RESEARCH ARTICLE

Beyond the AHI–pulse wave analysis during sleep for recognition of cardiovascular risk in sleep apnea patients

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Summary
Recent evidence supports the use of pulse wave analysis during sleep for assessing functional aspects of the cardiovascular system. The current study compared the influence of pulse wave and sleep study-derived parameters on cardiovascular risk assessment. In a multi-centric study design, 358 sleep apnea patients (age 55 ± 13 years, 64% male, body mass index 30 ± 6 kg m⁻², apnea–hypopnea index 13 [5–26] events per hr) underwent a standard overnight sleep recording. A novel cardiac risk index was computed based on pulse wave signals derived from pulse oximetry, reflecting vascular stiffness, cardiac variability, vascular autonomic tone and nocturnal hypoxia. Cardiovascular risk was determined using the ESC/ESH cardiovascular risk matrix, and categorized to high/low added cardiovascular risk. Comparisons between cardiac risk index and sleep parameters were performed for cardiovascular risk prediction. Apnea–hypopnea index, oxygen desaturation index and cardiac risk index were associated with high cardiovascular risk after adjustment for confounders (p = .002, .001, < .001, respectively). In a nested reference model consisting of age, gender and body mass index, adding cardiac risk index but not apnea–hypopnea index or oxygen desaturation index significantly increased the area under the receiver operating characteristic curve (p = .012, .22 and .16, respectively). In a direct comparison of oxygen desaturation index and cardiac risk index, only the novel risk index had an independent effect on cardiovascular risk prediction (p_{CRI} < .001, p_{ODI} = .71). These results emphasize the association between nocturnal pulse wave and overall cardiovascular risk determined by an established risk matrix. Thus, pulse wave analysis during sleep provides a powerful approach for cardiovascular risk assessment in addition to conventional sleep study parameters.

KEYWORDS
cardiac risk index, finger photoplethysmography, pulse variability, risk prediction, vascular stiffness
INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction, intermittent hypoxia, and frequent arousal from sleep. OSA is highly prevalent in the middle-aged population, and both cardiovascular (CV) function and sleep quality are negatively affected by the disorder (Benjafie filed et al., 2019). Episodic hypoxia and arousal from sleep activate the sympathetic nervous system and induce fundamental changes in autonomic and cardiovascular homeostasis during the course of an obstructive respiratory event (Hedner et al., 1988). Moreover, solid epidemiological evidence supports an association between OSA and cardiometabolic disease (Gunduz et al., 2019; Kent et al., 2013; Tkacova et al., 2014). Recent studies have identified several OSA phenotypes, including those prone to develop CV complications (Randerath et al., 2018).

Polysomnography (PSG) is the gold-standard for OSA assessment (Berry et al., 2012). The PSG recording typically includes a pulse oximetry signal for quantification of hypoxia. Other relevant PSG metrics are the apnea–hypopnea index (AHI), oxygen desaturation index (ODI), distribution of sleep stages, and the frequency of arousals from sleep. Recent studies have challenged the value of the AHI as a universal expression for OSA severity and associated CV risk (Pevernage et al., 2020; Randerath et al., 2018). Hence, there is a need for more precise markers for clinically relevant OSA and its associated CV risk.

Pulse wave analysis has been applied for the assessment of vascular properties like stiffness and aging (Laurent et al., 2016). For example, oscillometric assessment of the pulse wave contour has been used to prospectively evaluate peripheral vascular properties. Central vascular stiffness was shown to be a strong predictor of CV outcomes in large epidemiological studies (Ben-Shlomo et al., 2014). In line with these findings, we developed an oximeter-based pulse wave analysis algorithm that integrates quantification of multiple aspects including autonomic, vascular and cardiac activity during sleep (Grote et al., 2011). This method, which also includes traditional measures of hypoxia, was found to predict high CV risk as determined by established CV risk matrices (e.g. Framingham, SCORE, PROCAM) in an overnight recording of the finger pulse wave signal in patients with suspected OSA. Importantly, the association with CV risk prediction was considerably more precise with the overnight pulse wave analysis than with traditional daytime blood pressure assessment (Sommermeyer et al., 2014).

The current study aimed to compare the capacity of conventional sleep parameters, such as AHI and ODI, and the newly developed finger pulse wave analysis to identify individuals with high CV risk. Different methods were simultaneously applied during an overnight assessment in a large multi-centric sleep lab cohort. We hypothesized that pulse wave analysis was superior to measures of sleep quality and OSA severity for recognition of high CV risk.

