Utility of Overnight Pulse Oximetry and Heart Rate Variability Analysis to Screen for Sleep-Disordered Breathing in Chronic Heart Failure

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ABSTRACT

Background: Sleep-disordered breathing (SDB) is under-diagnosed in chronic heart failure (CHF). Screening with simple monitors may increase detection of SDB in a cardiology setting. This study aimed to evaluate the accuracy of heart rate variability analysis and overnight pulse oximetry for diagnosis of SDB in CHF patients.

Methods: 180 CHF patients underwent simultaneous polysomnography, ambulatory electrocardiography and wrist-worn overnight pulse oximetry. SDB was defined as an apnoea-hypopnoea index ≥15/hour. To identify SDB from the screening tests, the percent very low frequency increment (%VLFI) component of heart rate variability was measured with a pre-specified cutoff ≥2.23%, and the 3% oxygen desaturation index was measured with a pre-specified cutoff >7.5 desaturations/hour.

Results: 173 CHF patients had adequate sleep study data; SDB occurred in 77(45%) patients. Heart rate variability was measurable in 78 (45%) patients with area under the %VLFI receiver operating characteristic curve of 0.50. At the ≥2.23% cutoff, %VLFI sensitivity was 58% and specificity 48%. The 3% oxygen desaturation index was measurable in 171 (99%) patients with area under the curve of 0.92. At the pre-specified cutoff of >7.5 desaturations/hour, the 3% oxygen desaturation index had sensitivity 97%, specificity 32%, negative likelihood ratio 0.08 and positive likelihood ratio 1.42. Diagnostic accuracy was increased using a cutoff of 12.5 desaturations/hour, with sensitivity 93% and specificity 73%.

Conclusions: The high sensitivity and low negative likelihood ratio of the 3% oxygen desaturation index indicates that pulse oximetry would be of use as a simple screening test to rule out SDB in CHF patients in a cardiology setting. The %VLFI component of heart rate variability is not suitable for detection of SDB in CHF.

INTRODUCTION

Sleep-disordered breathing (SDB) occurs in ≥50% chronic heart failure (CHF) patients [1 2] and despite an independent association with increased mortality [3 4], it is under-diagnosed [5]. Identification of CHF patients with SDB is complicated by the absence of classic symptoms such as excessive daytime sleepiness [6]. Additionally, polysomnography is recommended for the diagnosis of SDB in CHF [7] but these patients are often seen in cardiology clinics and access to this investigation may be limited. There is a need for simpler methods to enable the screening of CHF patients for SDB.

Portable monitors such as overnight pulse oximetry have been used to diagnose obstructive sleep apnoea (OSA) in otherwise healthy adults but their utility in patients with comorbid medical conditions is unclear [8]. A recent international workshop report has highlighted the need for further research to evaluate the role of portable monitors in patients with SDB and CHF [9].

We have previously shown in a small study that analysis of heart rate variability (HRV) can be used to rule out SDB in patients with CHF [10]. HRV analysis can be performed during cardiological assessment and is potentially a convenient method to screen for SDB in CHF. The primary aim of this study was to prospectively evaluate the diagnostic performance of HRV analysis to detect SDB in a large number of CHF patients in a general cardiology setting. HRV analysis may not be possible in patients with cardiac arrhythmias or paced cardiac rhythm and our secondary aim was to evaluate pulse oximetry as a screening strategy for CHF patients unsuitable for HRV analysis. The following hypotheses were tested: 1) HRV analysis can be used to rule out SDB in patients with CHF; 2) Overnight pulse oximetry can be used to rule out SDB in CHF patients with atrial fibrillation, paced cardiac rhythm, frequent ectopic beats or artefact on ambulatory ECG monitoring; 3) HRV analysis has a higher accuracy than overnight pulse oximetry for the diagnosis of SDB in CHF.

Some of the results of this study have previously been presented in abstract form [11 12].

METHODS

Patients with low or preserved ejection fraction heart failure were recruited from cardiology outpatient clinics. Inclusion criteria required a diagnosis of CHF in accordance with European guidelines [13], no hospitalisation or change in medication for ≥4 weeks, and age 18 – 90 years. Patients receiving treatment for SDB were excluded. Eligible patients were invited to participate irrespective of clinical suspicion of SDB.

All patients underwent unattended polysomnography (SOMNOscreen, SOMNOmedics, Germany) with additional simultaneous recording with ambulatory electrocardiography (VistaPlus, Novacor, France) and wrist worn pulse oximetry (Pulsox 3i, Konica Minolta, Japan) on the same night. Patients were studied in their own home or in hospital according to their preference. Anthropometric measurements and clinical interview were completed before the sleep study with a behavioural maintenance of wakefulness test (OSLER) performed the next morning [14]. Full details of measurements are provided in the online supplement.

Polysomnography studies were analysed by one person unaware of the clinical status of the patient, using standard scoring criteria [15]. Apnoea was scored when nasal airflow reduced to <10% of baseline for ≥10 seconds. Hypopnoea was scored when nasal airflow reduced by ≥50% of baseline with a ≥3% oxygen desaturation and/or electroencephalographic arousal (see also online supplement). SDB was defined as an apnoea-hypopnoea index (AHI) ≥15/hour and was categorised as central sleep apnoea (CSA) or OSA.

The ambulatory electrocardiogram was recorded with a sampling frequency of 200Hz. HRV was analysed (Holtersoft, Novacor) during the period from midnight to 0600. Patients with paced cardiac rhythm, atrial fibrillation or >10% ectopic beats were excluded from HRV analysis. Manual editing was performed to ensure all QRS complexes were correctly identified. The spectral density of the heart rate increment was analysed for measurement of the percent very low frequency increment (%VLFI) [16].

This component represents the very low frequency power (0.01 – 0.05Hz) of the heart rate increment power expressed as the percentage of total power (0.01 – 0.5Hz). An a priori %VLFI cutoff of ≥2.23% was used to diagnose SDB [10]. Recommended time domain and spectral components of HRV were also measured [17].

The wrist worn pulse oximeter recorded oxygen saturation with a sampling time of 5 seconds and data storage frequency of 0.2Hz. Overnight pulse oximetry was analysed (Download 2001, Stowood Scientific Instruments, U.K.) for ≥3% oxygen desaturations during the 'time in bed' period recorded by the patient. The 3% oxygen desaturation index (3% ODI) was calculated as the mean number of ≥3% oxygen desaturations per hour, using the 'time in bed' as denominator. A pre-specified 3% ODI cutoff of >7.5 desaturations/hour was used to diagnose SDB.

Statistical Analyses

An a priori sample size of 180 CHF patients was calculated to be adequately powered (1 - β = 80%) to detect a one sided difference of >10% between the sensitivity/specificity of HRV and polysomnography, at a significance level (α) of 0.05 (see online supplement). Results are presented as median and interquartile range (IQR). Continuous variables were compared with Mann-Whitney or Kruskal-Wallis tests. Categorical variables were compared using Fisher's exact test or chi-square test. The diagnostic accuracy of the %VLFI and 3% ODI were compared by measurement of the area under the receiver-operating characteristic (ROC) curve. Sensitivity, specificity, predictive values and likelihood ratios for the %VLFI and 3% ODI were determined at the a priori cutoffs. Statistical analyses were performed using SPSS V16.0 (IBM, Chicago, USA).

RESULTS

354 CHF patients were identified who fulfilled the recruitment criteria, 180 of whom consented to participate (Figure 1). 173 patients with adequate polysomnography data were included in the analysis,

with median age 69.8 (58.8 to 76.8) years, 86% male (Table 1). Most patients had mild to moderate symptomatic CHF with New York Heart Association class I or II symptoms in 77% and median left ventricle ejection fraction 40% (28 to 59%). 132 (73%) CHF patients had overnight monitoring performed in their home.

