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Methodology for the nocturnal cardiac arrhythmia ancillary study of the ADVENT-HF trial in patients with heart failure with reduced ejection fraction and sleep-disordered breathing

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ABSTRACT

Background: Sleep disordered breathing (SDB) may trigger nocturnal cardiac arrhythmias (NCA) in patients with heart failure with reduced ejection fraction (HFrEF). The NCA ancillary study of the ADVENT-HF trial will test whether, in HFrEF-patients with SDB, peak-flow-triggered adaptive servo-ventilation (ASVpf) reduces NCA. To this end, accurate scoring of NCA from polysomnography (PSG) is required.
Objective: To develop a method to detect NCA accurately from a single-lead electrocardiogram (ECG) recorded during PSG and assess inter-observer agreement for NCA detection.
Methods: Quality assurance of ECG analysis included training of the investigators, development of standardized technical quality, guideline-conforming semi-automated NCA-scoring via Holter-ECG software and implementation of an arrhythmia adjudication committee. To assess inter-observer agreement, the ECG was analysed by two independent investigators and compared for agreement on premature ventricular complexes (PVC) /h, premature atrial complexes/h (PAC) as well as for other NCA in 62 patients from two centers of the ADVENT-HF trial.
Results: The intraclass correlation coefficients for PVC/h and PAC/h were excellent: 0.99 (95%- confidence interval [CI]: 0.99–0.99) and 0.99 (95%-CI: 0.97–0.99), respectively. No clinically relevant difference in inter-observer classification of other NCA was found. The detection of non-sustained ventricular tachycardia (18% versus 19%) and atrial fibrillation (10% versus 11%) was similar between the two investigators. No sustained ventricular tachycardia was detected.
Conclusion: These findings indicate that our methods are very reliable for scoring NCAs and are adequate to apply for the entire PSG data set of the ADVENT-HF trial.

Abbreviations: AF, Atrial fibrillation; ASV (pf), Adaptive servo-ventilation (peak flow triggered); BPM, Beats per minute; CI, Confidence interval; ECG, Electrocardiogram; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; HR, Heart rate; ICC, Intraclass correlation coefficient; Inv, Investigator; NCA, Nocturnal cardiac arrhythmias; NREM, Non-rapid eye movement; NSVT, Non-sustained ventricular tachycardia; PAC, Premature atrial complex(es); PSG, Polysomnography; PVC, Premature ventricular complex(es); RCT, Randomized controlled trial; REM, Rapid eye movement; SDB, Sleep-disordered breathing; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia.

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1. Introduction

>13 million people worldwide are affected by heart failure (HF) with a reduced ejection fraction (HFrEF), a condition that is associated with high morbidity and mortality [1,2]. Ventricular arrythmias, such as ventricular tachycardia (VT) and ventricular fibrillation, are associated with an increased risk of sudden cardiac death, which accounts for 50% of deaths in these patients [3]. Also, individuals with a high burden of premature ventricular complexes (PVC) (i.e. > 10/h [4] or > 4% [5] of total beats in HFrEF or > 30/h in the general population [6]) are at an increased risk of mortality [4–6]. A recent study showed that ablation of frequent PVC in patients with HFrEF improved functional, structural, neurohumoral status and survival [5]. Furthermore, frequent premature atrial complexes (PAC) are associated with increased risk for atrial fibrillation, brain ischemia and mortality [7].

About half of all individuals with HFrEF suffer from sleep-disordered breathing (SDB) [8,9]. SDB may lead to the progression of HF by exposing the heart to intermittent hypoxia, sympathetic activation, and vascular endothelial dysfunction [10–12]. In patients with HFrEF, SDB is independently associated with an increased incidence of malignant ventricular arrhythmias and appropriate cardioverter-defibrillator therapies [13].

The "Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Patients with Heart Failure and Sleep-disordered Breathing" trial (ADVENT-HF, # NCT01128816) is a randomized trial to test the effects of peak flow-triggered adaptive servo-ventilation (ASVpf) on survival and frequency of hospital admissions in a unique cohort of patients with HFrEF and co-existing obstructive or central sleep apnea [14]. All participants underwent overnight attended polysomnography (PSG) at baseline and one month later during which an electrocardiogram (ECG) was recorded continuously [14]. The eventual analysis of this trial will provide us with the opportunity to determine whether treatment of SDB has any influence on the burden of nocturnal cardiac arrhythmias (NCA) in a unique group of patients.

In order to do so, we must first establish a reliable method of detecting NCA. To accomplish this objective, it is necessary that scoring of PVC and other arrhythmias is accurate and consistent. To this end, the objective of the present study was to develop a method to detect NCA accurately from a single-lead ECG recorded during PSG and assess inter-observer agreement for NCA detection.

2. Methods

2.1. Study design

ADVENT-HF is a multi-national randomized trial testing the hypothesis that patients with HFrEF on optimal HF treatment randomized to receive ASVpf to treat co-existing SDB will experience a greater reduction in mortality and cardiovascular hospitalizations than patients randomized to a control group [14]. The NCA ancillary study of the ADVENT-HF trial provides analyses of nocturnal ECGs derived from PSG. In the current study, we describe methods to assess the quality of these nocturnal ECGs, to detect and quantify NCAs and assess inter-observer agreement on scoring them. The methodology was applied to a subset of the ADVENT-HF trial participants.

