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Sleep Circulation Time from Pulse Oximetry and Polysomnography: Predictive Value in Patients with Heart Failure with Reduced Ejection Fraction

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Highlights

Circulation time can be estimated from pulse oximetry during polysomnography from the measured recovery time of oxygen saturation

What are the main findings?

- Circulation time can be estimated from pulse oximetry during polysomnography (PSG) from the pulse oximetry-measured recovery time of oxygen saturation after an apnea or hypopnea event.
- All subjects with left ventricular ejection fraction ≤45% had prolonged circulation time (median of 27.8 seconds)

What are the implications of the main findings?

- Circulation time may be used to identify the presence of heart failure in polysomnography
- Those with sleep circulation time over 28.6 seconds on PSG should have an evaluation of cardiac function.

Abstract

Background: This study evaluated the use of circulation time (Tcirc) calculated from polysomnogram (PSG) with pulse oximetry to identify poor cardiac function with low left ventricular ejection fraction (EF). *Methods:* Subjects over 18 years with sleep apnea (apnea-hypopnea index (AHI) >5/hr) diagnosed by PSG who had transthoracic echocardiography (TTE) within 1 year of PSG were included in this retrospective study. Tcirc of each sleep stage (N2, N3, and REM) were measured and averaged and EF was recorded. Statistical analysis was done using Wilcoxon rank sum test, logistic regression and Youden index. *Results*: There were 89 subjects who met inclusion criteria, 14 with EF ≤45% (Group A) and 75 with EF ≥ 50% (Group B). All 14 Group A subjects had prolonged overall Tcirc with a median time of 27.8 seconds (range 14.1 - 39.6 sec), compared to Group B subjects with median Tcirc of 23.5 seconds (range 14.3 – 37.6 sec), p = 0.311. The optimal cut-point for overall sleep Tcirc with moderate discrimination (AUC = 0.6) was 28.6 sec. Those with total sleep Tcirc ≥ 28.6 sec were 2.5 x more likely to have low EF with OR =2.56 (95% CI, 0.55-11.16). *Conclusions:* In sleep apnea patients, total sleep Tcirc > 28.6 seconds is associated with low ejection fraction with specificity = 0.78.

Keywords: sleep apnea; apnea-hypopnea index; circulation time; ejection fraction; heart failure; pulse oximetry; polysomnography; cardiovascular disease; sleep-disordered breathing

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1. Introduction

1.1. Non-invasive transcutaneous pulse oximetry has long been utilized to estimate arterial oxygen saturation [1], facilitating the revelation of sleep-related hypoxemia in chronic obstructive pulmonary disease (COPD) [2–4] and sustained sleep hypoxemia-induced right ventricular dysfunction in COPD patients [5]. The intermittent sleep hypoxemia seen in obstructive sleep apnea (OSA) [6] leads to systemic sleep hypertension, left ventricular dysfunction and increased cardiovascular events [7]. Recently this measurement of nocturnal oxygen saturation via pulse oximetry has led to the concept of hypoxic burden [8] and the revelation of its correlation with right heart dysfunction [9], cardiovascular events [10] and mortality [11] in OSA. Azarbarzin et al found an association between hypoxic burden but not AHI and cardiovascular disease and all-cause mortality in men 65 years or older [12]. Oldenburg et al. showed that hypoxemic burden (defined as time spent with oxygen saturation <90%) is the strongest independent predictor for all cause mortality in HF patients. They use a cut off point of 22 minutes to best predict mortality [13].

1.2. We now realize that pulse oximetry in sleep apnea subjects during polysomnography (PSG) can be utilized to estimate not only hypoxic burden, but also the length of time for recovery of oxygen saturation after cessation of apnea and resumption of breathing: the circulation time (Tcirc), which is normally < 20 seconds.

1.3. The concept of sleep circulation time (Tcirc) has been described in the past. Tcirc is also known as the lung to periphery time. Hall et al. [14] hypothesized that lung-to-carotid body circulatory delay may explain the cycle length of periodic breathing, which is reflected by lung-to-finger or lung-to-ear circulation time, or otherwise known as the lung to periphery time. This can be identified on the PSG as the time interval from the start of hyperpnea following an apnea or hypopnea, to the lowest point (i.e. nadir) of oxygen saturation measured at a peripheral site by pulse-oximetry [15].

1.4. Presence of Sleep-disordered breathing (SDB) has been strongly associated with heart failure (HF) [16]. Both obstructive sleep apnea (OSA) and CSR are associated with increased mortality in those with HF [17,18]. Therefore, identifying markers in polysomnograms (PSGs) may aid the early identification and management of heart failure.