METHODS

Study subjects and data collection

A study flow chart is presented in Figure 1. The study design has previously been reported in detail (Sommermeyer et al., 2014). In brief, the study comprised 520 subjects with suspected OSA investigated at one of five tertiary sleep centres in Germany and Sweden. Twenty-five recordings were excluded due to irregular pulse wave signals (e.g. atrial fibrillation). A random subset of recordings (n = 115) was used to enable the training of a novel cardiac risk index (CRI; Sommermeyer et al., 2016). The current analysis contained the remaining subjects in the cohort (n = 380). Incomplete recordings lacking any parameter were removed prior to the analysis (n = 22). All subjects underwent a standard full-night sleep study. Clinical routines differed between centres, and a subgroup of 92 patients was studied with a polygraphic sleep test. The final analysis was, therefore, performed in two cohorts: the main analysis cohort (n = 358, assessing AHI, ODI and pulse wave parameters); and the PSG-subcohort (n = 266, assessing AHI, ODI, pulse wave parameters and additional sleep variables). Written informed consent was obtained from each participant prior to entry into the study, and the protocol was approved by the respective local Ethics Committee at each centre.

Sleep study

The polygraphic (PG) montage included finger pulse oximetry, respiratory effort and nasal-oral pressure. Signals used for pulse wave analysis were collected via a modified pulse oximeter module (ChipOx, Coriscience GmbH&Co.KG) integrated into a PG device (Sommnolab, SomnCheck/R&K, or SomnCheck II, Weimann Geraete fuer Medizin GmbH&Co.KG). Further details of the technical set-up have been described elsewhere (Sommermeyer et al., 2016).

The full night in-lab PSG was performed in accordance with standards set by the American Academy of Sleep Medicine (AASM; Iber et al., 2007). The PSG recordings were based on a complete montage, which included recordings of electroencephalography (EEG), electrooculography (EOG), chin and left/right anterior tibialis electromyography (EMG), and electrocardiography (ECG). The derived sleep variables included total sleep time (TST), parameters of sleep architecture (expressed as percent time spent in each sleep stage of TST), and periodic leg movement index.

All recordings were manually scored by trained sleep technicians in accordance with the AASM criteria (Iber et al., 2007). For classification of hypopnea events, a ≥ 4% desaturation criterion (PG/PSG), or an arousal (only PSG) were used. The frequency of apnea/hypopnea and hypoxic events (≥ 4%) was calculated as the AHI and the ODI, respectively.
2.3 | Pulse wave analysis during sleep

The overnight photoplethysmographic recording included a single unfiltered pulse wave signal that was used for all subsequent analyses. The following eight pulse wave parameters were computed according to the methodology earlier described in detail (Sommermeyer et al., 2016).

- The **pulse wave attenuation index** (PWA-I) – an index describing amplitude attenuations of 10%–30% from baseline per hour.
- The **pulse propagation time** (PPT) – the mean time-interval between the peak systolic pulse wave and the dicrotic notch.
- The **respiration-related pulse oscillation** (RRPO) – pulse rate variability in the frequency range of typical physiological breathing rate (0.15–0.4 Hz).
- The **pulse rate acceleration index** (PR-I) – number of pulse rate accelerations, defined as > 10% increases from baseline, per hour.
- The **hypoxia index** (SpO₂-I) – the number of ≥ 2% oxygen desaturations per hour.
- The **time below 90% SpO₂ (T < 90)** – indicating the time in significant hypoxia with a SpO₂ < 90%.
- The **time in symmetric desaturation** (TSD) – classification of periodically reoccurring symmetric desaturations as an indicator of central breathing disorders.
- The **difference between the PR-I and the SpO₂-I** – reflecting the chronotropic response to hypoxia.

Subsequently, the overall CRI was computed as a composite metric of these parameters (Sommermeyer et al., 2016). The computed CRI value varied between 0 (average CV risk) and 1 (increased CV risk).

2.4 | CV risk assessment according to conventional CV risk factor

The ESC/ESH risk matrix (Mancia et al., 2007) was used as a gold-standard to classify overall CV risk. This matrix is based on an
assessment of various risk factors, including demographics, anthropometrics, history of CV disease, blood pressure, smoking habits, glucose and lipid variables, and associated clinical conditions, to assign each subject to one out of five risk classes, ranging from "average cardiovascular risk" to "very high added cardiovascular risk". These classes are calibrated to indicate a 10-year added risk of CV disease of 0%, > 0%–15%, > 15%–20%, > 20%–30%, and > 30%, according to Framingham criteria (European Society of Hypertension-European Society of Cardiology Guidelines, 2003). We allocated each subject in one of two groups (low/high risk), containing those with average, low and moderate added risk, and those with high or very high added CV risk, respectively.