2.2. Participants

Potential participants were those screened for, or enrolled in, the ADVENT-HF trial at the Toronto University Health Network and Regensburg sites. Exclusion criteria for this study were: failing to meet the technical specifications (ECG recording with <100 Hz), insufficient ECG data due to technical difficulties, artifacts, or software incompatibilities (e.g. not exportable from PSG, not importable into the Holter-ECG software), or not meeting the technical quality criteria (quality score of 4: <50% automatic QRS detection by Holter-ECG software after signal amplification as per Table S1 in the online supplement). In addition, ECGs that did not fulfill the requirements for the semi-automated scoring of cardiac arrhythmia (score of 5: no consensus of the arrhythmia adjudication committee) were excluded (Table 1, Fig. 1).

2.3. Ethics

The ADVENT-HF trial was approved by each sités Research Ethics Board. Written informed consent was obtained from all patients prior to participation.

2.4. Polysomnography

A standardized overnight PSG was performed at baseline [14]. The PSGs were performed in all trial sites according to a standardized montage and protocol [14]. All PSGs were transferred electronically to the Core Sleep Laboratory at Toronto Rehabilitation Institute, where they were scored by only two technicians who sent timely feedback to the sending sites on the quality of the PSGs in order to maintain the highest quality of the data.

2.5. Semi-automated analysis of nocturnal electrocardiograms

During PSGs, ECG signals were derived continuously from a modified lead II [15]. The minimum sampling rate was 100 Hz [16]. The ECG channel was extracted from the PSG using the EDF + data format [17]. Further information on data extraction can be found in the online supplement. Arrhythmia analysis was performed with a commercially available ECG Holter software (custo diagnostic, version 5.4, custo med GmbH, Ottobrunn, Germany).

Table 1
Quality criteria for semi-automated analysis of nocturnal cardiac arrhythmias Abbreviations: PAC: premature atrial complex; PVC: premature ventricular complex; SVT: supraventricular tachycardia; VT: ventricular tachycardia.

Quality	Definition	Problems	Solutions
1	<5% questionable cardiac events	None	
2	Cardiac rhythm unclear	Hard to classify main cardiac rhythm (e.g., implanted pacemaker rhythm with underlying atrial fibrillation)	No further analysis, ***discuss between investigators (expert round).***
3	Hard to discriminate PAC and/or PVC and/or "normal" electric activity of the QRS complex. Hard to discriminate between SVT and VT.	PAC/PVC/"normal" QRS complex not distinguishable, atypical patterns. E.g., "broad complex" tachycardia in patients with implanted pacemaker.	If < 1% and/or<100 QRS complexes label as artifact for PVC/PAC. If higher number present and/or SVT/VT cannot be discriminated, no further analysis, ***discuss between investigators (expert round)***.
4	No consensus between investigators (expert round)	Investigators were not able to analyse/classify all events with certainty	Discuss with the ***arrhythmia adjudication committee***, if not able to classify, ***discard ECG.***
5	No consensus within the arrhythmia adjudication committee	Committee was not able to analyse/classify all events with certainty	***ECG discarded***

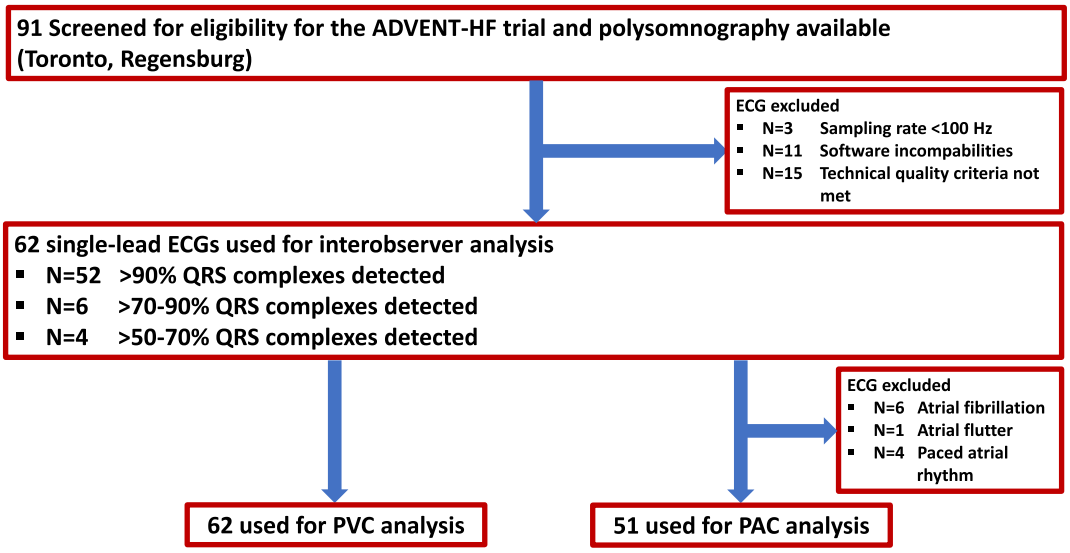

Fig. 1. Flowchart for assessment of nocturnal cardiac arrhythmias from the Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Patients with Heart Failure and Sleep-disordered Breathing (ADVENT-HF). Abbreviations: ECG: electrocardiogram; Hz: Hertz; PVC: premature ventricular complex; PAC: premature atrial complex.

