Supplementary material

This appendix is provided by the authors to give additional information about the research.

Ventricular arrhythmia in heart failure patients with reduced ejection fraction and central sleep apnoea

Christoph Fisser¹; Jannis Bureck¹; Lara Gall¹; Victoria Vaas¹; Jörg Priefert¹; Sabine Fredersdorf²; Florian Zeman²; Dominik Linz³,⁴,⁵,⁶; Holger Woehrle⁷; Renaud Tamisier⁸; Helmut Teschler⁹ Martin R Cowie¹⁰; Michael Arzt¹

¹ Department of Internal Medicine II, University Medical Centre Regensburg, Regensburg, Germany
² Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany
³ Department of Cardiology, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands
⁴ Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands
⁵ Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
⁶ Centre for Heart Rhythm Disorders, Royal Adelaide Hospital, University of Adelaide, Adelaide, Australia
⁷ Sleep and Ventilation Center Blaubeuren, Lung Center Ulm, Ulm, Germany
⁸ HP2 Laboratory, INSERM U1042, Grenoble Alpes University, Sleep laboratory, Pole Thorax et Vaisseaux, Grenoble Alps University Hospital, Grenoble, France
⁹ Department of Pneumology, AFPR, Ruhrlandklinik, West German Lung Center, University Medicine Essen, Essen, Germany
Faculty of Medicine, National Heart & Lung Institute, Imperial College London, London, United Kingdom

Correspondence: Christoph Fisser, MD, Department of Internal Medicine II, University Medical Centre Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany. Tel: +49 941 944 17284. Fax: +49 941 944 7282. Email: Christoph.Fisser@ukr.de
METHODS

**ECG analysis**

Analysis of ventricular and atrial arrhythmias in nocturnal 1-lead-ECGs is an established method that has been used in multiple observational [1–5] and interventional studies [6, 7]. Cardiac rhythm was analysed and categorised into atrial, ventricular and pacemaker rhythm. Atrial rhythm was classified as sinus rhythm, atrial flutter, atrial fibrillation or atrial pacemaker stimulation. Ventricular rhythm was classified as regular or pacemaker stimulation [1, 2, 4, 8]. As previously described [1, 2, 4], arrhythmias were scored as ventricular premature or normal sinus beats. Ventricular arrhythmias consisted of singular ventricular premature beats, couplets and non-sustained ventricular tachycardia (NSVT). Ventricular premature beats were defined as previously described [4, 8]. NSVT were defined as ≥4 consecutive ventricular premature beats with an average heart rate of ≥100 beats/minute [4, 8]. Absolute and relative values for arrhythmias based on recording time were recorded. In addition, the total ECG recording time was documented. Premature ventricular complex (PVC) >10,000/24 hours were calculated by dividing the sum of nocturnal PVC by the ECG recording time and extrapolating to 24 hours.

**Polysomnography core laboratory analyses**

Sleep studies were all scored in a blinded fashion by HP2 Sleep CoreLab, Alpes University, Grenoble, France using standard criteria [9, 10]. Sleep was scored manually by at least two scorers, a third scorer (senior scorer) also evaluated the recording when discrepancies were present between scorers. Recordings were randomly selected and double-checked for scoring quality by senior scorers. For quality control, all data were entered twice, and indexes were recalculated after data entry into the database and checked with PSG reports for consistency.
Senior scorers had >20 years’ training in sleep study scoring and central reading, and have worked with international sleep centres to assess scoring agreement between centres [11]. An apnoea was defined as a complete cessation of airflow for at least 10 seconds and a hypopnoea as a reduction of at least 50% in the nasal pressure signal or a decrease of 30–50% associated with either oxygen desaturation of at least 3% or an EEG arousal defined according to the latest AASM recommendation [9], both lasting for at least 10 seconds. Apnoeas were classified as obstructive or central according to the presence or absence of respiratory efforts and the shape of the respiratory curve of nasal pressure (flow limited aspect or not). In particular, attention was focused on hypopnoeas, which were classified as obstructive or central according to the presence or absence of respiratory efforts and the shape of the respiratory curve of nasal pressure (flow limited aspect or not) and according to the further criteria of Randerath et al. (paradoxical breathing, termination, arousal, sleep stages) [12]. The apnoea-hypopnoea index (AHI) was calculated and defined as the number of apnoeas and hypopnoeas per hour of sleep. The percentage of central events was calculated and defined as the ratio between central events (apnoea and hypopnoea) and all events (apnoea and hypopnoea).