2.5 Statistical analysis

The analysis was performed using R, version 3.5.3 (R Foundation for Statistical Computing). Descriptive data are presented in mean ± standard deviation or median with interquartile range, depending on the distribution pattern. Pearson's Correlation Coefficient was used to examine dependencies in the set of candidate parameters to identify possible confounding. For evaluating the predictive value of added parameters, we followed the guideline for evaluating novel risk markers, published by the American Heart Association (Hlatky et al., 2009). This is realized by the following steps.

- Reporting statistical relevance by assessing parameters’ p-values in a single variable model.
- Evaluating the additional value of the tested parameter after statistical adjustment for established risk factors.
- Evaluation of the models’ fit on the present dataset after adding the tested parameters, using the Akaike Information Criterion (AIC) together with a model comparison using the Likelihood Ratio Test.
- Evaluating the predictive value and capability of discrimination by analysing changes in the area under the ROC curve (receiver operating characteristic curve).

All PSG-variables were used as continuous variables, and data were tested for distribution patterns. For the between-group comparison of different study samples, we used Student’s t-test for normally distributed parameters, and Mann–Whitney U-test for non-normally distributed data. Pearson’s Chi-squared test was used for comparison of categorical variables. All following analyses have been performed using logistic regression models, predicting a binary outcome of low versus high added CV risk based on the gold-standard ESC/ESH risk matrix. Analyses have been performed to assess single parameter impact, as well as additional predictive value, when controlling for established risk factors. For this purpose, two different models have been fitted for each tested parameter. The first model contained a single predictor to assess its individual impact on CV risk. The second model controlled for age, gender and body mass index (BMI) to evaluate the additional predictive value. The AIC was used to assess the model’s likelihood of the resulting classification (Akaike, 1973). To evaluate the significance of changes in the model’s likelihood, a likelihood ratio (LR) test using chi-square statistics was performed. Area under the ROC curve (AUC) served as a marker for general model performance in terms of sensitivity and specificity. Differences in AUC between the different modelling approaches were tested using DeLong’s non-parametric test (DeLong et al., 1988). To address limitations of the study design, we conducted a sensitivity analysis to determine the effect of different sleep study protocols (PG and PSG) and study sites.

3 RESULTS

3.1 Group differences in anthropometric and sleep test-derived parameters

Subjects with elevated CV risk were older, had a higher BMI and differed significantly in terms of analysed pulse wave and PSG-derived parameters (Table 1).

3.2 Correlation analysis of pulse wave and sleep test-derived parameters

In the set of PSG parameters, we observed a high inter-correlation between the AH1 and ODI (r = .85, p < .001), as well as for sleep stages (N1 and N2, r = −.55; N1 and N3, r = −.44). Overall, pulse wave parameters showed weaker or no significant inter-correlation: the strongest correlation was found for the two pulse rate-related parameters RRPO and PR-I (r = .62, p < .001), followed by PPT and RRPO (r = .30, p < .001; Table 2).

3.3 Logistic regression models

All tested pulse wave parameters, as well as the ODI and the AH1, were significantly associated with CV risk classification (Table 3). However, time spent in sleep stages N2 and N3 was not associated with risk. When adjusting for age, gender and BMI, the associations with the risk classification were slightly weaker, while the time spent in specific sleep stages no longer influenced the outcome in these models.

3.4 Akaike Information Criterion (AIC)

The differences in AIC, resulting from any of the parameters of interest added to a reference model, are reported for the parameters previously found significant (Table 4). In addition, the p-value of the corresponding LR test is presented. All approaches resulted in significant improvements in the model. The model
containing the pulse wave-derived CRI had the highest likelihood of association.

### 3.5 Area under the ROC curve

The AUC of the ROC curve for the model containing age, gender and BMI was 0.821. When CRI was added into the model, the AUC increased to 0.853 (p = .012). The various investigated sleep parameters or the single pulse wave parameters did not add any further improvement over the reference model. Figure 2 visualizes the improvements in AUC for a selection of parameters from pulse wave-derived and conventional sleep-derived parameters.