2.5.1. Training of the investigators

ECGs were analysed by two experienced investigators(CMH and CF) who were trained according to the criteria defined by the ACC/AHA/ACP–ASIM Task Force on Clinical Competence in scoring of ECGs [18], and for Holter-ECG using definitions of cardiac arrhythmias conforming to published guidelines (see 2.5.4 for further details) [19–22]. They were blinded to the clinical data of the participants and to the allocated treatment of the participants. The ECGs were systematically assessed in the order outlined below.

2.5.2. Technical quality – detection of QRS complexes and exclusion of artifacts

The technical quality for the automatic detection of QRS complexes by the ECG Holter software was rated according to pre-specified criteria and measures to improve quality were applied in a standardized way (Table S1, online supplement). This rating encompassed the quality of the ECG signal and the technical ability of the software to detect the QRS complexes correctly. The latter is important to the functionality of this program, since some algorithms used to detect cardiac arrhythmias (e.g. PAC, pauses, mean heart rate) are based on RR-intervals.

If < 50% of all QRS were available to the investigators after signal amplification, the ECG was discarded. For an example, see figure S1 in the online supplement. In addition, portions of ECGs in which signals dropped out for at least 5 s, or in which >30% artifacts per 60 s occurred were excluded from the analysis.

2.5.3. Semi-automated scoring of cardiac arrhythmia and arrhythmia adjudication committee

The Holter-ECG software groups QRS complexes into templates according to their morphology and dichotomizes them into “normal” or ventricular patterns. Thereafter, it automatically generates cardiac arrhythmic events on a separate screen (PVC, couplets, VT, PAC, supraventricular tachycardia [SVT], atrial fibrillation [AF], bradycardia and pauses according to internal algorithms of the software and pre-set guideline-conforming thresholds (see 2.5.4 for further details) [19–22]. Each step was visually analysed and controlled by the investigators and appropriate changes were made.

To control for inter-observer variability, the investigators applied standardized quality criteria to identify difficult-to-interpret ECGs (Table 1) adapted from a recently published study [23]. If no consensus was achieved by these investigators, the ECG was submitted to the arrhythmia adjudication committee (see online supplement), including an experienced electrophysiologist (STS), for final arrhythmic event determination.

2.5.4. Guideline-conforming definitions of nocturnal cardiac arrhythmias

2.5.4.1. Cardiac rhythm. The predominant cardiac rhythm was considered to be that rhythm that occurred for at least 50% of the ECG recording time and included, intrinsic atrial or ventricular rhythm or paced rhythms. Atrial rhythm was classified as sinus, atrial flutter or atrial fibrillation (AF) or not classifiable (e.g., in case of paced ventricular rhythm). Paced rhythms were classified as either atrial, ventricular or atrio-ventricular sequential [23].

2.5.4.2. Ventricular arrhythmias. Ventricular arrhythmias were scored according to the 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement [19]. A PVC was defined as an early ventricular depolarization with or without mechanical contraction [19], a couplet as two consecutive PVC, and VT as a tachycardia (heart rate [HR] > 100 beats/min [bpm]) with three or more consecutive beats that originated from the ventricles independently of atrial or AV nodal conduction [19]. A non-sustained VT (NSVT) was scored as VT that spontaneously terminated within 30 s, and a sustained VT as VT that lasted > 30 s [19]. PVC were classified into uniform and multiform according to their QRS morphology. A high burden of PVC was defined as > 30 PVC/h and very high burden as > 4% of all QRS were PVC [5,6]. Idioventricular rhythm was scored as three or more consecutive PVC with a HR of up to 100 bpm that originate from the ventricles independent of atrial or atrioventricular nodal conduction [19].

2.5.4.3. Atrial arrhythmias. In order to clearly distinguish a PVC from a PAC, the latter was defined by a coupling interval to the preceding QRS complex (RR interval > 25% shorter than the mean RR interval of the preceding eight QRS complexes without any PVC) of basic rhythm before the event and a post-electrical activity pause after the event (<120% than the mean RR interval of the preceding eight QRS complexes before the PAC), a QRS duration of < 0.12 s unless aberration was suspected as previously described [24,25]. Supraventricular tachycardia was defined according to the 2019 ESC guidelines as at least three consecutive PAC at rates above 100 bpm, with the exception of sinus tachycardia and atrial fibrillation [20].

Sinus tachycardia was defined as a heart rate > 100 bpm with a P wave preceding each QRS complex with a normal P-wave axis [26]. Atrial fibrillation (AF) was scored (> 30 s continuous tracing) according to the 2020 ESC/EACTS Guidelines [21]. High AF burden was defined as > 50% of recording time spent in AF [27]. Atrial flutter was defined as follows: the ECG aspect of a regular atrial tachycardia with an atrial rate ≥ 240 beats/min lacking an isoelectric baseline between deflections [28].

2.5.4.4. Bradycardias. Bradycardia was defined as a heart rate < 50 bpm [22]. A pause was defined as a period of > 3 s without a QRS complex [22].

2.6. Relationship of cardiac arrhythmic events and sleep stages

Customized software, developed at the IRCCS Fondazione Don C. Gnocchi (I 20146 Milan, Italy) and Istituto Auxologico Italiano IRCSS (I 20145 Milan, Italy), was used to determine the relationship of the PVC and PAC to rapid-eye movement (REM) and non-rapid eye movement (NREM) sleep. Further details can be found in the online supplement.