1.5. There have been a few studies that use circulation time (Tcirc) as markers for heart failure and mortality. It was shown that prolonged sleep circulation time may be associated with worse outcome [19,20]. Hall et al. had demonstrated that Tcirc is prolonged in those patients with Cheyne-Stokes Respiration (CSR) associated with HF compared to idiopathic central sleep apnea. They also demonstrated that the lung to ear circulation time is inversely related to cardiac output [14]. Therefore, it is thought that prolonged Tcirc is an indicator for low cardiac output state. Kwon et al. also demonstrated similar results that the most significant factor associated with delayed lung to finger circulation time (LFCT) was the presence of HF, and prolonged LFCT was associated with greater CV and all-cause mortality [20].

1.6. Bitter et al. used cycle length in the diagnosis of central and obstructive sleep apnea (CSA/OSA) [21]. Circulatory delay (CD) was measured the same way as Tcirc. They found that in patients with heart failure with reduced left ventricular ejection fraction (HFrEF), CD was prolonged.

1.7. In our study, we sought to use Tcirc as marker for heart failure and to identify cut off points which may reliably indicate the presence of HFrEF.

2. Methods

2.1. Subjects

We included subjects who are 18 years or older, with sleep apnea defined as apnea-hypopnea index (AHI) >5/hr, diagnosed by PSG who also had transthoracic echocardiography (TTE) within 1 year of PSG. We excluded people with known diastolic dysfunction and EF ≥50%. Subject's demographic information including gender, age, ethnicity, BMI, and beta blocker usage were

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obtained from electronic medical records. TTE was reviewed and EF and diastolic function were recorded. PSGs for each patient were reviewed, AHI and oxygen desaturation time were obtained as well as circulation time (see below for circulation time measurements). This study was approved by Institutional Board Review at University of Southern California (HS-20-00769).

2.2. Circulation Time Measurements

Polysomnography was performed using Natus XLTEC Sleepworks version 9.6. This Natus polysomnography system Natus Medical Inc., Middleton, WI, USA; is a state-of-the-art standard used in many sleep disorders centers accredited by the American Academy of Sleep Medicine. Tcirc was measured from the start of hyperpnea following an apnea or hypopnea, to the oxygen saturation nadir measured by a Nonin pulse-oximeter with model 6000CA-WO2 sensor on the finger (Nonin Medical Inc., Plymouth, MN, USA). The Nonin pulse oximeter with PureSAT technology has been validated with precision of ±2.1 (https://www.nonin.com/resource/accuracy-and-superior-performance-of-puresat-and-purelight-oximetry-technologies/). Three Tcirc values were measured from the first, middle, and last third of each sleep cycle (stages N2, N3, and REM), and we then averaged nine Tcirc measurements from each of stages N2, N3, and REM stages as the average Tcirc. Total sleep Tcirc was defined as the combined average Tcirc between N2+N3+REM.

2.3. Statistical Analysis

Summary statistics were presented using frequency and percent for categorical variables and mean (SD) or median (IQR) for continuous variables, dependent on distribution. Independent samples t-test or Wilcoxon rank sum test, as appropriate, was used to evaluate differences in Tcirc time between subjects with EF ≥50% and EF ≤45%. Optimal cut-points for REM Tcirc average and total sleep Tcirc average were evaluated based on Youden's Index (criterion for maximizing sum of sensitivity and specificity). Diagnostic measures of accuracy (AUC, sensitivity, specificity) were used for interpretation and comparison of cut-points. Multivariable firth's logistic was used to evaluate the association between identified REM groups and likelihood of low EF (≤45%), while controlling for age, BMI, and patient beta blocker status. All tests were two-sided and a p-value < 0.05 was considered statistically significant. All analyses were done in R version 4.2.3.

3. Results

A total of 89 subjects were included, 14 subjects with EF ≤45% (Group A), 75 subjects with EF ≥ 50% (Group B). Patient characteristics are listed in Table 1.

Table 1. Demographics.

Variable	EF Level		P-value
	Normal EF - >50% (n=75)	**Low EF - <45%** (n=14)	
Age	64.0 (19.5) (min=23, max=94)	67.5 (23.3) (min=25, max=83)	0.414
Gender			
Male	52 (69.3%)	12 (85.7%)	0.333
Female	23 (30.7%)	2 (14.3%)	
Ethnicity			
White/Caucasian	32 (45.7%)	2 (16.7%)	0.004*
Black/AA	1 (1.4%)	2 (16.7%)	
Asian	5 (7.1%)	4 (33.3%)	
Hispanic	29 (41.4%)	3 (25.0%)	
Other	3 (4.3%)	1 (8.3%)	
BMI	30.1 (9.4)	30.6 (9.7)	0.978

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	(min=17.3, max=56.0)	(min=22.5, max=47.1)	
Type of Sleep Apnea			
Central	5 (6.7%)	2 (14.3%)	0.009*
Obstructive	66 (88.0%)	8 (57.1%)	
Complex	4 (5.3%)	4 (28.6%)	
On Beta Blocker			
No	49 (67.1%)	4 (28.6%)	0.007*
Yes	24 (32.9%)	10 (71.4%)	

Numbers represent median (IQR) for continuous variables and frequency (column percent) for categorical. *Significant at p<0.05.

