie Dr. Becker	Dr. E Becker	Castrop-Rauxel
Gemeinschaftspraxis PD Dr. Lankisch	Prof. M Lankisch	Düsseldorf
Helios Klinik Lengerich	Dr. M Hilgedieck	Lengerich

Site	Investigator(s)	City
Helios Klinikum Borna	Dr. U Müller	Borna
HELIOS Klinikum Erfurt	B Mross	Erfurt
HELIOS Klinikum Krefeld	Dr. M Streuter	Krefeld
HELIOS Krankenhaus Leisnig	Dr. W Krahwinkel	Leisnig
Herz- und Diabeteszentrum NRW	Dr. O Oldenburg	Bad Oeynhausen
Herzklinik Ulm Dr. Haerer und Partner	Dr. W Haerer	Ulm
Herzzentrum Bad Krozingen	Dr. W Zeh	Bad Krozingen
Herzzentrum Brandenburg	Dr. C Butter	Bernau
Herzzentrum Universität Dresden	Prof. R Strasser	Dresden
Jüdisches Krankenhaus Berlin	Prof. K Graf	Berlin
Kardiologie am Rotkreuzplatz	Dr. KS Liem	München
Kardiologie Brühl	Dr. J Pütz	Brühl
Kardiologie Gemeinschaftspraxis Dr. Tenholt	Dr. M Tenholt	Bochum
Kardiologie Kemnade	Dr. C Seifert	Bochum
Kardiologie Oberkassel	Dr. F Hauer	Düsseldorf
Kardiologie Praxis Dr. Bonnekamp	Dr. Bonnekamp	Essen
Kardiologische Praxis Dr. Arens	Dr. R Arens	Hagen

Site	Investigator(s)	City
Kardiologische Praxis Dr. Birkenhagen	Dr A Birkenhagen	Stollberg
Kardiologische Praxis Dr. Burkhard-Meier	Dr. C Burkhard-Meier	Viersen
Kardiologische Praxis Dr. Cierpka	Dr. R Cierpka	Hannover
Kardiologische Praxis Dr. Cord Müller	Dr. C Müller	Essen
Kardiologische Praxis Dr. Figura	Dr. T Figura	Rinteln
Kardiologische Praxis Dr. Golling	Dr. FR Golling	Dortmund
Kardiologische Praxis Dr. Gumbrecht	Dr. H Gumbrecht	Ochtrup
Kardiologische Praxis Dr. Horowitz	Dr. A Horowitz	Düsseldorf
Kardiologische Praxis Dr. Hötte	Dr. R Hötte	Hannover
Kardiologische Praxis Dr. Hug	Dr. J Hug	Günzburg
Kardiologische Praxis Dr. Isbruch	Dr. F Isbruch	Castrop-Rauxel
Kardiologische Praxis Dr. Krater	Dr. L Krater	Krefeld
Kardiologische Praxis Dr. Lodde	Dr. BP Lodde	Dortmund

Site	Investigator(s)	City
Kardiologische Praxis Dr. Raff	Dr. F Raff	Düsseldorf
Kardiologische Praxis Dr. Rudolf/ Dr. Bernhardt	Dr. HJ Rudolph	Worms
Kardiologische Praxis Dr. Schlichting	Dr. J Schlichting	Herne
Kardiologische Praxis Dr. Schön	Dr. N Schön	Mühldorf
Kardiologische Praxis Dr. Staubach	Dr. P Staubach	Bochum
Kardiologische Praxis Dr. Vrettos	Dr. Z Vrettos	Witten
Kardiologische Praxis Dr. Wetzel	Dr. T Wetzel	Dortmund
Kardiologische Praxis Dr. Wiethölter	Dr. K Wiethölter	Radebeul
Kardiologische Praxis Gütersloh	Dr. T Seifert	Gütersloh
Kardiologische Praxis Marschner	J Marschner	Bonn
Kardiologische Praxis Nienburg	Dr. N Proskynitopoulos	Nienburg
Kardiopraxis Rheinberg	G Weyers	Bergisch Gladbach
Kath. Kliniken Essen/Philippusstift	Prof. B Hailer	Essen
Klinik Augustinum München	Prof. M Block	München

Site	Investigator(s)	City
Klinik Lazariterhof	Prof. G Bönner	Bad Krozingen
Klinikum Coburg GmbH	Dr. AM Sinha	Coburg
Klinikum Dahme-Spreewald GmbH	Dr. P Waurick	Königs Wusterhausen
Klinikum der Universität Köln	Dr. H Reuter	Köln
Klinikum der Universität zu Köln	Dr. H Reuter	Köln
Klinikum Hannover Oststadt-Heidehaus	Prof. B Schönhofer	Hannover
Krankenhaus Bethanien	Prof. S Möhlenkamp	Moers
Krankenhaus Bethanien Moers	Dr. T Voshaar	Moers
Krankenhaus Reinbek St. Adolf-Stift	Dr. A Aydin	Reinbek
Kreiskrankenhaus Stollberg GmbH	Dr. L Griesbach	Stollberg
Lukaskrankenhaus GmbH	Prof. M Haude	Neuss
Lungenärzte am Rotkreuzplatz	Dr. K Storck	München
Lungenfachklinik Immenhausen	Prof. S Andreas	Immenhausen
Lungenklinik Hemer	Dr. M Westhoff	Hemer
Malteser Krankenhaus St. Hildegardis	Prof. M von Eiff	Köln
MECS Cottbus GmbH	Dr F Käßner	Cottbus

