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Temporal association of ventricular arrhythmias and respiratory events in heart failure patients with central sleep apnoea

Valentin Guenzler [a,*], Michael Arzt [a], Marjorie Grimm [a], Amelie Ebert [a], Florian Zeman [b], Dominik Linz [c,d,e,f], Holger Woehrle [g], Renaud Tamisier [h], Martin Cowie [i], Christoph Fisser [a]

[a] Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany
[b] Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany
[c] Department of Cardiology, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands
[d] Department of Cardiology, Radboud University Medical Centre, Nijmegen, the Netherlands
[e] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[f] Centre for Heart Rhythm Disorders, Royal Adelaide Hospital, University of Adelaide, Adelaide, Australia
[g] Sleep and Ventilation Centre Blaubeuren, Lung Centre Ulm, Ulm, Germany
[h] Grenoble Alpes University, HP2 Laboratory, INSERM, Grenoble Alps University Hospital, U1300, Grenoble, France
[i] Faculty of Medicine, National Heart & Lung Institute, Imperial College London, London, United Kingdom

A B S T R A C T

In contrast to obstructive sleep apnoea, the peak of sympathetic tone in central sleep apnoea occurs during the hyperventilation phase. To explore the temporal association of premature ventricular complex (PVC) burden in the context of the apnoea/hypopnoea-hyperpnoea cycle, the duration of apnoea/hypopnoea was defined as 100 %. We assessed the PVC burden throughout the apnoea/hypopnoea-hyperpnoea cycle during the periods of ±150 % in 50 % increments before and after the apnoea/hypopnoea phase. In this subanalysis of 54 SERVE-HF patients, PVC burden was 32 % higher in the late hyperventilation period (50–100 % after apnoea/hypopnoea) compared to the apnoea/hypopnoea phase.

1. Brief communication

The risk of sudden cardiac death is increased in heart failure patients with ventricular arrhythmias. Approximately 50 % of heart failure patients with reduced left ventricular ejection fraction (HFrEF) have moderate-to-severe sleep-disordered breathing (SBD) [1]. Of these, approximately 50 % have predominant central sleep apnoea (CSA) [1]. A high arrhythmia burden (>30 premature ventricular complexes [PVCs] per hour) has been observed in heart failure patients with CSA compared to those without SDB [2]. However, in a non-automated single-centre analysis in OSA and CSA patients, the timely pattern of PVC occurrence in relation to the apnoea/hyperventilation cycle was contrasting due to different activation of the sympathetic system [3].

Therefore, the present analysis aimed to investigate the temporal association of PVC burden in patients with central sleep apnoea and heart failure in the context of the apnoea/hypopnoea-hyperventilation cycle.

In this cross-sectional analysis of the SERVE-HF major substudy (NCT00733343), the main inclusion criteria were, according to the major substudy, age ⩾22 years, symptomatic chronic heart failure (New York Heart Association (NYHA) class III/IV, or class II with ⩾1 heart failure-related hospitalisation in the previous 24 months) and reduced left ventricular ejection fraction (LVEF ⩽45 %) [4]. Key exclusion criteria were insufficient ECG data (e.g. technical interference) and a low rate of PVC (⩽ 30/h) [5].

The substudy protocol was approved by the appropriate local or regional ethics committees [110420d/110420f (Adelaide), 2011-06-303 (Brisbane), HREC-D 153-11 (Melbourne), HPH323 (Perth), HREC/11/WMEAD/124 (Sydney), 27PZT/2012 (Czech Republic), H-D-2008-034 (Denmark), 293/13/03/01/2011 (Finland), 08-RESM-1 (France), 010/1553 (Germany), AA11 (The Netherlands), 2009/2083/REK vest (Norway), dnr M38-08 (Sweden), Rif CE 2581 (Switzerland), 08/H1307/41 (UK)] [4]. The trial was conducted according to Good Clinical Practice and the Principles of the Declaration of Helsinki 2002. All participants gave written informed consent.

Substudy evaluations, such as demographics or polysomnography (PSG), were performed at the baseline visit [4]. All PSGs were centrally scored in a blinded fashion (HP2 Sleep CoreLab, Université d'Alpes, Grenoble, France) according to the American Academy of Sleep Medicine (AASM) [4]. ECG data were derived from full overnight PSG. Data

* Corresponding author. Department of Internal Medicine II, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053, Regensburg, Germany.
E-mail address: valentin.guenzler@ukr.de (V. Guenzler).