2.7. Inter-observer analysis

An inter-observer analysis between the two investigators (CMH, CF) was performed to ensure accurate and consistent scoring of the ECG variables described above. Each investigator scored the ECG blind to the scoring of the other investigator. For comparison of PAC patients with AF, atrial flutter or a paced atrial rhythm were excluded.

2.8. Statistics

Data are reported as n, percent, or median followed by inter-quartile range. The intraclass correlation coefficient between the two investigators was calculated for assessments of PVC/h and PAC/h, based on a mean rating (k = 2) absolute agreement, 2-way mixed effects model with 95%-confidence interval (CI). Intraclass correlation coefficients were interpreted as follows: below 0.50: poor, between 0.50 and 0.75: moderate, between 0.75 and 0.90: good, above 0.90: excellent [29]. Furthermore, the agreement between the investigators for PVC/h and PAC/h was assessed using the Bland-Altman procedure [30]. Estimated biases (mean difference between the two methods) are given together with their 95% confidence intervals (CIs). The 95% limits of agreement (2 × standard deviations of the difference) are also reported. Other NCA were assessed as categorical variables and case matched between the investigators. SPSS software statistical package version 26.0 (SPSS Inc, Chicago, IL, USA) and R [31] using the "epade" and "BlandAltmanLeh" package were used.

3. Results

3.1. Inter-observer reliability

Of 91 PSGs, 62 had ECGs that were of sufficiently high quality to be included in the analysis (Fig. 1). Scoring of cardiac arrhythmic events on these ECGs was compared between the two investigators. Analysed ECG time was about one hour shorter than the total recording time due to loss of signal or artifacts. The number of analysed QRS complexes was similar between the investigators.

Table 2 shows that there was very good agreement on classification of all ECG variables between the two investigators. In particular, scoring of all PVC variables was identical between the two investigators. The only differences in identification of arrhythmias were minor; the investigators assigned one atrial rhythm and two ventricular rhythms differently (AF vs unknown, and ventricular pacing vs intrinsic rhythm).

Results were similar for PVC/h (n = 62) and PAC/h (n = 51). A Bland-Altman analysis for comparison of PVC/h and PAC/h is depicted in Fig. 2 A and B, respectively. The mean difference for PVC/h was −2.6/h (95% CI −4.8 to 0.3, limits of agreement −19.9 to 14.8) and for PAC/h −0.5/h (95% CI −1.8 to −0.2, limits of agreement −31.6/h to 30.6/h).

The number of participants with a high and very high PVC burden was similar. There was a slightly larger difference between investigators in adjudication of multiform PVC. Small differences regarding couplets, NSVT, idioventricular rhythm and supraventricular tachycardias were noted. No sustained VT was detected. The number of pauses, bradycardias and the mean heart rate were identical. Examples of atrial fibrillation, PVC, NSVT and PAC are shown in Figs. 3–6.

The intraclass correlation coefficients for PVC/h and PAC/h were excellent: 0.99 [95%-confidence interval (CI): 0.99–0.99] and 0.99 [95% CI: 0.97–0.99], respectively. Sensitivity analysis including all ECGs with > 70% QRS detection and those with > 90% QRS detection yielded similar results (Table S2 and S3). They were also excellent for total and analysed ECG time, QRS complexes (n) and mean heart rate during the night, further details are shown in Table 2.

The intraclass coefficients for PVC/h in NREM sleep were excellent at 0.99 (95% CI: 0.99–1.0; n = 62) and, for REM sleep were moderate at 0.83 (95% CI: 0.74–0.89; n = 60, two individuals had no REM sleep). They were similarly excellent for PAC/h in NREM and REM sleep 0.95 (95% CI: 0.93–0.97; n = 51, and 0.97 (0.96–0.98; n = 49, two individuals had no REM sleep), respectively. There was no difference between PVC/h and PAC/h during NREM and REM sleep for either

Table 2
Holter-ECG findings per investigator.

Variable n = 62	Investigator 1	Investigator 2	Measurement of agreement*
Total ECG time (h)	7.6 [6.9; 8.1]	7.6 [6.9; 8.1]	0.97 (0.95–0.98)
Analyzed ECG time (h)	6.7 [5.9; 7.5]	6.6 [5.6; 7.4]	0.92 (0.88–0.95)
QRS complex, n	24,758 [20595; 27777]	24,402 [19909; 27619]	0.94 (0.91–0.96)
Atrial rhythm			
Sinus rhythm	44 (71%)	44 (71%)	60/62 (97%)
Atrial fibrillation	6 (10%)	7 (11%)	
Atrial flutter	1 (2%)	1 (2%)	
Paced atrial rhythm	4 (7%)	4 (7%)	
Unknown	7 (11%)	6 (10%)	
Ventricular rhythm			
Intrinsic	45 (73%)	47 (76%)	60/62 (97%)
Paced	17 (27%)	15 (24%)	
Atrio-ventricular sequential pacing	4 (7%)	4 (7%)	62/62 (100%)
PVC/h	15 [1; 68]	15 [2; 71]	0.99 (0.99–0.99)
PVC > 10/h	33 (53%)	32 (52%)	61/62 (98%)
PVC > 30/h	39 (63%)	39 (63%)	62/62 (100%)
PVC burden > 4% of QRS	11 (18%)	11 (18%)	62/62 (100%)
Patients with multiform PVCs	54 (87%)	45 (73%)	51/62 (82%)
Patients with couplets	26 (42%)	28 (45%)	58/62 (94%)
Patients with NSVT	12 (19%)	11 (18%)	61/62 (98%)
Patients with idioventricular rhythm	3 (5%)	4 (6%)	61/62 (98%)
PAC/h (n = 51) ‡	1.3 [0.5; 7.4]	1.0 [0.4; 7.4]	0.99 (0.97–0.99)
Patients with SVT	10 (16%)	8 (13%)	60/62 (97%)
Patients with pauses	0	0	62/62 (100%)
Patients with bradycardia	10 (16%)	10 (16%)	62/62 (100%)
Mean heart rate during the night (bpm)	59 [54; 65]	59 [54; 65]	1.00 (1.00–1.00)