Diagnosis of SDB from Polysomnography

The median AHI was 13.5 (7.2 to 24.8) events/hour. SDB was diagnosed in 77 (45%) CHF patients with OSA in 53 (31%) patients and CSA in 24 (14%). As there was only a small number of CHF patients with CSA, all CHF patients with SDB were analysed as a single group. Body mass index, neck circumference and hip:waist ratio were significantly higher in CHF patients with SDB (Table 2). There were no significant differences in New York Heart Association class, brain natriuretic peptide (BNP) or left ventricle ejection fraction between CHF patients with and without SDB. Subjective and objective measures of sleepiness were similar irrespective of the presence or absence of SDB, but CHF patients with SDB had significantly more stage 1 sleep and higher arousal index (Table 3).

Diagnostic Accuracy of HRV

HRV was measurable in 78 (45%) CHF patients; the most common reasons for unsuitability for HRV measurement were paced cardiac rhythm or atrial fibrillation in 74 (43%) patients. Patients in whom HRV was measurable were significantly younger ($p = 0.006$) with a lower median BNP ($p < 0.001$) and a trend to higher left ventricle ejection fraction ($p = 0.08$) compared to those in whom HRV could not be measured (Table E1 in online supplement).

In the 78 (45%) CHF patients in whom HRV was measurable, SDB occurred in 36 (46%). The %VLFI component of HRV had a poor diagnostic accuracy for detection of SDB with an area under the %VLFI ROC curve of 0.50 (95% confidence interval 0.37 – 0.63, $p = 0.99$) (Figure 2). At the a priori cutoff of $\geq$2.23%, the %VLFI had sensitivity 58%, specificity 48%, positive likelihood ratio 1.11 and negative likelihood ratio 0.88 for diagnosis of SDB (Table E2).

The %VLFI was not correlated with the AHI (Spearman's rho 0.005) and there was no significant difference in %VLFI according to the presence or absence of SDB (median %VLFI: CHF patients without SDB, 2.46% (1.45 to 4.41); CHF patients with SDB, 2.32% (1.19 to 5.08), p = 0.99). SDB was categorized as OSA in 31 (40%) patients with median %VLFI 2.35% (1.35 to 5.41); in 5 (6%) patients with CSA, median %VLFI was 0.78% (0.58 to 4.18). There was no significant difference between %VLFI in CHF patients with OSA, CSA or without SDB (p = 0.39).

The diagnostic accuracy of %VLFI was assessed using alternative AHI thresholds of ≥5, ≥20 and ≥30 events/hour for diagnosis of SDB. The area under the %VLFI ROC curve was similar at all AHI thresholds with no significant change in sensitivity or specificity (Table E2).

Diagnostic Accuracy of Overnight Pulse Oximetry

Overnight pulse oximetry could be analysed in 171 (99%) CHF patients in whom SDB was present in 76 (44%). There was good agreement between 3% ODI and AHI (mean difference = -0.2 events/hour; Figure E1) with correlation coefficient (Spearman's rho) of 0.84 (Figure E2). The 3% ODI had an area under the ROC curve of 0.92 (95% C.I. 0.88 - 0.96) for detection of SDB in CHF, indicating high diagnostic accuracy (Figure 3a). At the a priori cutoff of >7.5 desaturations/hour for diagnosis of SDB in CHF, two false negative results occurred with sensitivity 97% and negative likelihood ratio 0.08 (Table 4). However, at this cutoff there were 65 false positive results with specificity 32% and positive likelihood ratio 1.42. In a post hoc analysis, a 3% ODI cutoff of >12.5 desaturations/hour reduced the number of false negative oximetry studies to 26, specificity increased to 73% (95% C.I. 64 – 81%), sensitivity 93% (95% C.I. 86 – 97%) and negative likelihood ratio 0.09 (95% C.I. 0.04 – 0.21).

To investigate the utility of overnight pulse oximetry for diagnosis of SDB in CHF patients unsuitable for HRV analysis, the diagnostic accuracy of the 3% ODI was assessed in 94 patients in whom %VLFI was not measurable. In this subgroup, the 3% ODI had area under the ROC curve (AUC) of 0.92 (95% C.I. 0.86 - 0.98; Figure 3b). At the cutoff of >7.5 desaturations/hour, the 3% ODI had sensitivity 98%,

specificity 24%, positive likelihood ratio 1.28 and negative likelihood ratio 0.10 for diagnosis of SDB in CHF patients unsuitable for HRV analysis (Table 4).

Diagnostic Accuracy of HRV Analysis versus Overnight Pulse Oximetry

To compare HRV analysis and overnight pulse oximetry for detection of SDB in CHF, the diagnostic accuracy of the 3% ODI was assessed in 77 patients in whom %VLFI was measurable (Table 4). In this subgroup, the 3% ODI had AUC of 0.91 (95% C.I. 0.85 - 0.98; Figure 3c) which was significantly greater than the AUC for the %VLFI ($p < 0.0001$).

DISCUSSION

The main findings of this study were that the %VLFI component of HRV was unable to discriminate between the presence or absence of SDB in patients with CHF. Moreover, it could be measured in less than half of the CHF patients. In contrast, the 3% ODI was measurable in 99% of CHF patients, with an AUC of 0.92 indicating high accuracy for diagnosis of SDB. The 3% ODI had a superior diagnostic accuracy to the %VLFI for detection of SDB in CHF.

Portable monitors provide a cost effective approach to improve access to OSA testing [18]. The simplest portable monitors record one or two physiological parameters with high accuracy for diagnosis of OSA in otherwise healthy adults [19 20]. The utility of these monitors to diagnose SDB in patients with comorbid cardiovascular disease has been identified as a research priority [9]. The findings of the present study help address this evidence gap.

HRV analysis has been proposed as a simple screening test for detection of OSA [21 22]. The occurrence of SDB in CHF increases HRV [23], with increased very low frequency (<0.04Hz) oscillations in heart rate occurring during CSA [23 24] or OSA [23 25]. In individuals without CHF, the %VLFI has sensitivity 78 - 91% and specificity 34 - 70% for diagnosis of OSA [26 27]. In our previous

study of 33 CHF patients in whom HRV was measurable, the %VLFI had a sensitivity of 85% and specificity of 65% for diagnosis of SDB at an optimum cutoff of ≥2.23% [10]. The current study was designed to be adequately powered to prospectively evaluate this cutoff and has shown that the %VLFI can not be used to identify SDB in CHF. It is likely that the larger sample size and greater statistical power of the current study has provided a more accurate measure of the diagnostic utility of %VLFI in patients with CHF, highlighting the need for adequately powered trials in this area [9]. Moreover, our findings concur with those of Damy et al., who have also reported that %VLFI has a poor accuracy for SDB diagnosis in 54 CHF patients [28].

Potential reasons for the absence of a correlation between the %VLFI and AHI in patients with CHF include a reduction in HRV due to impaired autonomic cardiac reactivity [29]. Cardiac autonomic regulation and spectral components of HRV are significantly reduced by ageing [30] and the median age of patients in this study was higher than previous studies. Comorbidities such as diabetes, present in 26% of patients in this study, may have impaired autonomic function and reduced HRV. Cardiovascular medications are also likely to have influenced HRV in this study as beta blockers and ACE inhibitors can both increase the high frequency component of HRV through modulation of vagal cardiac input [31 32].

Concomitant sleep disorders could potentially have influenced any relationship between the %VLFI and AHI. Periodic limb movements (PLM) occur frequently in CHF patients [1] and are associated with a significant increase in the %VLFI [26 33]. In the current study, a periodic limb movement index (PLMI) ≥5/hour was observed in 111 (64%) CHF patients. However there was no correlation between %VLFI and PLMI (Spearmans rho 0.01) and median %VLFI was not significantly different in patients with PLMI ≥5/hour compared to those with PLM <5/hour. Insomnia and sleep fragmentation unrelated to SDB are also prevalent in CHF and can increase the %VLFI [26]. In the current study, there was no correlation between the %VLFI and arousal index (Spearmans rho 0.034). Therefore, we do not think these factors

contributed to the present findings.