**Subset analysis: occurrence of PVC/h in phases with CSR in sleep stage n2**

The occurrence of PVC/h in sleep stage N2 was compared between episodes with and without CSR. Sleep stage N2 was chosen because it was the most common sleep stage in the current cohort (Table S2) and according to literature [13, 14]. Inclusion criteria according to previous literature [13, 14] were sinus rhythm and PVC >30/h of total recording time. Exclusion criteria were cardiac pacemaker rhythm, atrial fibrillation, missing sleep stages, no CSR or PVC in sleep stage N2, and no ECG recognition by automated ECG software (Custo Med, Ottobrunn, Germany; Figure S1).
**ECG scoring: quality assurance and inter-observer variability**

To control inter-observer variability, the four trained investigators (LG, JB, CF, MA) applied standardised quality criteria to identify difficult-to-interpret ECGs (Table S1). If no consensus was achieved, an experienced electrophysiologist-cardiologist (SF) was consulted for final arrhythmic event determination. All investigators were blinded with respect to clinical data and intervention.

To assess interobserver variability, 20 consecutive ECGs were independently examined by the two investigators (LG, JB), who scored the arrhythmias. The intraclass correlation coefficient (ICC) for a random sample of 20 sleep studies was 0.90 (0.75–0.96; p<0.001) for PVC, which is comparable with previous important analyses of nocturnal ECGs in cohorts with PSG [1–3].
Figure S1. Flow chart for the cross-sectional ancillary analysis of participants from the SERVE-HF major sub-study and for the temporal association between Cheyne-Stokes respiration (CSR) and ventricular arrhythmias in sleep stage N2.

AF, atrial fibrillation; ECG, electrocardiogram; PVC, premature ventricular complex.
Table S1. Quality criteria for ECG analysis

| Quality | Definition                                      | Problems                                                      | Solutions                                                                 |
|---------|------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------|
| 0       | No questionable cardiac events                 | No cardiac arrhythmic events with uncertain classification    | --                                                                        |
| 1       | Lots of artefacts, technical interference       | Hard to classify cardiac events                               | Discuss questionable events in expert round, if necessary, classify ECG as not evaluable |
| 2       | Cardiac rhythm unclear                         | Hard to classify main cardiac rhythm                           | Discuss cardiac events in expert round                                     |
| 3       | Hard to discriminate premature atrial complex (PAC) and premature ventricular complex (PVC) | PAC and PVC show untypical patterns                           | Discuss cardiac events in expert round                                     |
| 4       | No consensus in expert round                   | Expert round was not able to analyse/classify all events with certainty | Discuss with external expert electrophysiologist/cardiologist             |
Table S2. Respiratory characteristics

|                         | Total (n=239) | PVC ≤30/h (n=134)<sup>a</sup> | PVC >30/h (n=105)<sup>b</sup> | p-value |
|-------------------------|---------------|-------------------------------|-------------------------------|---------|
| AHI [events/h TST]      | 39±15         | 40±16                         | 38±12                         | 0.180   |
| Apnea Index [events/h TST] | 23±18          | 23±19                         | 23±16                         | 0.780   |
| Central AHI of total AHI [%] | 78±16          | 78±17                         | 79±16                         | 0.855   |
| Oxygen desaturation index [events/h TST] | 34±19          | 35±20                         | 33±18                         | 0.372   |
| Oxygen saturation [%]    |               |                               |                               |         |
| Mean                    | 92.9±2.3      | 92.8±2.4                      | 92.9±2.1                      | 0.833   |
| Minimum                 | 80.6±7.2      | 80.9±6.6                      | 80.2±7.8                      | 0.372   |
| Time with oxygen saturation <90%, TST [%] | 18.6±27.7      | 20.9±32.6                     | 15.7±19.4                     | 0.131   |
| Amount of CSR, n (%)    |               |                               |                               | 0.010   |
| <20% of TRT             | 78 (33%)      | 53 (40%)                      | 25 (24%)                      |         |
| ≥20% of TRT             | 161 (67%)     | 81 (60%)                      | 80 (76%)                      |         |
| Epworth Sleepiness Scale score† | 7.0±4.6       | 7.3±4.8                       | 6.7±4.2                       | 0.323   |
| Sleep stages TST [%]    |               |                               |                               |         |
| N1                      | 28.7±19.8     | 29.6±20.5                     | 27.4±19.0                     | 0.415   |
| N2                      | 50.7±18.7     | 49.3±18.4                     | 52.6±19.0                     | 0.179   |
| SWS                     | 5.5±8.9       | 6.1±9.1                       | 4.8±8.6                       | 0.262   |
| Rapid eye movement      | 15.1±8.0      | 15.1±8.1                      | 15.2±8.0                      | 0.892   |
| TST [min]               | 296.2±81.4    | 301.3±81.1                    | 289.8±81.7                    | 0.284   |
| Sleep efficiency [%]    | 67.2±21.8     | 67.4±17.7                     | 67.0±27.0                     | 0.895   |