Data are presented as median and interquartile range.
*Between both raters using intraclass correlation coefficient (ICC) with 95% confidence interval for continuous variables and n (%) for categorical variables.
‡ Without atrial fibrillation, atrial flutter and paced atrial rhythm.
Abbreviations: ECG: electrocardiogram; h: hour, PVC: premature ventricular complex; NSVT: non-sustained ventricular tachycardia; PAC: premature atrial complex; bpm: beats per minute; SVT: supraventricular tachycardia.

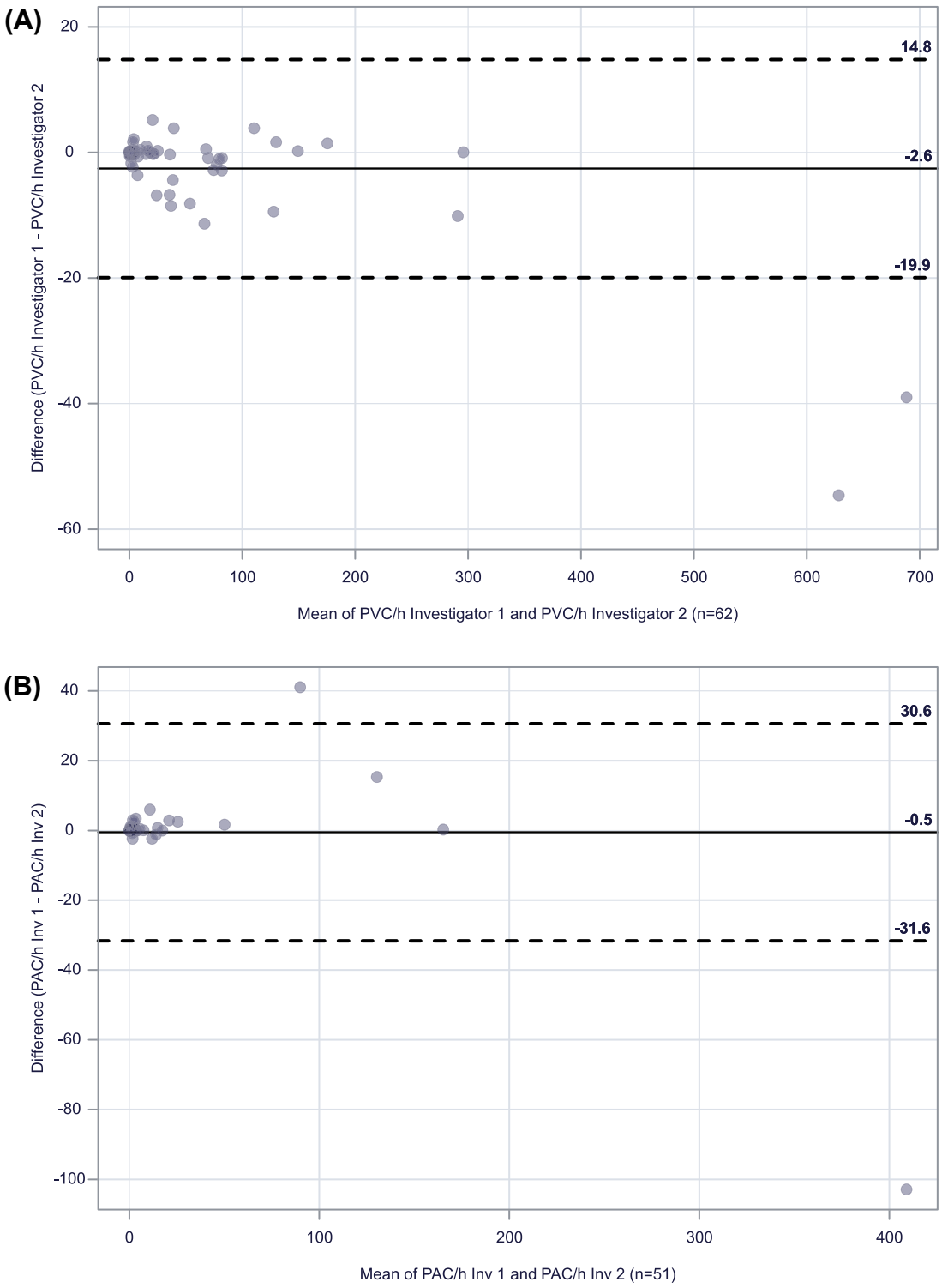

Fig. 2. Bland-Altman plot (solid line depicts the mean bias, the dashed lines depict limits of agreement) comparing scoring of the two investigators for the 62 subjects. Each dot represents one participant. Darker dots represent overlapping results. **A)** Premature ventricular complex per hour (PVC/h). **B)** Premature atrial complex per hour (PAC/h). Abbreviation: Inv: investigator.

investigator (Table S4). In the case of atrial fibrillation, this arrhythmia was present throughout the night, so there was no difference in atrial fibrillation burden per hour between NREM and REM sleep.