Overnight pulse oximetry was simultaneously investigated as a simple screening test for the detection of SDB in CHF. Measurement of ≥2% or ≥4% oxygen desaturations has been reported to have high sensitivity to detect SDB in patients with low ejection fraction CHF [34 35]. In the current study, the AUC for the 3% ODI indicated a high diagnostic accuracy for detection of SDB in patients with low and preserved ejection fraction heart failure. At the a priori cutoff of >7.5 desaturations/hour, the 3% ODI had high sensitivity with a clinically useful negative likelihood ratio of 0.08, and would therefore be of greatest clinical use to rule out SDB in CHF.

If overnight pulse oximetry was used as the initial investigation in a phased testing approach to detect SDB in CHF, further sleep studies would not have been required in 32 (33%) CHF patients without SDB. However, at the cutoff of >7.5 desaturations/hour, 3% ODI had poor specificity and low positive likelihood ratio. The diagnostic specificity of 3% ODI was increased at a cutoff of >12.5 desaturations/hour without reduction in sensitivity. Using the 3% ODI cutoff of >12.5 desaturations/hour would have correctly identified and saved further sleep studies in 69 (73%) CHF patients without SDB.

A limitation of the present study is that paced cardiac rhythm or atrial fibrillation prevented HRV analysis in 43% of CHF patients. Whilst HRV may still be measurable in patients with cardiac resynchronisation therapy (CRT) who are not atrial paced, and Cheyne-Stokes respiration can increase very low frequency HRV in patients with atrial fibrillation [36], the results of the current study suggest that this would be of no value to screen for SDB in CHF. A second consideration is that we did not meet our desired sample size as HRV could not be analysed in all 180 CHF patients recruited. However, further studies of the utility of %VLFI for diagnosis of SDB in CHF may not be an efficient use of resources; our results indicate a sample size of 780 CHF patients suitable for HRV analysis would be required to be adequately powered to exclude a >0.5% difference in %VLFI between CHF patients with and without SDB. A third consideration is that the small number of CHF patients with CSA precluded

comparison of the diagnostic accuracy of overnight pulse oximetry between patients with CSA and OSA. However, overnight oximetry has previously been reported to have 100% sensitivity for CSA in CHF [34] and in the current study, there were no false negative oximetry results in patients with CSA.

A strength of this study is the recruitment of a heterogeneous population of CHF patients from cardiology clinics, 34% of whom had an ejection fraction ≥50%. Many previous studies have only enrolled patients with low ejection fraction heart failure but up to 50% of CHF patients have heart failure with preserved ejection fraction [37], and SDB may contribute to cardiac dysfunction in these patients [38]. In addition, despite inclusion of CHF patients with comorbidities including COPD and asthma which may influence overnight oxygen saturation, the diagnostic accuracy of the 3% ODI was high with AUC of 0.92. However, this may have contributed to the low specificity of pulse oximetry at the cutoff of >7.5 desaturations/hour.

In summary, in CHF patients recruited from a cardiology setting, the 3% ODI cutoff of >7.5 desaturations/hour had a high sensitivity of 97% and low negative likelihood ratio of 0.08 for diagnosis of SDB in CHF patients. Specificity of the 3% ODI was increased to 73% without reduction in sensitivity at an optimum 3% ODI cutoff of 12.5 desaturations/hour. In contrast, the %VLFI had a poor diagnostic accuracy and it can not be recommended to screen for SDB in patients with CHF. Overnight pulse oximetry would be of greatest clinical use to rule out SDB in patients with CHF, helping to reduce pressure on sleep laboratory facilities and prioritise those patients who may require more detailed sleep studies.

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FIGURE LEGENDS

Figure 1. Flow diagram to show recruitment of CHF patients and inclusion in heart rate variability analysis

Figure 2. %VLFI ROC curve for diagnosis of SDB (AHI $\geq$15/hour) in patients with chronic heart failure. AUC = area under curve

Figure 3. ROC curves showing diagnostic accuracy of 3% ODI for diagnosis of SDB in all CHF patients (n = 171; Figure 3a), in CHF patients in whom %VLFI could not be measured (n=94; Figure 3b) and CHF patients in whom %VLFI was measured (n=77; Figure 3c). AUC = area under curve.

TABLE 1. CLINICAL CHARACTERISTICS OF CHRONIC HEART FAILURE PATIENTS (n = 173)

Clinical Characteristic	Value
Age (years)	69.8 (58.8 – 76.8)
Male (n,%)	148 (85.5)
BMI (kg/m^2)	29.1 (25.4 – 32.7)
Neck size (cm)	40.0 (38.0 – 43.0)
Waist/Hip ratio	1.02 (0.98 – 1.06)
Diabetes (n,%)	44 (25)
COPD/Asthma (n,%)	34 (20)
Ischemic cardiomyopathy (n,%)	89 (51)
Beta blocker therapy (n,%)	126 (73)
ACEI/ARB therapy (n,%)	157 (91)
Atrial fibrillation (n,%)	52 (30)
Cardiac pacing (n,%)	50 (29)
NYHA classification (I/II/III/IV)	24/110/37/2
BNP (pg/ml)	118 (55 – 239)
Left Ventricular ejection fraction (%)	40 (28 – 58)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker; NYHA = New York heart Association; BNP = B-type natriuretic peptide.

Data are presented as median (interquartile range), or number (%) of patients.

TABLE 2. COMPARISON OF CLINICAL CHARACTERISTICS IN CHRONIC HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP-DISORDERED BREATHING

	No SDB (n = 96)	SDB (n = 77)	P Value
Age (years)	71.9 (59.4 – 77.6)	66.7 (57.1 – 75.0)	0.08
Male (n, %)	81 (84)	67 (87)	0.67
BMI (kg/m^2)	27.4 (24.8 – 31.6)	30.8 (27.8 – 35.4)	<0.001
Neck size (cm)	39.0 (37.0 – 41.0)	42.0 (39.5 – 43.0)	<0.001
Waist/Hip ratio	1.01(0.96 – 1.05)	1.03(0.99 – 1.07)	0.04
Diabetes (n, %)	22 (23)	22 (29)	0.48
COPD/Asthma (n, %)	27 (28)	7 (9)	0.002
Ischemic cardiomyopathy (n, %)	54 (56)	35 (46)	0.17
Beta blocker therapy (n, %)	62 (65)	64 (83)	0.009
ACEI/ARB therapy (n, %)	87 (91)	70 (91)	1.0
Atrial fibrillation (n, %)	26 (27)	26 (34)	0.41
Cardiac pacing (n, %)	25 (26)	26 (34)	0.32
NYHA classification (I/II/III/IV)	12/64/20/0	12/46/17/2	0.37
BNP (pg/ml)	128 (69 – 201)	107 (42 – 322)	0.97
Left Ventricle Ejection Fraction (%)	40 (28 – 58)	43 (32 – 58)	0.76

SDB = sleep-disordered breathing. See Table 1 for definition of additional abbreviations.