### 3.6 Nested analysis for the direct comparison of pulse wave and PSG-derived parameters

In the final evaluation, we fitted a model containing the strongest parameters from both methodologies, the novel risk index CRI from pulse wave and the ODI from conventional PSG. In order to control for a possible relation between the predictors, an interaction term was introduced in the model. However, while the CRI was highly significant (p = .001) in this model, neither the single variable influence of the ODI nor the joint interaction term were significant (p = .708 and p = .776, respectively). Figure 3 illustrates that the CRI further improved the model quality when the ODI was already entered (AIC change 16.5, p < .001), while the ODI

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**TABLE 1 Descriptive data of the study cohort: data presented as median [IQR] or mean ± SD**

|                          | Low risk                           | High risk                          | Between group difference (p-value) |
|--------------------------|------------------------------------|------------------------------------|-----------------------------------|
| **Anthropometrics**      |                                    |                                    |                                   |
| Age (years)*[a]          | 49.6 ± 12.8                        | 62.5 ± 10.0                        | < .001***                         |
| BMI (kg m⁻²)[a]          | 29.0 ± 6.0                         | 31.1 ± 6.3                         | .002†                             |
| Male gender (%)[a]       | 63                                 | 66                                 | .496                              |
| Current smoker (%)[a]    | 30                                 | 36                                 | .196                              |
| Systolic blood pressure (mmHg)[a] | 127.4 ± 13.4            | 139.2 ± 19.9                       | < .001**                          |
| Hypertension (%)[a]      | 39                                 | 76                                 | < .001***                         |
| Diabetes (%)[a]          | 5                                  | 34                                 | < .001***                         |
| **Pulse wave analysis during sleep** |                        |                                    |                                   |
| CRI (%)[a]               | 0.3 ± 0.3                          | 0.7 ± 0.3                          | < .001***                         |
| PPT (ms)[a]              | 177.2 ± 46.5                       | 152.2 ± 27.2                       | < .001***                         |
| RRPO*                   | 37.6 ± 13.2                        | 30.3 ± 11.6                        | .001†                             |
| PWA-I (n per hr)[a]      | 33.3 ± 10.6                        | 29.9 ± 9.9                         | .003‡                             |
| PR-I (n per hr)[a]       | 36.3 ± 21.5                        | 25.3 ± 22.1                        | < .001***                         |
| SpO₂-I (n per hr)[a]     | 29.1 ± 15.9                        | 40.0 ± 20.5                        | < .001***                         |
| PR-I–SpO₂-I (n per hr)[a]| 7.2 ± 21.7                         | −14.7 ± 23.7                       | < .001***                         |
| TSD (min)[a]             | 5.0 ± 9.8                          | 21.8 ± 40.6                        | < .001***                         |
| T < 90 (min)[a]          | 13.7 ± 48.9                        | 46.9 ± 89.6                        | < .001***                         |
| **Sleep test data**      |                                    |                                    |                                   |
| ODI (n per hr)[a]        | 6.2 [1.8–13.2]                     | 13.5 [6.5–28.6]                    | < .001***                         |
| AHI (n per hr)[a]        | 8.9 [3.3–20.3]                     | 18.7 [9.5–36.6]                    | < .001***                         |
| TST (hr)[b]              | 5.7 ± 1.1                          | 5.3 ± 1.5                          | .029*                             |
| Sleep stage N1 (%)[b]    | 14.7 ± 13.5                        | 18.2 ± 16.3                        | .062                              |
| Sleep stage N2 (%)[b]    | 53.6 ± 14.5                        | 53.1 ± 16.6                        | .810                              |
| Sleep stage N3 (%)[b]    | 17.8 ± 11.6                        | 17.0 ± 14.0                        | .644                              |
| REM sleep (%)[b]         | 14.0 ± 7.5                         | 11.7 ± 7.5                         | .013*                             |
| Periodic leg movement index (n per hr)[b] | 21.2 ± 22.3 | 29.4 ± 29.9 | .016* |

Asterisks indicating parameters’ significance (0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘•’ 0.1 ‘’).  
[a]Main-cohort (n = 358, with n = 215 for low-risk group, n = 143 for high-risk group).  
[b]PSG-subcohort (n = 266, with n = 155 for low-risk group, n = 111 for high-risk group).
has no significant additive effect on top of the CRI (AIC change 
−2.0, p = .356).

### 3.7 Sensitivity analysis

We performed sensitivity analyses to address factors that may have influenced the sleep scoring results. A binary variable to define the type of sleep study (PG or PSG) and a categorical variable that separated the contribution of sleep centres were added to the model. The results confirmed that the AHI was slightly underestimated in PG recordings, but this difference did not impact on the outcome. Sleep centres showed a minor difference on average severity of CV risk, but no significant difference on the effect of sleep parameters. The CRI was independent to these influences in all tested models.

