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

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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 (Pco2). Periodic breathing was more likely in men, patients with atrial fibrillation, older patients, and as left ventricular ejection fraction and awake Pco2 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

Heart failure (HF) is a relatively common condition, occurring in 1% to 2% of the adult population in Western countries. 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. Despite advances in care, rates of hospitalization and readmission remain high, 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. One such
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 SpO2), and minimum oxygen saturation (min SpO2) 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) guidelines24 ≤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 HF-REF; 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
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, 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
Sleep Apnea Phenotypes in Heart Failure  Arzt et al

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. 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 pre-event 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.

In contrast to SERVE-HF, 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 (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%. 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).

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 SaO2, and PCO2. 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 SchlHF 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.
Sleep Apnea Phenotypes in Heart Failure

The majority of patients (59%) showed 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 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

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

| Phenotype | 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/m² | 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* |
| Al, per h | 19±19* | 21±16 | 24±18* |
| cAHI/AHI, % | 6±6* | 54±17* | 92±6* |
| Mean SaO₂, % | 92±3* | 93±2 | 93±3* |
| Minimum SaO₂, % | 78±9* | 80±8* | 81±7* |
| Time with SaO₂<90%, min | 62±78 | 51±69 | 50±70 |
| Awake PCO₂, 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%); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnea (defined as cAHI/AHI >0.19%); OSA-CSA, obstructive sleep apnea+central sleep apnea (defined as cAHI/AHI >20% and <80%); PCO₂, partial pressure of carbon dioxide; SaO₂, oxygen saturation.

| Phenotype | <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/m² | 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* |
| Al, per h | 19±17* | 20±15* | 30±17* |
| cAHI/AHI, % | 34±33* | 73±22* | 82±15* |
| Mean SaO₂, % | 93±3 | 93±2 | 92±3 |
| Minimum SaO₂, % | 79±8* | 81±6* | 79±9 |
| Time with SaO₂<90%, min | 52±72 | 49±64* | 68±79* |
| Awake PCO₂, 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; CSA, central sleep apnea (defined as cAHI/AHI >80%); LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnea (defined as cAHI/AHI >0.19%); OSA-CSA, obstructive sleep apnea+central sleep apnea (defined as cAHI/AHI ≥20.0% and <80%); PCO₂, partial pressure of carbon dioxide; SaO₂, oxygen saturation.

*P<0.05 OSA vs OSA-CSA.
†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 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).
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 PCO₂ 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 PCO₂ (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...
LVEF, atrial fibrillation, and lower $\text{PCO}_2$ 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 3. Prevalence of periodic breathing (defined as Cheyne-Stokes respiration [CSR] ≥20%) according to sleep apnea type. CSA indicates central sleep apnea (defined as $\text{cAHI/\text{AHI}} \geq 80.0\%$); OSA, obstructive sleep apnea (defined as $\text{cAHI/\text{AHI}} \leq 19.9\%$); OSA+CSA, obstructive sleep apnea+central sleep apnea (defined as $\text{cAHI/\text{AHI}} \geq 20\%$ to 79.9%). AHI indicates apnea-hypopnea index; $\text{cAHI}$, central AHI.

Figure 4. Forest plot of risk factors for central sleep apnea (higher $\text{cAHI/\text{AHI}}$ percentage) and obstructive sleep apnea (lower $\text{cAHI/\text{AHI}}$ percentage). AHI indicates apnea-hypopnea index; BMI, body mass index; $\text{cAHI}$, central AHI; CI, confidence interval; LVEF, left ventricular ejection fraction; min, minimum; NYHA, New York Heart Association; $\text{PCO}_2$, partial pressure of carbon dioxide; $\text{SaO}_2$, oxygen saturation.

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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 PCO2.

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 PCO2 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 PCO2, 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 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; PCO2, partial pressure of carbon dioxide; SaO2, 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; PCO2, partial pressure of carbon dioxide; SaO2, oxygen saturation.

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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, 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.

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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 Female | OSA-Male | OSA-CSA Female | OSA-CSA Male | CSA Female | CSA-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 SaO₂, %*           | 92±3       | 92±3     | 92±2           | 93±2         | 93±2       | 93±3     |
| Minimum SaO₂, %*        | 77±9       | 78±9     | 80±7           | 80±8         | 81±6       | 81±7     |
| Time with SaO₂ <90%, min↑ | 64±83 | 61±77    | 57±77          | 50±68        | 52±54      | 50±71    |
| Awake pCO₂, 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%); pCO2, partial pressure of carbon dioxide; SaO2, 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)         | 0 (0)             | 5319 (77)    | 0 (0)             | 6876 (100)  | 0 (0)             |
| 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 SaO₂, %         | 93±3              | 1 (0)             | 93±2         | 4497 (85)         | 93±3        | 4498 (65)         |
| Minimum SaO₂, %      | 80±8              | 1 (0)             | 83±7         | 4498 (85)         | 81±8        | 4499 (65)         |
| Time with SaO₂ <90%, min | 54±72   | 12 (1)           | 34±66        | 4500 (85)         | 47±71       | 4512 (66)         |
| Awake pCO₂, 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%);
pCO₂, partial pressure of carbon dioxide; SaO₂, oxygen saturation.
### Appendix

#### SchlaHF investigators (all from Germany)

| Site                                      | Investigator(s)                        | City       |
|-------------------------------------------|----------------------------------------|------------|
| Ambulantes Cardiovasculäres Centrum       | Dr. K Schlotterbeck                    | Ravensburg|
| Ravensburg                                |                                        |            |
| Ambulantes Herzzentrum Kassel             | Dr. A Utech                            | Kassel     |
| 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 | Prof. C Angermann                     | Würzburg               |
| 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. HJ Rudolph            | Worms        |
| Dr. Rudolf/ Dr. Bernhardt                 | Dr. J Schlichting         | Herne        |
| Kardiologische Praxis                     | Dr. N Schön               | Mühldorf     |
| Dr. Schöning                              | Dr. P Staubach            | Bochum       |
| Kardiologische Praxis                     | Dr. Z Vrettos             | Witten       |
| Dr. Vrettos                              | Dr. T Wetzel              | Dortmund     |
| Kardiologische Praxis                     | Dr. K Wiethölter          | Radebeul     |
| Dr. Wiethölter                            | Dr. T Seifert             | Gütersloh    |
| Kardiologische Praxis                     | J Marschner               | Bonn         |
| Gütersloh                                 |                           |              |
| Kardiologische Praxis Nienburg            | Dr. N Proskynitopoulos   | Nienburg     |
| Kardiopraxis Rheinberg                    | G Weyers                  | Bergisch Gladbach |
| Kath. Kliniken                            | Prof. B Hailer            | Essen        |
| Essen/Philippusstift                      |                           |              |
| 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. Adolff-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       | Schöenefeld/ OT       |
| 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.-Josefs-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 | Prof. P Alter            | Marburg  |
| Marburg                                        |                          |          |
| Universitätsklinikum Gießen/Marburg, Standort| Prof. U Koehler          | Marburg  |
| 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   | Dr. A Steffen   | Lübeck         |
| Lübeck                                          |                 |                |
| Universitätsklinikum Schleswig-Holstein, Campus | Dr. F Bode      | Lübeck         |
| Lübeck                                          |                 |                |