Data are presented as median (interquartile range), or number (%) of patients

TABLE 3. COMPARISON OF SLEEPINESS AND MEASUREMENTS OF SLEEP IN CHRONIC HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP-DISORDERED BREATHING

	No SDB (n = 96)	SDB (n = 77)	P Value
Epworth Score	7 (4 – 10)	7 (5 – 10)	0.45
OSLER duration (minutes)	40 (39 – 40)	40 (27 – 40)	0.18
HADS Score	12 (6 – 17)	11 (6 – 16)	0.78
Total Sleep Time (minutes)	355 (285 – 401)	351 (295 – 408)	0.55
Stage 1 sleep (% TST)	25 (14 – 42)	32 (21 - 48)	0.02
Stage 2 sleep (% TST)	39 (27 - 52)	38 (21 – 46)	0.15
Deep sleep (% TST)	11 (6 – 18)	10 (6 – 17)	0.73
REM sleep (% TST)	19 (15 – 25)	17 (13 – 24)	0.41
Sleep efficiency (%)	69 (61 – 80)	74 (63 – 81)	0.26
Arousal Index (events/hour)	16 (13 – 22)	24 (19 – 36)	<0.001
AHI (events/hour)	7.6 (4.1 – 11.0)	27.0 (19.2 – 40.6)	
Time SpO2 <90% (% TST)	1.1 (0.1 – 19.8)	8.3 (1.8 – 22.7)	<0.001
Baseline SpO2 (%)	93 (91 – 95)	94 (92 – 95)	0.62
3% ODI*(events/hour)	9.1 (6.2 – 13.0)	24.4 (17.9 – 37.7)	<0.001
Periodic Limb Movement Index (events/hour)	14 (2 – 33)	11 (3 – 42)	0.78

Definition of abbreviations: OSLER = Oxford sleep resistance test; HADS = Hospital Anxiety and Depression score; TST = Total sleep time; REM = Rapid eye movement; AHI = Apnoea-hypopnoea index; SpO2 = Oxygen saturation; ODI = Oxygen desaturation index

Data are presented as median (interquartile range).

*3% ODI measured from wrist worn pulse oximeter.

TABLE 4. DIAGNOSTIC ACCURACY OF 3% OXYGEN DESATURATION INDEX FOR DETECTION OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Area under ROC curve
All CHF patients* (n = 171)	97 (91 – 100)	32 (22 – 41)	53 (45 – 62)	94 (79 – 99)	1.42 (1.24 – 1.64)	0.08 (0.02 – 0.34)	0.92 (0.88 – 0.96)
CHF patients without %VLFI measurement* (n = 94)	98 (87 – 100)	24 (13 – 35)	49 (38 – 60)	93 (66 – 100)	1.28 (1.10 – 1.50)	0.10 (0.01 – 0.76)	0.92 (0.86 – 0.98)
CHF patients with %VLFI measurement* (n = 77)	97 (85 – 100)	41 (26 – 57)	59 (47 – 72)	94 (73 – 100)	1.66 (1.28 – 2.16)	0.07 (0.01 – 0.48)	0.91 (0.85 – 0.98)

Definition of abbreviations: ROC receiver operating characteristic; CHF chronic heart failure; %VLFI % very low frequency increment of heart rate variability

*Diagnostic accuracy values were assessed using the a priori cutoff of >7.5 desaturations/hour for diagnosis of sleep-disordered breathing, and are presented with 95% confidence interval

FIGURE 1.

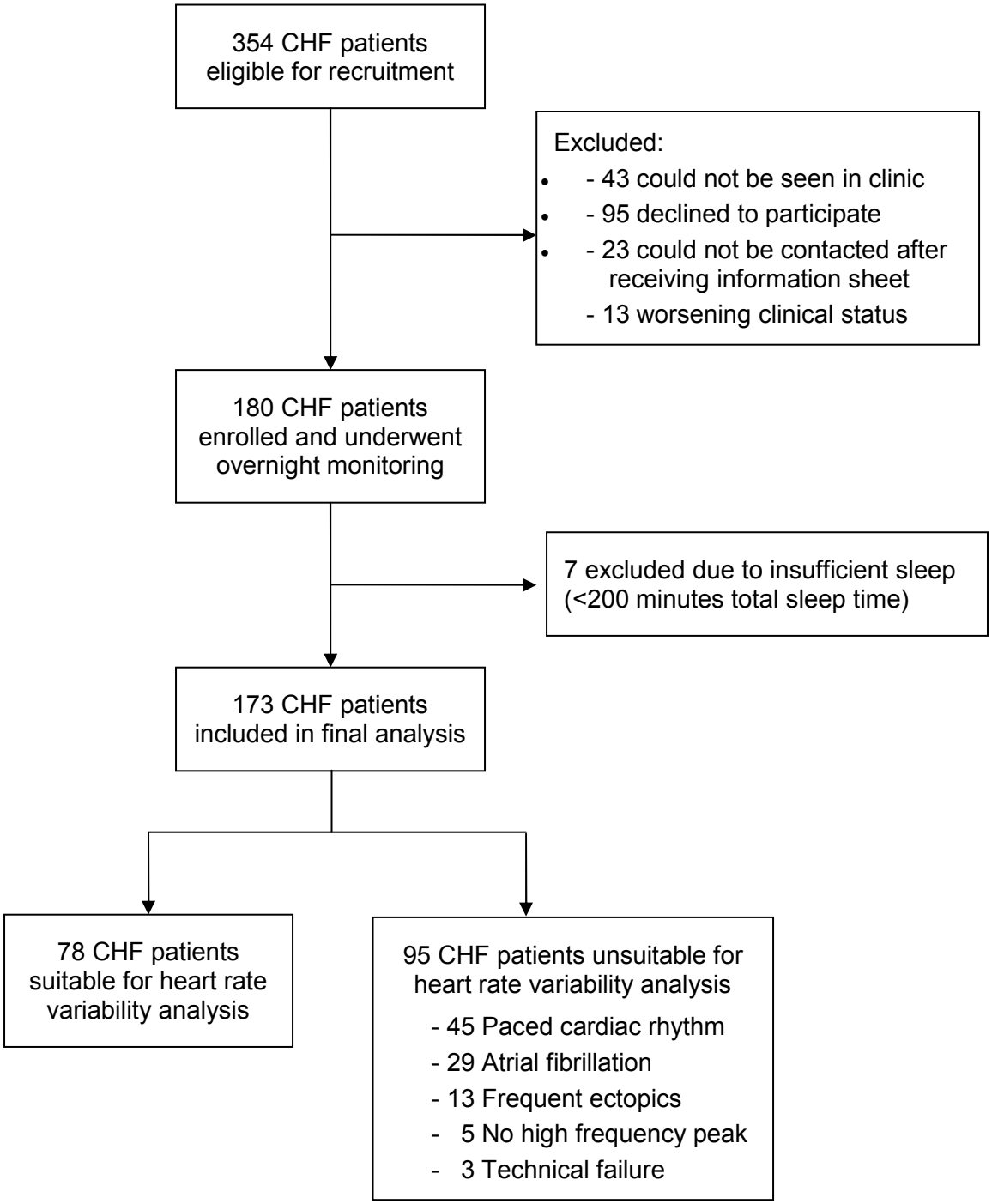
354 CHF patients eligible for recruitment
Excluded:
- 43 could not be seen in clinic
- 95 declined to participate
- 23 could not be contacted after receiving information sheet
- 13 worsening clinical status
180 CHF patients enrolled and underwent overnight monitoring
7 excluded due to insufficient sleep (<200 minutes total sleep time)
173 CHF patients included in final analysis
78 CHF patients suitable for heart rate variability analysis
95 CHF patients unsuitable for heart rate variability analysis
- 45 Paced cardiac rhythm
- 29 Atrial fibrillation
- 13 Frequent ectopics
- 5 No high frequency peak
- 3 Technical failure

FIGURE 2.