4. Discussion

In this manuscript, we describe methods to ensure the accuracy and high quality of ECG analyses to detect and quantify NCAs from PSGs. This included extensive training of investigators and development of standardized technical quality criteria, standardized guideline-conforming semi-automated NCA-scoring as well as the implementation of an arrhythmia adjudication committee. Applying these methods, we have demonstrated excellent inter-observer agreement on scoring of both PVC/h and PAC/h from a single-lead ECG from PSGs in a subset of

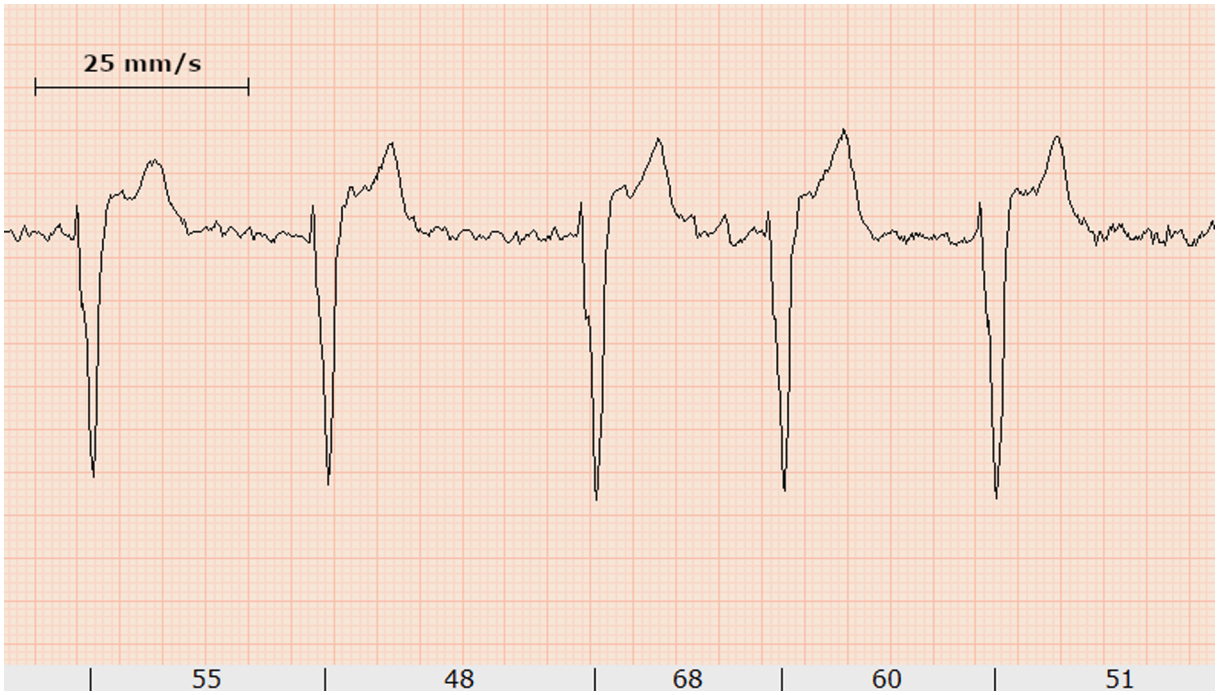

Fig. 3. Example of atrial fibrillation. The vertical line on the bottom of the ECG corresponds with a detected QRS complex. The numbers between the vertical lines indicate the calculated heart rate. Abbreviation: mm/s: millimetre per second.