### 4 DISCUSSION

The main findings in this cohort of sleep apnea patients are the following. (a) Markers of intermittent hypoxia (ODI) and event frequency (AHI) derived from sleep studies were moderately associated with CV risk, whereas sleep stages and markers of sleep fragmentation were not. (b) Pulse wave-derived parameters reflecting skin sympathetic activity (PWA-I), vascular stiffness (PPT) and cardiac reactivity (PR-I) during sleep were strongly associated with CV risk. (c) All pulse wave-derived parameters showed significant differences between low and high CV risk groups, and contributed significantly to single variable prediction models, confirming their independent relevance for CV risk prediction. Because the inter-correlations between those parameters were limited, combined information from these parameters, defined as the CRI, appeared to be more useful. In fact, the combined CRI parameter showed the strongest association with CV risk assessment and outranged the PSG variables. Our study suggests that advanced pulse wave analysis during sleep may be a useful and additive tool for improved classification of CV risk in OSA patients.

Sleep-disordered breathing is associated with a high prevalence of CV disease. Indeed, several epidemiological studies demonstrate that both conditions share common risk factors, including older age, male gender and elevated BMI (Heinzer et al., 2015; Newman et al., 2001; Peppard et al., 2000; Young et al., 2002). AHI and ODI, as measures of respiratory event frequency, have been used to evaluate the association between respiratory disorders during sleep and CV disease. In line with our findings, a large cross-sectional study based on an analysis of the European Sleep Apnoea Database highlighted the importance of ODI in the context of hypertension prevalence (Tkacova et al., 2014). However, several studies showed only weak associations between the AHI or the ODI and CV outcomes like incident CV disease (Shahar et al., 2001) or CV death (Punjabi et al., 2009). A European expert panel recently stated that further research is warranted to develop novel diagnostic instruments that allow for an adequate classification of CV function and risk in OSA patients (Randerath et al., 2018).

Our data support other reports suggesting a strong association between hypoxic patterns determined by an advanced analysis of signals recorded in patients with OSA (Terrill, 2020). Our current findings show strong effects of ODI, SpO₂-I, TSD, and time spent below 90% saturation on CV risk. Poor sleep quality and short sleep duration have been associated with increased CV risk in population-based studies (Tobaldini et al., 2019). However, the current study does not support an independent association between the proportion of slow-wave sleep, rapid eye movement sleep, or sleep duration and CV risk after adjustment for anthropometric factors in this cohort of OSA patients. This may in part be explained by a potential selection bias in our cohort that contains an overrepresentation of patients with sleep disturbances and cardiometabolic disease.

### Table 2 Inter-correlations for pulse wave and PSG variables (Pearson’s correlation coefficients, significant marked in bold)

| Pulse wave analysis | RRPO | PR-I | SpO₂-I | PWA-I |
|---------------------|------|------|--------|-------|
| PPT                 | 0.30 | 0.24 | 0.02   | 0.17  |
| RRPO                | –    | 0.62 | 0.05   | 0.10  |
| PR-I                | –    | –    | 0.27   | 0.12  |
| SpO₂-I              | –    | –    | –      | –0.15 |

| Sleep test data   | AHI   | TST  | Sleep stage N1 (%) | Sleep stage N2 (%) | Sleep stage N3 (%) | REM sleep (%) | Periodic leg movement index |
|-------------------|-------|------|---------------------|--------------------|--------------------|---------------|-----------------------------|
| ODI               | 0.85  | 0.00 | 0.10                | 0.09               | −0.11              | −0.19         | 0.24                        |
| AHI               | –     | −0.02| 0.12                | 0.05               | −0.10              | −0.18         | 0.31                        |
| TST               | –     | −0.03| 0.06                | 0.19               | 0.25               | −0.11         | 0.21                        |
| Sleep stage N1 (%)| –     | –    | −0.55               | −0.44              | −0.11              | 0.21          |                             |
| Sleep stage N2 (%)| –     | –    | −0.37               | −0.33              | −0.06              | −0.12         |                             |
| Sleep stage N3 (%)| –     | –    | –                   | –                  | –                  | –             | −0.13                       |
| REM sleep (%)     | –     | –    | –                   | –                  | –                  | –             |                             |