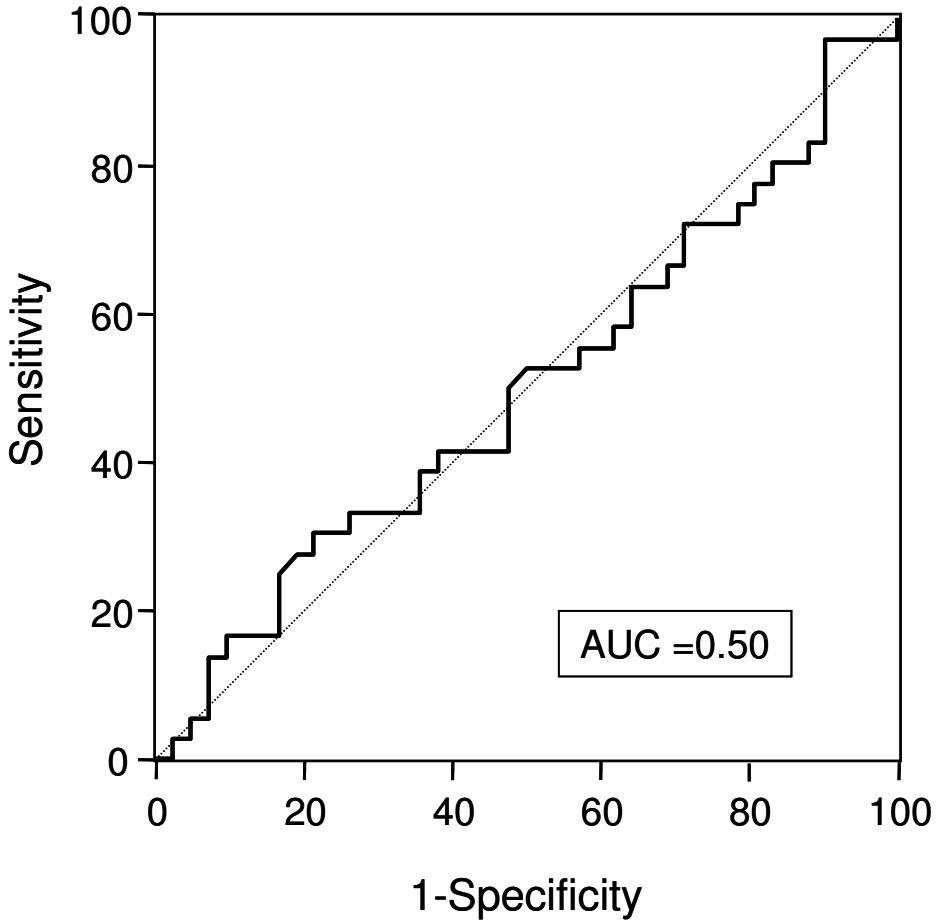
100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
1-Specificity
AUC =0.50

FIGURE 3

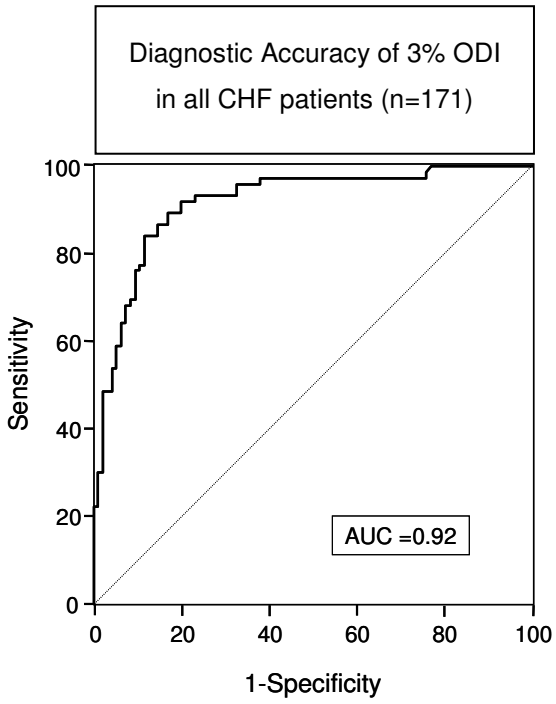

Figure a

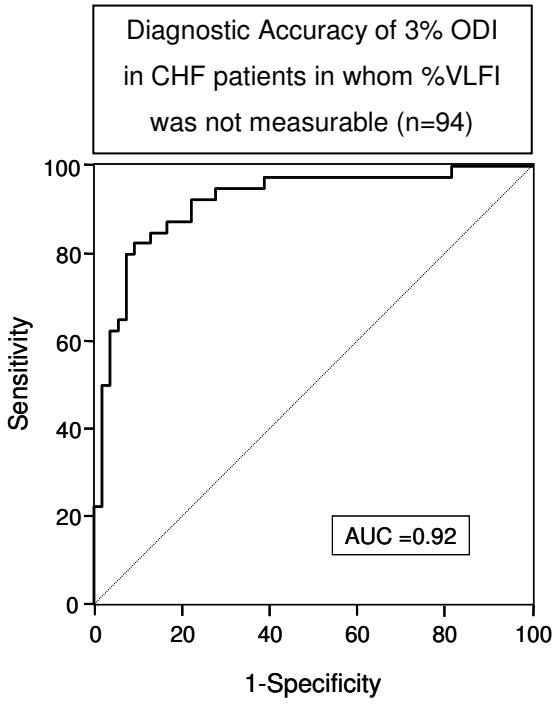

Figure b

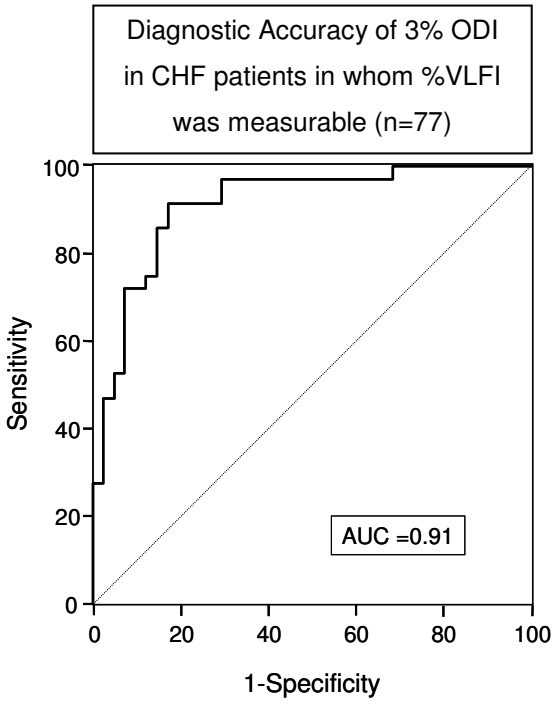

Figure c

ONLINE DATA SUPPLEMENT

Utility of Overnight Pulse Oximetry and Heart Rate Variability Analysis to Screen for Sleep-Disordered Breathing in Chronic Heart Failure

Neil R. Ward, Martin R. Cowie, Stuart D. Rosen, Vitor Roldao, Manuel De Villa, Theresa A. McDonagh, Anita K. Simonds, Mary J. Morrell

METHODS

This study received ethical approval from the Brompton, Harefield and NHLI research ethics committee (COREC 07/Q0404/32) and participants gave informed consent before participation.

Patients with low or preserved ejection fraction heart failure were recruited from cardiology outpatient clinics between November 2007 and May 2010

Measurements

Polysomnography (PSG) data was recorded with an ambulatory polysomnography system (SOMNOscreen, SOMNOmedics GmBH, Germany). Electroencephalogram (C3/A2; C4/A1), electroculogram and submental electromyogram (EMG) were recorded for analysis of sleep. Thoracoabdominal movements, nasal pressure and oxygen saturation were measured to assess respiration. The polysomnography oximeter updated oxygen saturation with each heart beat and used an averaging time of 4 heart beats; thus at a heart rate of 70 beats per minute, the oximeter averaging time would be 3.4 seconds which is similar to that recommended by the American Academy of Sleep Medicine [E1]. Snoring was detected with a tracheal microphone

and bilateral anterior tibialis EMG was monitored for identification of leg movements. Body position was monitored by an inbuilt sensor within the SOMNOscreen recording unit.