Site	Investigator(s)	City
Mediclin Rehazentrum Spreewald	Dr. W Kamke	Burg/ Spreewald
Missionsärztliche Klinik Würzburg	Prof. B Janey	Würzburg
MVZ am Küchwald	Dr. W Dänschel	Chemnitz
POLIKUM Friedenau	Dr. MO Grad	Berlin
Praxis Dr. Anselm Bäumer	Dr. A Bäumer	Köln
Praxis Dr. Ebeling	Dr. O Ebeling	Schönefeld/ OT Waltersdorf
Praxis Dr. Frieske	Dr. R Frieske	Aachen
Praxis Dr. Fröhlich	Dr. T Fröhlich	Ratingen
Praxis Dr. Gerritsen	Dr. R Gerritsen	Waldkraiburg
Praxis Dr. Hein	Dr. H Hein	Reinbek
Praxis Dr. Hohensee	Dr. H Hohensee	Dresden
Praxis Dr. Kestermann	Dr. O Kestermann	Rheine
Praxis Dr. Nebel	Dr. W Nebel	Rheine
Praxis Dr. Rau	Dr. T Rau	Essen
Praxis Dr. Schnabel	Dr. A Schnabel	Meißen
Praxis Dr. Stratmann	Dr. M Stratmann	Dortmund
Praxis Dr. Tekiyeh	Dr. M Tekiyeh	Essen
Praxis Dres. Böhme/Linke	Dr. M Linke	München

Site	Investigator(s)	City
Praxis für Kardiologie Dr. med. Hewing	Dr. R Hewing	Münster
Praxis für Kardiologie Dr. med. Menz	Dr. V Menz	Menden
Praxis für Kardiologie Ratingen	Dr. KF Schmitz	Ratingen
Praxis für Lunge, Herz und Schlaf	Dr. H Storm	Bielefeld
Praxis Westend	Dr. U Kühne	Berlin
Prof. Franzen Institut - Apel	Dr. C Apel	Köln
Prof. Franzen Institut	Prof. D Franzen	Köln
Ruhrlandklinik Essen	Prof. H Teschler	Essen
Schlaflabor Breisgau	Dr. W Randelshofer	Bad Krozingen
Schwerpunktpraxis Kardiologie Drs. Ophoff/Fritzsch	Dr. N Ophoff	Essen
Siloah Krankenhaus	Prof. A Franke	Hannover
St. Elisabeth-Hospital Herten gGmbH	Dr. H Neubauer	Herten
St.-Josephs-Hospital	Dr. J Börgel	Bochum
St.-Vinzenz Hospital	Dr. S Winter	Köln-Nippes
Stiftungsklinik Weißenhorn	Dr. M Miller	Weißenhorn
Studiengesellschaft IFAZ GbR	Dr. K Jocham	Memmingen
Thoraxklinik Heidelberg gGmbH	Dr. A Benz	Heidelberg

Site	Investigator(s)	City
Unfallkrankenhaus Berlin	Dr. L Bruch	Berlin
Universität Leipzig - Herzzentrum	Dr. M Sandri	Leipzig
Universitätsklinik Bergmannsheil	Dr. HW Duchna	Bochum
Universitätsklinik Mannheim	Prof. T Kälsch	Mannheim
Universitätsklinikum Aachen	Dr. A Schuch	Aachen
Universitätsklinikum Bonn	Dr. D Skowasch, Dr. R Andrié	Bonn
Universitätsklinikum Essen	Prof. T Neumann	Essen
Universitätsklinikum Freiburg	Prof. S Sorichter, Prof. A Zirlik	Freiburg
Universitätsklinikum Gießen/Marburg Standort Marburg	Prof. P Alter	Marburg
Universitätsklinikum Gießen/Marburg, Standort Marburg	Prof. U Koehler	Marburg
Universitätsklinikum Hamburg-Eppendorf	Dr. C Sinning	Hamburg
Universitätsklinikum Heidelberg	Dr. L Frankenstein	Heidelberg
Universitätsklinikum Mannheim	Dr. J Maurer	Mannheim
Universitätsklinikum Münster/WWU	Prof. P Young, Dr. J Stypmann	Münster

Site	Investigator(s)	City
Universitätsklinikum Regensburg	Prof. M Arzt	Regensburg
Universitätsklinikum Schleswig-Holstein Campus Lübeck	Dr. A Steffen	Lübeck
Universitätsklinikum Schleswig-Holstein, Campus Lübeck	Dr. F Bode	Lübeck