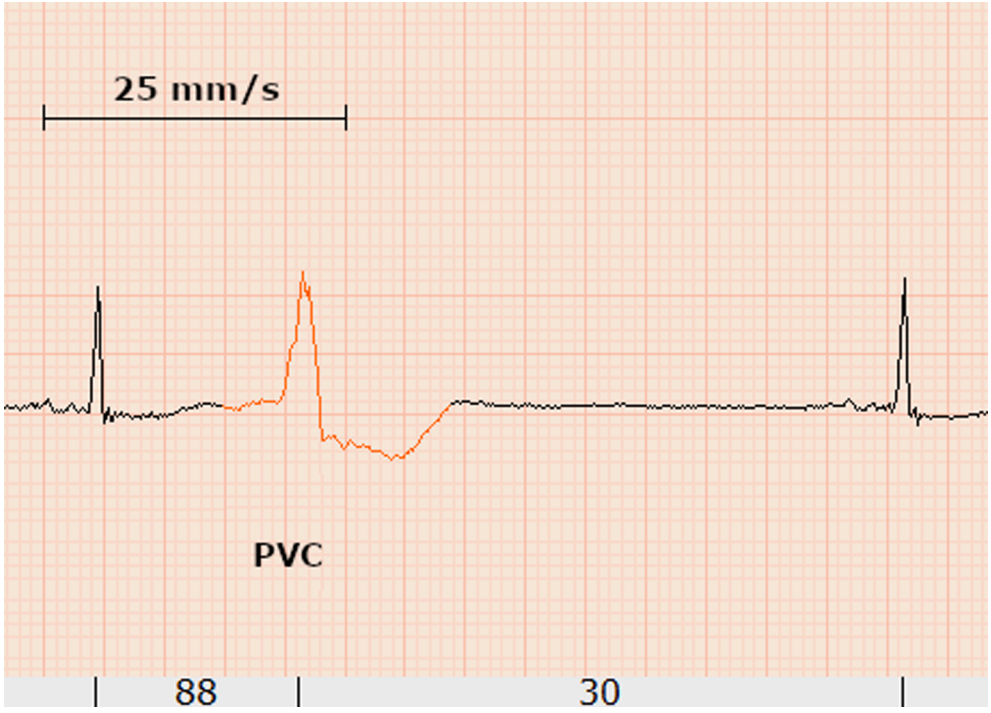

Fig. 4. Example of a PVC in orange. The vertical line on the bottom of the ECG corresponds with a detected QRS complex. The numbers between the vertical lines indicate the calculated heart rate. Abbreviation: PVC: premature ventricular complex; mm/s: millimetre per second.

the ADVENT-HF patient population. Furthermore, there were no clinically relevant differences between the investigators in scoring of any of the other reported variables including predominant underlying rhythm, ventricular and atrial arrhythmic events and mean heart rate.

4.1. Methods for quality assurance

Employing quality assurance methods is essential in a population with HFrEF, in whom wide QRS complexes and both atrial and ventricular pacing are common [23,32], in order to achieve similar inter-observer agreement on electrocardiographic variables using a single-lead ECG recorded during PSG compared to studies in which

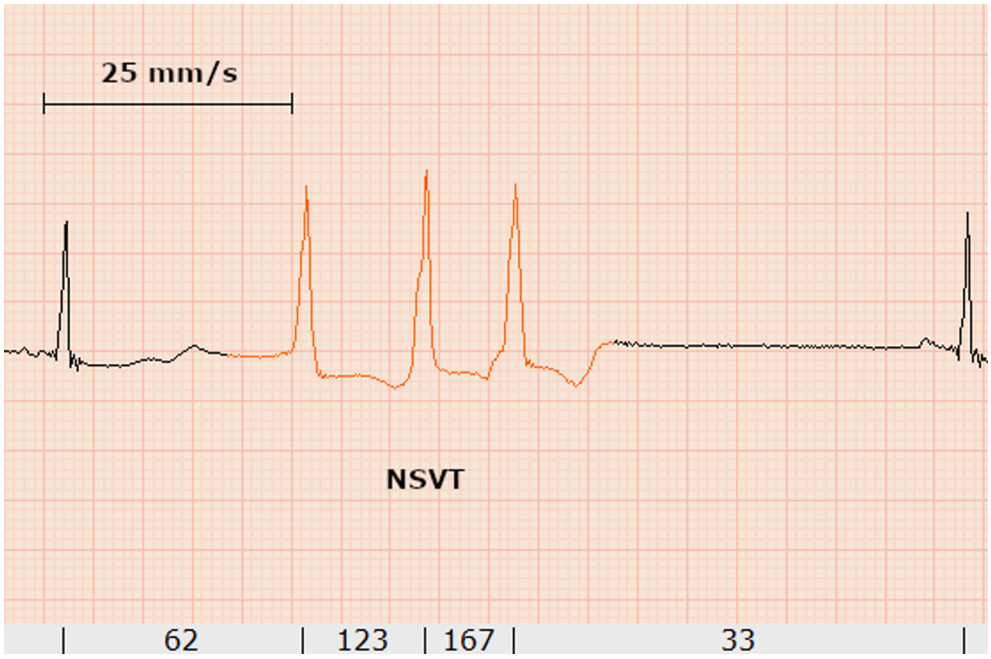

Fig. 5. Example of a NSVT in orange. The vertical line on the bottom of the ECG corresponds with a detected QRS complex. The numbers between the vertical lines indicate the calculated heart rate. Abbreviation: NSVT: non-sustained ventricular tachycardia; mm/s: millimetre per second.