Ambulatory electrocardiography was recorded synchronously using a commercial Holter monitor (VistaPlus, Novacor, Paris, France) to allow analysis of heart rate variability. Recording electodes were placed bilaterally below the sternoclavicular joints and over the 5th intercostal spaces in the anterior axillary line, with a fifth electrode located over the 4th intercostal space to the right of the sternal margin. A two channel ECG was recorded at a sampling rate of 200Hz. Data was recorded to a compact flash card which was downloaded and stored on a personal computer using proprietary software (Holtersoft, Novacor, France) the morning after each study.

Overnight finger pulse oxygen saturation was also recorded with a separate wrist worn oximeter (Minolta Pulsox 3i, Konica Minolta, Osaka, Japan) used with a flexible finger probe (Konica Minolta Probe LM-5C) applied to a finger adjacent to the PSG oximeter. The recording characteristics of the Pulsox 3i include a sampling and averaging time of 5 seconds with a measurement value stored every 5 seconds. The oximeter was manually started by the researcher after attachment of all monitoring equipment. On the morning after the study, oximetry data was downloaded and stored on a personal computer using dedicated software (Download 2001, Stowood Scientific Instruments, Oxford, UK).

All patients were asked to keep a diary to record the time that they turned out the light after going to bed and the time that they awoke the next morning.

A structured clinical interview was conducted on the evening of the sleep study, to enquire about normal sleeping habits, snoring, sleep related symptoms, comorbid medical conditions and medication usage. Subjective daytime sleepiness was quantified with the Epworth sleepiness scale [E2] and the Hospital Anxiety and Depression score [E3] was used to screen for mood disorders. Anthropometric characteristics including height, weight, and circumference of neck,

waist and hip were measured. Spirometry was performed with the patient in a seated position, using a handheld spirometer (Vitalograph 2120, Maids Moreton, UK).

Heart failure severity was assessed subjectively using the New York Heart Association classification [E4] and objectively by assay of B-type natriuretic peptide (BNP) and echocardiographic assessment of cardiac size and function. A blood sample for BNP assay (Triage BNP, Biosite Inc, California, USA) was collected from each participant on the morning after their sleep study. Echocardiography data was obtained by analysis of echocardiograms which had been performed as part of each patients routine clinical care. All echocardiograms were analysed by the same experienced echocardiographer who was unaware of the results of the other investigations.

Data Analysis

Polysomnography studies were scored by the same experienced polysomnographer who was unaware of the ambulatory ECG or pulse oximetry results. Sleep was scored according to standard criteria [E5]. Recommended definitions were used for analysis of respiratory events [E5]. Apnoea was scored when nasal airflow was reduced to <10% of baseline for $\geq$ 10 seconds. Obstructive apnoeas were scored when the thoracoabdominal effort signals showed continuing respiratory excursions, whilst central apnoea was scored when respiratory efforts were absent. Hypopnoea was scored using the American Academy of Sleep Medicine 'alternative' rule, when nasal airflow reduced by $\geq$ 50% of baseline with an associated oxygen desaturation of $\geq$3% and/or an EEG arousal from sleep [E5]. Obstructive hypopnoea was scored in the presence of snoring, flattening of the nasal pressure airflow signal or out of phase thorax and abdominal effort signals. Central hypopnoea was scored when all these features were absent. The mean number of apnoeas and hypopnoeas per hour of sleep was expressed as the apnoea-hypopnoea index (AHI). SDB was defined as an AHI $\geq$15 events/hour and was further

categorised as obstructive or central sleep apnoea according to the predominant type of respiratory event.

Anonymised ambulatory ECG recordings were analysed with a commercial software program (Holtersoft, Novacor, Rueil-Malmaison, France). CHF patients with paced cardiac rhythm for >10% of all QRS complexes, atrial fibrillation or >10% of ectopic beats were excluded from HRV analysis. Manual editing of the automated scoring was performed to ensure QRS complexes were correctly identified and to correct misidentified ectopic beats or artefact. Time spent on manual editing was limited to 20 minutes to ensure the technique was not too time consuming for use in the clinical setting. HRV was analysed during the period from midnight to 0600 [E6, E7]. In addition to measurement of recommended time domain and spectral components of HRV [E8], the spectral density of the heart rate increment (HRI) was also measured. Fourier transform was used to analyse the interbeat interval increment series through consecutive 16 min signal blocks to identify very low frequency oscillations in HRV. The %VLFI represents the percentage of the power in the very low frequency range (0.01 to 0.05 Hz) of the HRI power spectrum, expressed relative to the total spectral density power (0.01 – 0.5 Hz) [E9]. The diagnostic accuracy of %VLFI is increased when a simultaneous high frequency (HF) peak in the HRI power spectrum can be identified [E10]. Absence of the HF peak may occur in autonomic dysfunction, increasing the risk of a false negative result when %VLFI is used to screen for OSA [E10]. CHF patients without an identifiable HF peak were excluded from this analysis.

Sample Size Calculation

The required sample size was calculated to be adequately powered (1-β = 80%) to detect a one sided difference of >10% between the sensitivity/specificity of HRV and polysomnography at a significance level of 0.05. As there is no true gold standard for diagnosis of SDB, polysomnography was considered the reference standard and the method of Lui and

Cumberland was used to determine the number of patients required [E11]. The %VLFI component of HRV has previously been reported to have a sensitivity of 85% and specificity of 65% to detect SDB in CHF [E6]. Using these values, it was calculated that 110 true positives were required to detect a >10% difference in sensitivity between polysomnography and %VLFI, whilst 180 true negatives were required to detect a >10% difference in specificity.

RESULTS

Characteristics of CHF patients in whom HRV was measurable are compared to patients unsuitable for HRV analysis in Table E1

Use of different %VLFI cutoffs for SDB diagnosis

A %VLFI cutoff of ≥2.4% has been reported to be the optimal cutoff value for detection of OSA in patients without CHF [E5]. In the current study, use of this threshold did not improve the diagnostic accuracy of %VLFI (Table E4).

Diagnostic accuracy of the %VLFI was also calculated using the sleep diary times ($\%VLFI_{diary}$). There was no significant improvement in sensitivity (56%), specificity (43%) or $\%VLFI_{diary}$ AUC curve using this method (Table E4).

Comparison of Alternative Measures of HRV in CHF patients with SDB

Spectral and time domain components of HRV were also quantified in the 78 CHF patients in whom HRV was measurable (Table E5). There was a significant increase in absolute low frequency (LF) power in CHF patients with OSA compared to CHF patients without SDB or with CSA, although this difference was not seen when LF power was expressed in normalised units (nu). The percentage of adjacent NN intervals which differ by >50 milliseconds (pNN50) and the square root of the mean of the squares of differences between adjacent NN intervals (RMSSD)

time domain measurements (indicating rapid changes in heart rate through vagal modulation) also differed significantly between CHF patients without SDB and those with OSA and CSA. These HRV parameters showed improved diagnostic accuracy compared to %VLFI with AUC of 0.69 (95% confidence interval 0.57 - 0.80) for absolute LF power, 0.71 (95% C.I. 0.60 - 0.83) for pNN50, and 0.70 (95% C.I. 0.58 - 0.81) for RMSSD (ROC curves not shown).

Comparison of Accuracy of %VLFI and 3% ODI for SDB diagnosis in CHF

%VLFI was measurable in 78 CHF patients, with AUC of 0.50 (standard error 0.067) for diagnosis of CHF. 3% ODI was measured in 77 of these 78 CHF patients (one overnight pulse oximetry technical failure) with AUC of 0.91 (standard error 0.033). There was a significant difference in area beneath the %VLFI and 3% ODI ROC curves of 0.41 (standard error 0.074; $p < 0.0001$).