AHI, apnea–hypopnea index; ODI, oxygen desaturation index; PPT, pulse propagation time; PR-I, pulse rate acceleration index; PWA-I, pulse wave attenuation index; REM, rapid eye movement; RRPO, respiration-related pulse oscillation; SpO₂-I, hypoxia index; TST, total sleep time.
**Table 3** Logistic regression models for the prediction of high CV risk class—each line shows coefficient and significance level for a single predictor in an unadjusted or adjusted model

|                  | Unadjusted   |            | Adjusted for age, gender, BMI |            |
|------------------|--------------|------------|-------------------------------|------------|
|                  | Coefficient  | p-Value    | Coefficient                  | p-Value    |
| **Pulse wave analysis** |             |            |                              |            |
| CRI (%)<sup>a</sup> | +0.037       | < .001***  | +0.026                       | < .001***  |
| PPT (ms)<sup>a</sup> | -0.018       | < .001***  | -0.012                       | .007**     |
| RRPO              | -0.049       | < .001***  | -0.025                       | .027*      |
| PWA-I (n per hr)<sup>b</sup> | -0.032      | .003**     | -0.035                       | .006**     |
| PR-I (n per hr)<sup>a</sup> | -0.025      | < .001***  | -0.012                       | .071       |
| SpO<sub>2</sub>-I (n per hr)<sup>a</sup> | +0.033       | < .001***  | +0.025                       | .002**     |
| PR-I–SpO<sub>2</sub>-I (n per hr)<sup>b</sup> | -0.044      | < .001***  | -0.028                       | < .001***  |
| TSD (min)        | +0.042       | < .001***  | +0.031                       | .001***    |
| T < 90 (min)     | +0.008       | < .001***  | +0.005                       | .010*      |
| **Sleep test data** |             |            |                              |            |
| ODI (n per hr)<sup>a</sup> | +0.045       | < .001***  | +0.029                       | .001**     |
| AHI (n per hr)<sup>a</sup> | +0.037       | < .001***  | +0.023                       | .002**     |
| TST (hr)<sup>b</sup> | -0.226       | .023*      | -0.029                       | .801       |
| Sleep stage N1 (%)<sup>b</sup> | +0.016      | .057       | +0.010                       | .302       |
| Sleep stage N2 (%)<sup>b</sup> | -0.002      | .805       | +0.006                       | .546       |
| Sleep stage N3 (%)<sup>b</sup> | -0.005      | .632       | -0.013                       | .276       |
| REM sleep (%)<sup>b</sup> | -0.042      | .014*      | -0.029                       | .146       |
| Periodic leg movement index (n per hr)<sup>b</sup> | +0.012      | .014*      | +0.003                       | .574       |

AHI, apnea–hypopnea index; BMI, body mass index; CRI, cardiac risk index; ODI, oxygen desaturation index; PPT, pulse propagation time; PR-I, pulse rate variability; PWA-I, pulse wave attenuation index; REM, rapid eye movement; RRPO, respiratory-related pulse oscillations; SpO<sub>2</sub>-I, hypoxia index; T < 90, time below 90% SpO<sub>2</sub>; TSD, time in symmetric desaturation; TST, total sleep time.

Asterisks indicating parameters’ significance (0 *** 0.001 **** 0.01 *** 0.05 * 0.1 ‘).  
<sup>a</sup>Main-cohort (n = 358).  
<sup>b</sup>PSG-subcohort (n = 266).

Pulse wave parameters assessed during daytime rest, such as pulse wave velocity or vascular stiffness determined by peripheral arterial tonometry, have been extensively used to assess CV risk in prospective studies and in various clinical protocols (Kim & Kim, 2019). For example, application of a photoplethysmographic signal to assess blood pressure was described in several studies, highlighting the link between hypertension and pulse wave aberrations (Elgendi et al., 2019). Vascular stiffness measured by applanation tonometry (Arteriograph) or oscillometric pulse wave velocity (Spygmocor) were validated against gold-standard methodology in prospective, large-scale epidemiological studies (Townsend et al., 2015). However, these assessments reflect short time windows in awake patients. We argued that photoplethysmography during the sleep period may enable a unique, undisturbed and extended period to assess vascular reactivity. During nighttime, overall sympathetic activity is decreased and, compared with awake state during daytime, the influence of non-standardized stressors is likely to be reduced by sleep. Fluctuations of the pulse wave amplitude and heart rate can be observed, suggesting an opportunity to capture autonomic nervous and CV function not seen during daytime. Indeed, the individual pulse wave parameters have been extensively validated in our previous studies, showing their potential to reflect independent properties of the vascular system (Grote & Zou, 2017). The analysis of nocturnal PWA may also be applied to predict daytime blood pressure and hypertension (Zou et al., 2009), or the analysis of PPT changes during sleep has been shown to reflect functional vascular properties (Svedmyr et al., 2016). The methodology also enables assessment of CV function during various stages of sleep, as well as identifying vascular stiffness during rapid eye movement sleep in patients with chronic obstructive pulmonary disease (Grote et al., 2017). Other applications include effects on nasal positive airway pressure therapy in OSA patients (Randerath et al., 2016). Finally, the HypnoLaus study, a population-based cohort study including ambulatory PSG assessment of a representative Swiss adult population (Hirotsu et al., 2020), recently demonstrated that pulse wave attenuation frequency, duration and slope were independent predictors of prevalent hypertension in this population whereas conventional PSG variables were not. In addition, pulse rate accelerations related to apneic events predicted all cause and cardiovascular mortality in two large population-based cohorts (Azarbarzin et al., 2021). Despite the different methodologies used, results from these
TABLE 4 Difference in the AIC, together with LR-test for added parameters to a reference model containing age, gender, BMI (main-cohort n = 358)