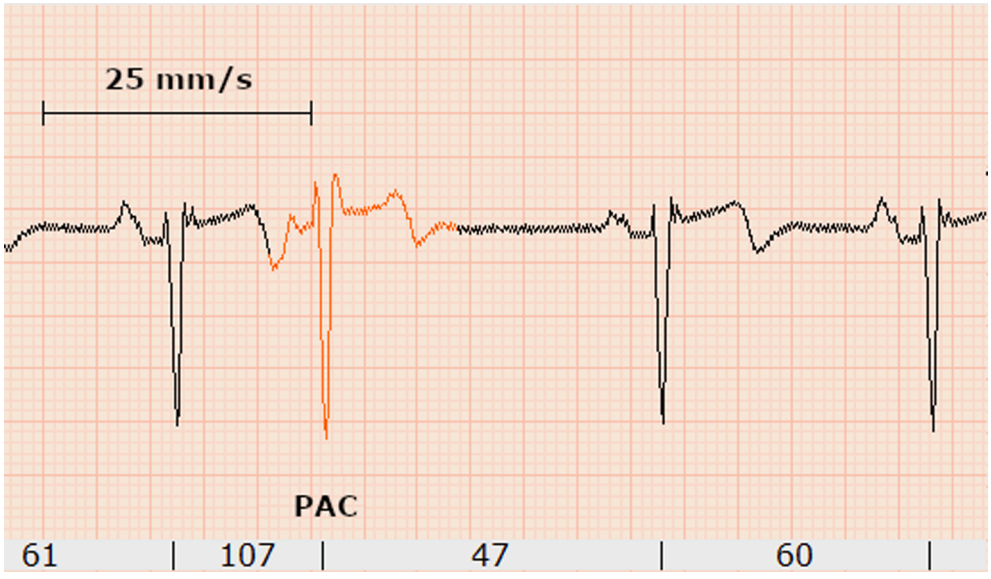

Fig. 6. Example of a PAC in orange. The vertical line on the bottom of the ECG corresponds with a detected QRS complex. The numbers between the vertical lines indicate the calculated heart rate. Abbreviation: PAC: premature atrial complex; mm/s: millimetre per second.

participants did not have overt heart disease [33,34]. Therefore we implemented stringent training of the investigators for ECG analysis according to standardized guidelines [18]. Such training of investigators has not been reported in previous studies using single-lead ECGs during PSGs in subjects with HFrEF [23,35–38].

Furthermore, in the present study standardized technical specifications and quality criteria for the detection of QRS complexes by the Holter ECG software (Table S1, online supplement) as well as standardized criteria for exclusion of artifacts and dropped out signals are outlined. In only one other study using a single-lead ECG derived from PSG did the authors describe their quality criteria for the analysed ECGs, but did not address technical and scoring aspects of the ECG separately since they did not use dedicated ECG-Holter software [23]. Furthermore, none of the previous studies reported explicit reasons for ECG exclusion (e.g. percentage of automatic QRS detection) or exact criteria for why portions of the ECG were excluded [23,33,35–38]. We also defined a scale to describe difficulties in classifying cardiac arrhythmic events and provided a standardized pathway for assessing these ECGs which included an arrhythmia adjudication committee. While some studies have indicated that an experienced cardiologist arbitrated difficult to interpret ECGs [23,39], implementation of a dedicated arrhythmic adjudication committee in our study is unique.

Importantly, semi-automated analysis and scoring of NCAs from ECGs recorded during PSG was based on the most recent guidelines for cardiac arrhythmic events [19–22]. Definitions of these events have substantially changed over the last years. Crucially, a wide QRS complex

is not a mandatory scoring criterion for a PVC [19]. In particular, in several other studies in patients with HFrEF [23,33,35–38] the definition of PVC was not based on current guidelines [19]. We have applied these methods to a unique cohort of patients who had a combination of HFrEF and either obstructive or central sleep apnea. We are not aware of any other study of this nature in a comparable group of subjects.

Furthermore, no study using single-lead ECG in subjects with HFrEF has included such a wide spectrum of cardiac arrhythmias including tachycardic and bradycardic events [23,33,35–38].

4.2. Inter-observer analysis

Our excellent intraclass correlation coefficients [29] for PVC and PAC are comparable to two other studies using single-lead ECGs recorded during PSG [23,33] and to a study using data from Holter-ECGs while patients were undergoing PSG on the same day [34]. Previous studies included participants from the general population [33,34] and HFrEF patients with CSA in another [23]. All studies showed excellent agreement between investigators with intraclass correlation coefficients ≥ 0.9, but used much smaller sample sizes ($n = 20$ to 25) for their inter-observer analysis [23,33,34]. We did not find any clinically relevant differences in scoring of other NCAs such as AF and non-sustained VT, similar to another study [34]. A unique aspect of our study is that we assessed the inter-observer agreement on scoring of PVC/h and PAC/h separately in REM and NREM sleep. We found excellent agreement for PVC/h and PAC/h in both instances, except for PVC/h in REM sleep which was still moderately-good.

4.3. Limitations

One limitation was that the ECG recording was confined to one night, so we could not assess daytime cardiac arrhythmias [40]. Another is that it is unclear if these results can be applied to other Holter-ECG software, since these might rely on different algorithms. Due to our rigorous quality assessment some ECGs had to be excluded from the analysis, so that only reliable data were analysed.

In addition, distinguishing between PVC and PAC seems to be more difficult using single-lead ECG monitoring (patch monitoring) compared to three-lead ECG Holter monitoring in some cases [41,42]. In any event, we found excellent inter-observer agreement using single-lead ECGs from PSGs. Furthermore, no difference in the number of VTs and the burden of atrial fibrillation was noted [41]. These studies highlight that single-lead ECG findings can be reliably interpreted. Also, the present study had the largest sample size for an inter-observer analysis of PVC and PAC using single-lead ECG during PSG recording.

4.4. Summary and conclusion

Based on highly standardized methods of semi-automated guideline-conforming scoring of NCAs from PSG, this study demonstrated exceedingly high levels of agreement between the two trained investigators for scoring of both PVC/h and PAC/h. Furthermore, there were no clinically relevant differences between them in scoring of any of the other reported variables including predominant underlying rhythm, mean heart rate and ventricular and atrial arrhythmic events. These findings indicate that our methods are very reliable for scoring NCAs. Accordingly, these techniques should provide an appropriate means of scoring nocturnal ECGs for the entire PSG data set of the ADVENT-HF trial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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