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E7 Vazir A, Dayer M, Hastings PC, et al. Can heart rate variation rule out sleep-disordered breathing in heart failure? Eur Resp J, 2006. **27**(3):571-577.

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E9 Roche F, Duverney D, Court-Fortune I, et al. Cardiac interbeat interval increment for the identification of obstructive sleep apnea. Pacing Clin Electrophysiol, 2002. **25**(8):1192-1199.

E10. Poupard L, Court-Fortune I, Pichot V, et al. Use of high-frequency peak in spectral analysis of heart rate increment to improve screening of obstructive sleep apnoea. Sleep Breath. 2011 Dec;**15**(4):837-43

E11. Lui, K.J. and W.G. Cumberland, Sample size determination for equivalence test using rate ratio of sensitivity and specificity in paired sample data. Control Clin Trials, 2001. **22**(4):373-89

TABLE E1. COMPARISON OF CHRONIC HEART FAILURE PATIENTS SUITABLE AND UNSUITABLE FOR HEART RATE VARIABILITY ANALYSIS

	Patients suitable for HRV analysis (n = 78)	Patients unsuitable for HRV analysis (n = 95)	P Value
Age (years)	66.2 (53.7 – 74.8)	72.2 (60.7 – 77.1)	0.006
Male (n,%)	67 (86)	81(85)	1.0
BMI (kg/m^2)	30.1 (26.8 – 32.9)	28.5 (25.0 – 32.6)	0.10
Neck circumference (cm)	40.5 (38.3 – 42.3)	40.0 (37.5 – 43.0)	0.87
Waist/Hip ratio	1.02 (0.98 – 1.06)	1.02 (0.97 – 1.06)	0.67
Ischemic cardiomyopathy (n,%)	43 (55)	46 (48)	0.45
NYHA (I/II/III/IV)	13/49/16/0	11/61/21/2	0.47
BNP (pg/ml)	69 (29 – 157)	170 (100 – 320)	<0.001
Left ventricle EF (%)	44 (32 – 58)	37 (27 – 57)	0.08
Epworth Score	7 (4 – 10)	7 (4 – 10)	0.60
OSLER duration	40.0 (39.3 – 40.0)	40.0 (22.2 – 40.0)	0.28
Total Sleep Time (mins)	353 (284 – 405)	349 (291 – 400)	0.82
Sleep efficiency (%)	73 (60 – 81)	72 (62 – 80)	0.66
Arousal Index (events/hour)	19.5 (13.5 – 27.2)	18.5 (13.5 – 26.4)	0.49
AHI (events/hour)	13.6 (6.4 – 25.8)	12.8 (7.2 – 24.1)	0.84
Time SaO2 <90% (% TST)	1.8 (0.2 – 19.5)	4.8 (0.8 – 22.1)	0.30
PLMI (events/hour)	6.2 (1.5 – 23.9)	19.1 (4.0 – 49.1)	0.01

Definition of abbreviations: BMI = body mass index; NYHA = New York heart association class; BNP = B-type natriuretic peptide; EF = ejection fraction; OSLER = Oxford sleep resistance test; AHI = apnoea-hypopnoea index; SaO2 = finger pulse oxygen saturation; TST = total sleep time; PLMI = Periodic Limb Movement Index

Data are presented as median (interquartile range), or number (%) of patients

TABLE E2. DIAGNOSTIC ACCURACY OF %VLFI FOR DETECTION OF SLEEP-DISORDERED BREATHING IN PATIENTS WITH CHRONIC HEART FAILURE*

% VLFI parameter	%VLFI threshold	SDB diagnostic threshold (AHI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood ratio	Negative Likelihood ratio	Area under ROC curve
$\%VLFI_{0-6}$	≥2.23	≥5	59 (47 – 71)	59 (35 – 82)	84 (73 – 95)	29 (14 – 44)	1.43 (0.78 – 2.63)	0.70 (0.42 – 1.15)	0.55 (0.39 – 0.71)
		≥15	58 (42 – 74)	48 (33 – 63)	49 (34 – 64)	57 (41 – 74)	1.11 (0.75 – 1.66)	0.88 (0.53 – 1.44)	0.50 (0.37 – 0.63)
		≥20	56 (37 – 75)	45 (32 – 59)	33 (19 – 47)	69 (53 – 84)	1.02 (0.67 – 1.57)	0.97 (0.57 – 1.65)	0.49 (0.34 – 0.63)
		≥30	63 (39 – 86)	47 (34 – 59)	23 (11 – 36)	83 (70 – 95)	1.17 (0.75 – 1.83)	0.80 (0.40 -1.59)	0.54 (0.37 – 0.70)
	≥2.4	≥15	47 (31 – 64)	50 (35 – 65)	45 (29 – 61)	53 (37 – 68)	0.94 (0.60 – 1.49)	1.06 (0.69 – 1.63)	0.50 (0.37 – 0.63)
$\%VLFI_{diary}$	≥2.23	≥15	56 (39 – 72)	43 (28 – 58)	45 (31 – 60)	53 (36 – 70)	0.97 (0.66 – 1.44)	1.04 (0.63 – 1.72)	0.48 (0.35 – 0.61)

Definition of abbreviations: % VLFI = % very low frequency increment of heart rate variability; SDB = sleep-disordered breathing; AHI = apnoea hypopnoea index; ROC = curve receiver operating characteristic curve; $\%VLFI_{0-6}$ = %VLFI measured between midnight and 0600; $\%VLFI_{diary}$ = %VLFI measured according to diary sleep time.

*Results are presented with 95% confidence interval

TABLE E3. SPECTRAL AND TIME DOMAIN HEART RATE VARIABILITY PARAMETERS IN CHRONIC HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP-DISORDERED BREATHING

	No SDB (n = 41)	OSA (n = 31)	CSA (n = 5)	P Value*
VLF power (absolute)	3526 (2162 – 7513)	4150 (2835 – 6624)	4960 (3050 – 8012)	0.73
LF power (absolute)	299 (161 – 629)§	515 (391 – 1366)§	380 (89 – 3860)	0.009
LF power (nu)	68.4 (55.8 – 77.8)	70.7 (57.8 – 82.7)	66.0 (49.0 – 84.5)	0.77
HF power (absolute)	116 (51.8 – 215)	281 (123 – 468)	123 (46 – 1965)	0.30
HF power (nu)	31.6 (22.2 – 44.2)	29.3 (17.3 – 42.2)	34.1 (15.5 – 51.0)	0.77
LF/HF ratio	2.16 (1.27 – 3.51)	2.41 (1.26 – 4.78)	1.94 (1.20 – 6.50)	0.82
SDNN	68 (55 – 99)	78 (67 – 97)	89 (55 – 118)	0.40
SDANN	50 (37 – 72)	47 (39 – 66)	51 (34 – 77)	0.92
SDNNI	35 (27 – 42)	41 (36 – 55)	41 (30 – 54)	0.10
pNN50 (%)	2.12 (0.92 – 7.49)§	8.81 (3.32 – 18.58)§	12.68 (3.04 – 20.44)	0.006
RMSSD	24 (20 – 36)§	35 (27 – 57)§	36 (22 – 110)	0.01
Mean NN	921 (819 – 1061)	948 (860 – 1036)	944 (862 – 1008)	0.86

VLF = Very low frequency; LF = Low frequency; HF = High frequency; nu = normalised units; SDNN = standard deviation of NN intervals; SDANN = standard deviation of average NN interval during all 5 minute epochs throughout recording; SDNNI = mean of the standard deviations of NN intervals during all 5 minute epochs throughout recording; pNN50 = proportion of adjacent NN intervals which differ by >50 milliseconds; RMSSD = the square root of the mean of the squares of differences between adjacent NN intervals; NN = normal to normal interbeat interval

*p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test. §$p<0.005$ for difference between CHF patients with OSA and patients without SDB ('No SDB')

Data are presented as median (interquartile range)