| Parameter          | AIC-difference | p-Value (LR-test) |
|--------------------|----------------|-------------------|
| CRI                | 29.26          | < .001***         |
| PPT                | 5.73           | .005**            |
| RRPO               | 2.95           | .026              |
| PWA-I              | 5.77           | .005**            |
| PR-I               | 1.33           | .068              |
| SpO2-I             | 8.21           | .001**            |
| PR-I–SpO2-I        | 16.68          | < .001***         |
| TSD                | 14.30          | < .001***         |
| T < 90             | 5.47           | .006**            |
| ODI                | 10.80          | < .001***         |
| AHI                | 7.80           | .002**            |

AHI, apnea–hypopnea index; AIC, Akaike Information Criterion; CRI, cardiac risk index; LR, likelihood ratio; ODI, oxygen desaturation index; PPT, pulse propagation time; PR-I, pulse rate variability; PWA-I, pulse wave attenuation index; RRPO, respiratory-related pulse oscillations; SpO2-I, hypoxia index; T < 90, time below 90% SpO2; TSD, time in symmetric desaturation.

Asterisks indicating parameters' significance (0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘•’ 0.1 ‘’).

Prospective population-based studies strongly support our approach and suggest that incorporating multiple different features of a vascular signal may be a useful tool for CV risk classification.

FIGURE 2 Comparison of area under receiver operating characteristic (ROC) curves, together with a test for difference to the reference model containing age, gender and body mass index (BMI). ROC curves of different logistic regression models, containing a single tested parameter together with age, gender and BMI. The reference model contains only age, gender and BMI. Reported p-values refer to DeLong's non-parametric test for differences in area under the curve, compared with the reference model. Abbreviations: AHI, apnea–hypopnea index; AUC, area under the curve; CRI, cardiac risk index; ODI, oxygen desaturation index; PPT, pulse propagation time; PWA, pulse wave attenuation index.

FIGURE 3 Nested model comparisons, adding the strongest parameters from pulse wave analysis and conventional polysomnographic (PSG) sleep screening. Schematic visualization of nested logistic regression models. Successively adding parameters reveals their additional predictive value; asterisks indicating coefficient's significance in logistic regression model (0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘•’ 0.1 ‘’). Abbreviations: AIC, Akaike Information Criterion; LR: p, p-value derived from likelihood ratio test.
4.1 | Strengths and limitations

Previous studies addressing pulse wave analysis during sleep and CV risk assessment did not specifically focus on the detailed analysis of sleep test-derived parameters in overnight studies. This study is to our knowledge the first clinical cohort exploring the difference between PSG and pulse wave-derived parameters in relation to overall CV risk in an OSA patient population. We can, on the one hand, confirm previous results highlighting the connection between sleep apnea and cardiometabolic risk (McNicholas & Bonsigore, 2007) and, on the other hand, show the additional information embedded in the pulse wave signal currently not used as part of a standardized sleep lab procedure.

The multi-centric study design increases the generalizability of our findings, but comes also with limitations. Conventional sleep-derived metrics, such as the AHI, are characterized by inter-scorer variability. Even though our sensitivity analysis did not show significant differences between the effect of AHI on CV risk estimation in different centre subcohorts, variability in scoring may in part explain the AHI’s weaker model performance. Conversely, the pulse wave-related CRI is computed automatically and showed a robustness, which makes this parameter useful for application in multicentric settings.

Furthermore, the study used a standardized assessment of recognized CV risk factors according to the well-established ESC/ESH risk matrix (Mancia et al., 2007). In line with the recent update of the ESC/ESH recommendations for CV risk classifications (Piepoli et al., 2016), the pulse wave-derived CRI showed a strong association with other risk classifier systems like the Framingham Score or the SCORE system (Sommermeyer et al., 2014). Using risk scores to evaluate the predictive value of the CRI in cross-sectional study design, rather than using prospective outcome data, is a major limitation of this study. Adjusting our models for the influence of age, gender and BMI may over-adjust the model as the ESC/ESH risk score is already highly dependent on these factors. Obviously, age, gender and BMI are not sufficient to address general CV risk but, in this application, these parameters serve as a good reference for the prediction of the high ESC/ESH risk group (with a sensitivity/specificity AUC of 0.82). Additional sensitivity analysis including smoking and blood pressure as strong risk predictors did confirm our previous results without adding additional insights.