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sets were analysed semi-automatically using commercially available ECG-Holter software (custodiagnostic, version 5.4, customed GmbH, Ottobrunn, Germany) and visually by two trained investigators according to standard definitions, with high interobserver agreement for PVCs (95 % confidence interval: 0.90 (0.75–0.96), $p < 0.001$). The investigators were blinded to the clinical data and had access only to the ECG channel and pre-scored PSG sleep stages [6].

A case-crossover study design was used to analyse a temporal association between apnoea/hypopnoea and ventricular arrhythmias. The burden of ventricular events was defined as the ratio of PVCs per normal beats associated with and without respiratory events during the most frequent sleep stage (N2), including the most apnoea/hypopnoea-hyperventilation cycles of all sleep stages [3].

To explore a temporal association of PVC exposure in the context of the apnoea/hypopnoea-hyperventilation cycle, the duration of apnoea/hypopnoea was defined as 100 %. Fig. 1A shows schematically the phases of the apnoea/hypopnoea-hyperventilation cycle. PVC exposure was analysed according to the respective phases that were automatically adjusted by Microsoft Excel® (Richmond, VA, USA) based on the duration of the respiratory event.

According to a random subset analysis of this study population (n = 15), the early phase of hyperventilation was defined as the period from the end of the respiratory event to plus 50 % and the late phase of hyperventilation as 50–100 % after the respiratory event, similar to previous existing literature [3,7]. The phases 100–150 % after the respiratory events and the phases before the respiratory events (minus 50 % to the breathing event and minus 100 % to minus 50 %) were considered normal breathing. If there was a preceding respiratory event within minus 100 %, the corresponding phase was shortened to the end of the preceding event.

Categorical data are presented as absolute and relative frequencies, normally distributed quantitative data as mean ± standard deviation. Data entry and calculation were performed with the software package SPSS 29.0 (Chicago, IL, USA).

54 patients from the SERVE-HF major substudy were eligible for this analysis. The study population was predominantly overweight elderly men with severe HFrEF and severe central sleep apnoea (Table 1). The vast majority were on current HFrEF therapy. 5 (9 %) of patients received a specific antiarrhythmic drug, mainly amiodarone.

Median PVC burden was 2.11 % in the apnoea-hypopnoea phase (Figs. 1B), 2.48 % in the early (respiratory event to 50 %) and 2.79 % in the late hyperventilation phase (50%–100 %), representing relative increases of 17 % ($p = 0.55$) and 32 % ($p = 0.58$), respectively, compared with the apnoea-hypopnoea phase. During normal breathing, either before or after the apnoea-hypopnoea-hyperventilation cycle (minus 100 % to minus 50 %, minus 50 % to the respiratory event, 100–150 % after the respiratory event) the PVC burden was similar to the apnoea/hypopnoea phase and less than in the hyperventilation phase. In addition, the increase in PVC in patients with HFrEF in the late hyperventilation phase may be a consequence of the delayed maximal sympathetic activation after apnoea and the delayed lung-to-chemoreceptor transit time. Similarly, heart rate increased by 2.6 % from the apnoea/hypopnea to the hyperventilation phase (60.6 beats per minute during the respiratory event vs. 62.2 beats per minute during the late hyperventilation phase, $p \leq 0.001$). Additionally, in a sensitivity analysis of our study group, patients with a lower hypoxaemic burden (T90 < 44 min) had a 48.6 % increase of PVC burden in the late hyperventilation phase (3.12 vs. 2.74; $p \leq 0.001$).

First, consistent with previous single-centre observations [3,8] using non-automated, unblinded analysis, our results showed a trend of a higher frequency of PVCs during hyperventilation than in apnoea in HFrEF patients with CSA. Automated analysis contributes to more standardised and larger analyses.