Values are mean ± standard deviation, median (interquartile range) or number of patients (%). AHI, apnoea-hypopnoea index; CSR, Cheyne-Stokes respiration; ODI, oxygen desaturation index (3%); PVC, premature ventricular complex; REM, rapid eye movement; TRT, total recording time; TST, total sleep time; SWS, slow wave sleep.

†Scores on the Epworth Sleepiness Scale range from 0 to 24, with higher scores indicating more daytime sleepiness.

<sup>a</sup>Data available for 132/134 patients with PVC ≤30/h.

<sup>b</sup>Data available for 104/105 patients with PVC >30/h.
### Table S3. Baseline characteristics for patients included in the subset analysis

|                                | Patients (n=19) |
|--------------------------------|-----------------|
| Age, years                     | 66.4±9.9        |
| Male, n (%)                    | 19 (100%)       |
| Body mass index, kg/m²         | 28.5±4.4        |
| Diabetes mellitus, n (%)       | 8 (42%)         |
| NYHA class, n (%)              |                 |
| I or II                        | 8 (42%)         |
| III                            | 11 (58%)        |
| IV                             | 0 (0%)          |
| BNP, pg/mL²                    | 1718.5±1861.2   |
| Six-minute walk distance, m    | 366.4±126.0     |
| LVEF*, %                       | 31.6±7.5        |
| Heart failure aetiology, n (%) |                 |
| Ischaemic                      | 12 (63%)        |
| Other                          | 7 (37%)         |
| Blood pressure, mmHg           |                 |
| Systolic                       | 118.4±18.4      |
| Diastolic                      | 70.1±11.3       |
| Implanted device, n (%)        |                 |
| None                           | 7 (37%)         |
| Non-CRT pacemaker              | 0 (0%)          |
| ICD                            | 9 (47%)         |
| CRT-P                          | 0 (0%)          |
| CRT-D                          | 3 (16%)         |
| Rhythm, n (%)                  |                 |
| Sinus rhythm                   | 19 (100%)       |
| Atrial fibrillation            | 0 (0%)          |
| Other                          | 0 (0%)          |
| Diurnal heart rate, beats/min  | 67.0±13.2       |
| Diurnal QRS duration, ms       | 123.8±26.8      |
| Diurnal QRS >120 ms, n (%)     | 9 (47%)         |
| Bundle branch block, n (%)     |                 |
| Right                          | 1 (5%)          |
| Left                           | 5 (26%)         |
| Other                          | 2 (11%)         |
Cardiac medication, n (%)  
ACEI or ARB 17 (90%)  
β-blocker 18 (95%)  
Aldosterone antagonist 12 (63%)  
Diuretic 17 (90%)  
Cardiac glycoside 0 (0%)  
Anti-arrhythmics 1 (5%)  
Creatinine†, mg/dL\textsuperscript{b} 1.3±0.4  
eGFR, mL/min/1.73m\textsuperscript{2}\textsuperscript{b} 60.8±18.7  
Hemoglobin, mg/dL\textsuperscript{b} 14.7±1.3  

Values are mean ± standard deviation, or number of patients (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRT, cardiac resynchronisation therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

*Locally measured data, up to ≤3 months prior to the trial.
†Locally measured data after enrolment in the trial.
\textsuperscript{a}Data available for 14/19 patients.
\textsuperscript{b}Data available for 17/19 patients.
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