Modern statistical analysis methodology was applied in accordance with recommended contemporary standards of the American Heart Association (Hlatky et al., 2009). The analysis protocol aimed to highlight the importance of specific parameters derived during standard sleep test procedures in sleep medicine. Therefore, statistical methods have been chosen to only predict severe cases, while controlling for the most important risk factors. Indeed, we introduced a potential selection bias in this OSA cohort towards an overrepresentation of increased CV risk relative to a population-based cohort. The high-risk class constituted 40% of patients in the cohort. In addition, it is possible that the impact of OSA on CV risk differs according to the presence or absence of previous CV disease (Zapater et al., 2020). Indeed, we showed previously that the pulse wave-derived CRI was significantly higher in OSA patients with a previous CV event (Sommermeyer et al., 2014). However, our study was underpowered to model a prediction for the entire CV risk spectrum, but we identified a clear trend of stepwise increasing AHI/ODI and pulse wave parameters from low to intermediate to high CV risk classes (data not shown). Further studies using advanced pulse wave analysis in population-based studies will be needed to clarify this issue.

4.2 | Clinical relevance

There is an evident potential for application of an advanced pulse wave analysis in clinical sleep recordings. According to current standards, oximetry devices by default only record oxygen saturation or pulse rate, but we advocate plethysmographic pulse wave signals to be included in sleep recordings to take full advantage of the potential of such signals. There is a strong interest in simplified and cost-efficient methods for home sleep testing, especially in the analysis of parameters derived from finger pulse wave signal (Zou et al., 2006). For the task of CV risk assessment, our results suggest that PSG-specific parameters may be redundant if the pulse wave signal is analysed for the purpose of CV risk assessment.

5 | CONCLUSIONS

A pulse wave-derived CRI from sleep recordings was validated in patients with suspected OSA. Novel parameters derived from nocturnal pulse wave analysis provided a better approach for CV risk assessment compared with conventional parameters from standard sleep studies. In addition, pulse wave signals contained information on top of that provided by the most prominent CV risk factors like age, BMI and gender. An oximeter-based photoplethysmographic signal is available in almost all instruments for diagnosis of sleep-disordered breathing. The use of an advanced pulse wave analysis for estimation of CV risk may add important information to the routine sleep diagnostic procedure. Prospective evaluations of these novel biomarkers are warranted.

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CONFLICT OF INTEREST
CS, DZ and DS have reported no conflicts of interest. TP received grants from Cidelec, Löwenstein Medical, Novartis. He received consulting fees and speaker fees from Bayer Healthcare, Cerebra, Jazz Pharmaceutical, Löwenstein Medical, Neuwirth Medical, National Sleep Foundation and owns shares of Advanced Sleep Research, Nukute, The Siestagroup. IF has received research grants from Löwenstein, Philips and ResMed, and consultancy fees from Inspire and ResMed. JH reports outside the submitted work grants from Philips Respironics, ResMed, Desitin, Bayer and Itamar. He also reports speaker fees and/or advisory services from Somnomed, Bayer, and Desitin. He has two licenced patents related to sleep apnea therapy. JF reports institutional fees from Weinmann during the conduct of the study and personal fees from Weinmann, ResMed and Inspire Medical outside the submitted work. WR reports personal fees and travel grants from Weinmann, Heinen & Löwenstein, Resmed, Philips Respirisons, Inspire and Bioprojet. BS reports grants from Weinmann during the conduct of the study. LG reports support from Weinmann GMBH for the sampling of study data and the development of pulse wave analysis. Outside the submitted work he reports grants from Bayer, Philips, Resmed, Desitin, and Itamar Medical. He also reports speaker fees from Resmed, Philips, Astra Zeneca, and Itamar outside the submitted work. LG has a patent on sleep apnea therapy licensed.

AUTHOR CONTRIBUTIONS
Project design: CS, LG, JH, DZ. Data collection: DZ, TP, IF, JH, JF, WR, BS, DS, LG. Data analysis: CS, Data interpretation: CS, LG, JH, DZ, DS. Manuscript writing: CS, DZ, TP, IF, JH, JF, WR, BS, DS, LG.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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