Secondly, this study showed a transient stepwise increase in PVC burden with a maximum in the late hyperventilation phase after a preceding apnoea/hypopnoea. The extent of relative PVC increase in this

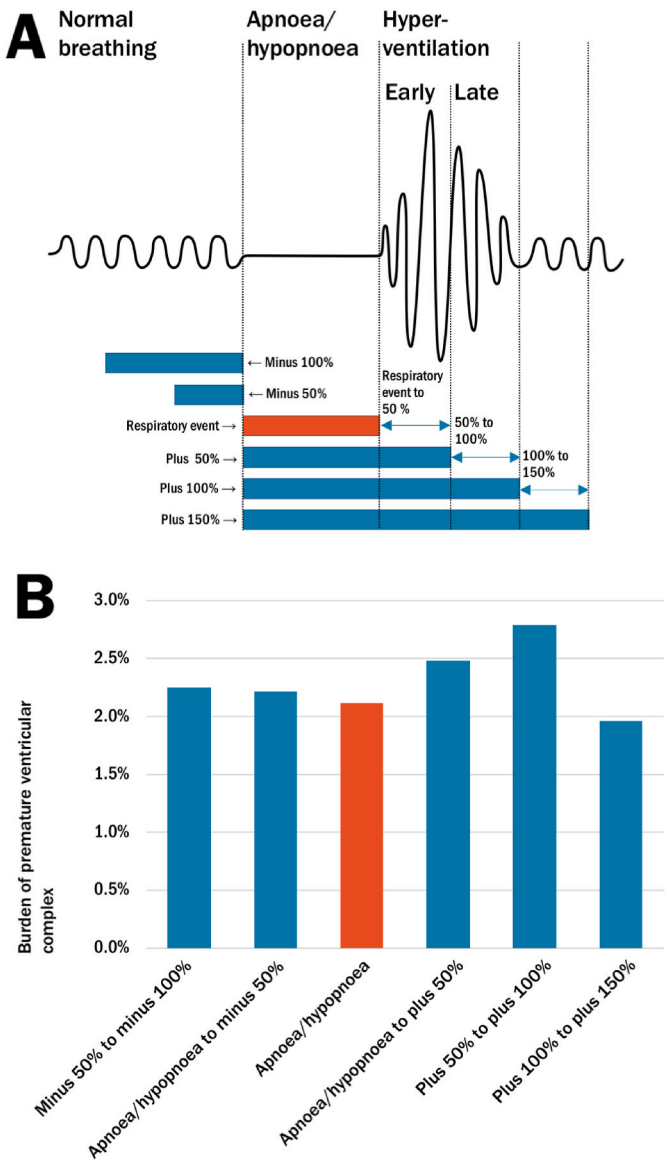

Fig. 1. Fig. 1A) Schematic graph of an apnoea/hypopnoea-hyperventilation-cycle with periods of normal breathing. The apnoea/hypopnoea is marked in red. The early phase of hyperventilation was the period from the end of the respiratory event to plus 50 % and the late phase of hyperventilation as 50–100 % after the respiratory event. The phases 100–150 % after the respiratory event and the phases before the respiratory events (minus 50 % to respiratory event and minus 100 to minus 50 %) were considered as normal breathing. Fig. 1B) There is a stepwise relative increase of PVC burden by +17 % and +32 % from the apnoea/hypopnoea to the early and late hyperventilation phase. During normal ventilation the burden of premature ventricular complexes was similar compared to the apnoea/hypopnoea phase. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

analysis was similar to Ryan et al. (32 % vs. 37 %) [3]. The pathophysiological aspects thought to be involved include myocardial stretching by Cheyne-Stokes-Respiration inducing intrathoracic pressure changes in CSA, causing mechano-electrical dissociation and subsequent ventricular ectopy [5]. In addition, the increase in PVC in patients with HFrEF in the late hyperventilation phase may be a consequence of the delayed maximal sympathetic activation after apnoea and the delayed lung-to-chemoreceptor transit time [9]. This is supported by the significant increase in heart rate during both the early and late hyperventilation phases, which also reflects the activation of

Table 1
Baseline and respiratory characteristics.