Figure E1

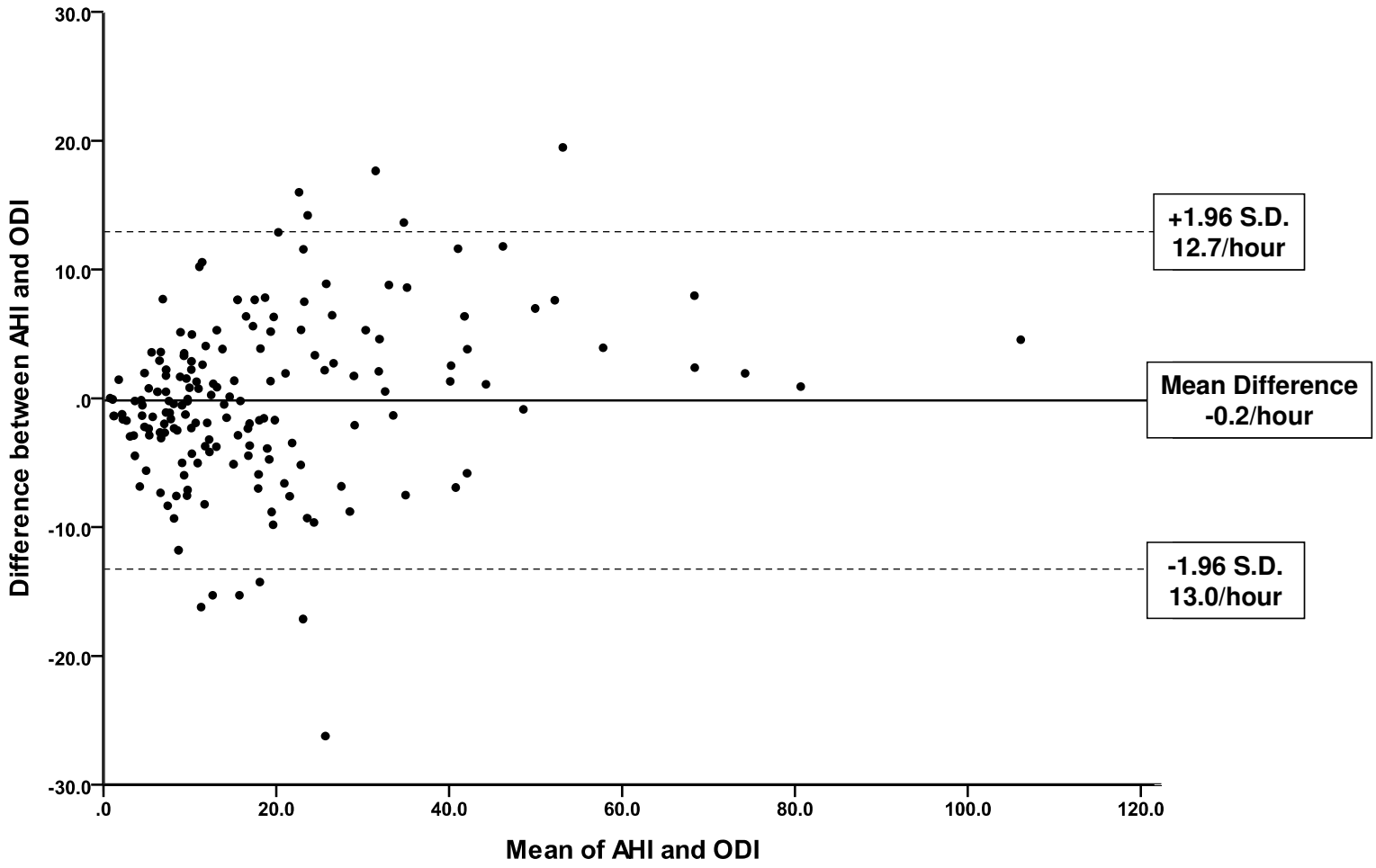

Figure E1. Bland-Altman plot showing mean difference and 95% limits of agreement for measured apnoea hypopnoea index (AHI) and 3% oxygen desaturation index (ODI) in CHF patients. (S.D. = standard deviation)

Figure E2

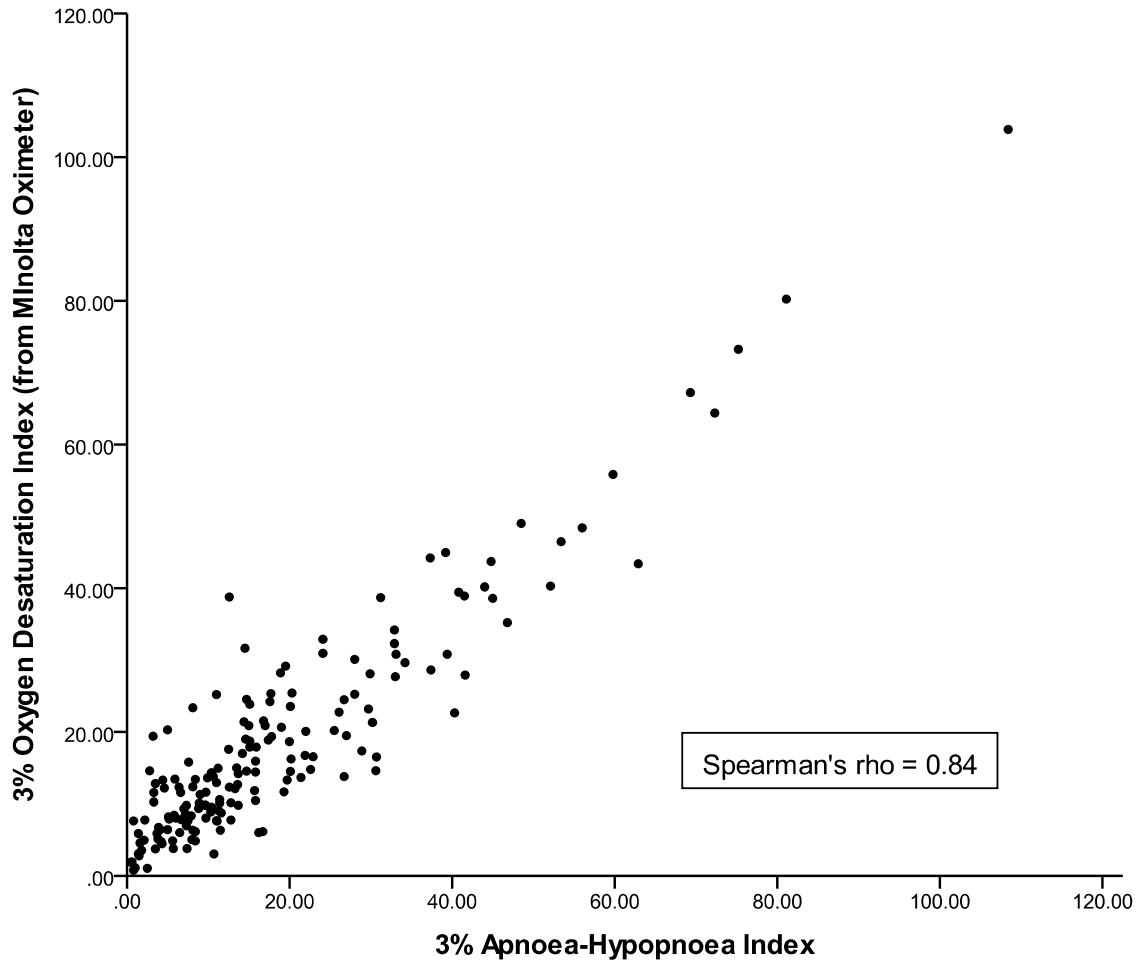

Figure E2. Correlation between apnoea hypopnoea index and 3% oxygen desaturation index in CHF patients