Baseline characteristics	(n = 54)
Age, years	67 ± 10
Male, n (%)	52 (96)
Body mass index, kg/m^2	30.1 ± 5.8
Diabetes mellitus, n (%)	29 (54)
Blood pressure, mmHg	
Systolic	123 ± 16
Diastolic	74 ± 12
Nocturnal Holter ECG heart rate, beats/min	73 ± 14
QRS duration, ms	132 ± 33
QRS >120 ms, n (%)	27 (50)
Bundle branch block, n (%)	
Right	5 (9)
Left	12 (22)
Other	13 (24)
NYHA class, n (%)	
II	18 (33)
III	36 (67)
LVEF[b], %	33 ± 9
Heart failure aetiology, n (%)	
Ischaemic	29 (54)
Other	25 (46)
Any implanted device, n (%)	26 (48)
Non-CRT pacemaker	1 (2)
ICD	15 (28)
CRT-P	1 (2)
CRT-D	11 (20)
Creatinine[a], mg/dL	1.4 ± 0.6
Cardiac medication, n (%)	
ACEI or ARB	51 (94)
β-receptor blocker	46 (85)
Aldosterone antagonist	22 (41)
Diuretic	47 (59)
Cardiac glycoside	14 (26)
Antiarrhythmics	5 (9)
Respiratory characteristics	
AHI, events/h TST	37.1 ± 12.6
Apnoea index, events/h TST	22.1 ± 16.2
cAHI, % of AHI	74.6 ± 18.6
Oxygen desaturation index[c], events/h TST	33.4 ± 20.6
Oxygen saturation, %	
Mean	93 ± 2
Minimum	80 ± 9
Time with oxygen saturation <90 %, min	44 ± 52

Data are expressed as number of patients (%), or mean ± standard deviation; ACEI, angiotensin-converting enzyme inhibitor; AHI, apnoea-hypopnoea index, ARB, angiotensin receptor blocker; cAHI, central apnoea-hypopnoea index; CRT, cardiac resynchronisation therapy; CRT-D, CRT with defibrillator; CRT-P, CRT with pacemaker; CSR, Cheyne Stokes respiration; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TRT, total recording time; TST, total sleeping time.

[a] Locally measured data after enrolment in the trial.

[b] Locally measured data, up to ≤3 months prior to the trial.

[c] The oxygen desaturation index is the number of times that the blood oxygen level drops by ≥ 3 percentage points from baseline per hour of recording time.

sympathetic nerve activity. Additionally, the data indicating a more pronounced effect of PVC increase in patients with a lower hypoxaemic burden reflecting a healthier population.

Further mechanistic studies and arrhythmia analysis are needed to investigate these aspects in a prospective context and to validate the results in a general population of heart failure patients, also taking into account the effects of the relative duration of hyperventilation on sympathetic nervous activation [10]. Furthermore, it is important to consider daytime analysis as there are indications that Cheyne-Stokes respiration during the day is associated with a higher ventricular burden [11,12].

Due to the study design, a direct causal relationship cannot be established. Only nocturnal PVCs were analysed; however, PVCs are similarly distributed over 24 h [13]. To demonstrate an association of respiratory events on PVC, patients with a low burden of PVC were excluded. The results therefore cannot be generalized to patients with a low PVC burden. Intrathoracic pressure, tidal volumes and markers of autonomic dysfunction were not assessed. All patients were treated with guideline-directed medication for heart failure at the time of the trials. The results need to be interpreted in the light of evolving guidelines, which may differ in recommendations.

Activation of the sympathetic tonus is associated with respiratory events in the case of SDB. Our study demonstrated that there is a 32 % relative increase in PVC burden during the late hyperventilation phase than during apnoea/hypopnoea, which differs from observations made in OSA. This finding could be a potential avenue for treatment in reducing a high PVC burden, which is a known risk factor for sudden cardiac death.

CRediT authorship contribution statement

Valentin Guenzler: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Michael Arzt:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Marjorie Grimm:** Software, Formal analysis. **Amelie Ebert:** Methodology, Investigation. **Florian Zeman:** Writing – review & editing, Formal analysis. **Dominik Linz:** Supervision, Methodology, Formal analysis. **Holger Woehrle:** Methodology, Investigation, Funding acquisition, Conceptualization. **Renaud Tamisier:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Martin Cowie:** Project administration, Funding acquisition, Conceptualization. **Christoph Fisser:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

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HW was a former employee of ResMed during the SERVE-HF study. RT has received consulting fees from Agiradom (Healthcare provider) and grant support from ResMed.

MC has received consulting fees from ResMed and Respicardia, and grant support through his Institution from ResMed, Bayer and Abbott. HT has received consulting fees, grant support, and hardware and software for the development of devices from ResMed.

MA has received consulting fees from ResMed, Philips Respironics, Boehringer-Ingelheim, NRI, Novartis, JAZZ Pharmaceuticals, Bayer, Inspire and Bresotec, and grant support from ResMed FoundationResMed Foundation, Philips Respironics and the Else-Kroener Fresenius Foundation (2018_A159) outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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