3.1. Circulation Time

All 14 Group A subjects had prolonged overall Tcirc with a median time of 27.8 sec, compared to Group B subjects with median Tcirc of 23.5 sec (Table 2).

Table 2. Medium circulation time. Table. Mean (Standard deviation) values of total sleep circulation time by EF level.

Variable	**EF Level**		**P-value**
	Normal EF - ≥50% (n=75)	**Low EF - ≤45%** (n=14)	
Circ. time during total sleep (N2+N3+REM)	23.5 (7.3)) (min=14.3, max=37.6)	27.8 (3.9) (min=14.1, max=39.6)	0.311

Numbers represent median (IQR).

3.2. Optimal Cut Points for Circulation Time

The optimal cut-point for total sleep Tcirc average with moderate discrimination (AUC = 0.60. CI 0.39-0.81) was 28.6 sec, with sensitivity = 0.5 and specificity =0.78 (Table 3). Those with total sleep Tcirc ≥ 28.6 seconds were 2.5 times more likely to have low EF (OR = 2.56; 95% CI = 0.55-11.16) shown in Table 3.

Table 3. Optimal Cut-Point Analysis for Prediction of Low EF.

Variable	Optimal Cut-point Value	AUC (95% CI)	Sensitivity	Specificity
N2 + N3 + REM Avg.	28.6	0.60 (0.39 – 0.81)	0.50	0.78

AUC = Area Under Receiver Operator Characteristic (ROC) Curve.

3.3. Beta Blocker Use and Circulation Time

Patients who are not on beta blockers were less likely to have prolonged Tcirc (OR=0.84; 95% CI 0.03 – 26.70) as shown in Table 4. Whereas those with beta blocker use, were more likely to have prolonged Tcirc ≥ 28.6 seconds (OR= 1.30; 95% CI = 0.19 – 8.86), Table 5.

Table 4. Multivariable logistic regression of patients not on beta blocker.

Variable	Estimate	Odds Ratio (95% CI)	P-value
Tcirc during total sleep (N2+N3+REM)			
≤ 28.6	Reference	Reference	
> 28.6	-0.179	0.84 (0.03 – 26.70)	0.919

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Table 5. Multivariable logistic regression of patients on beta blocker.

Variable	Estimate	Odds Ratio (95% CI)	P-value
Tcirc during total sleep (N2+N3+REM)			
≤ 28.6	Reference	Reference	
> 28.6	0.261	1.30 (0.19 – 8.86)	0.790

3.4. AHI and Oxygen Desaturation Time

The subjects in Group A had a median AHI of 40.8 (range 6.8 – 109) compared to those in Group B (AHI of 20.7 (range 5 – 136), p = 0.247), Table 6. Group A subjects had a median oxygen desaturation time (< 88%) of 9.55 minutes (3.8 – 30.1 min) versus those in Group B with median of 6.1 min (range 0.1 – 159 min), Table 7.

Table 6. AHI by EF level.

Variable	EF Level		P-value
	Low EF (≤45%) (n=14)	**Normal EF (≥50%)** (n=76)	
AHI	40.8 (30.4) (min=6.8, max=109.0)	20.7 (17.7) (min=5.0, max=136.0)	0.247

Numbers represent median (interquartile range).

Table 7. Desaturation time & percent desaturation by EF level.

Variable	EF Level		P-value
	Low EF (≤45%) (n=8)	**Normal EF (≥50%)** (n=63)	
Desaturation Time	9.55 (17.2) (min=3.8, max=30.1)	6.10 (23.8) (min=0.1, max=159.0)	0.378
Percentage Desaturation	3.7 (3.5) (min=1.4, max=24.0)	2.9 (13.3) (min=0, max=99.5)	0.567

Numbers represent median (interquartile range).

4. Discussion

4.1. AHI and Hypoxic Burden in Heart Failure with Reduced Ejection Fraction

Over the last few decades, the data on association between AHI and HF and cardiovascular mortality has been conflicting. Punjabi et al. showed correlation of AHI with all-cause mortality and coronary artery disease in men age 40-70 years old, especially in those with AHI >30/h, but not with women or with men > 70 years. [22]. The data correlating AHI and HFrEF is sparse. A prospective study done by Gottlieb et al. [23] demonstrated AHI to be associated with HF in men. They showed that men with AHI ≥ 30/hr were 58% more likely to develop HF in comparison to those with AHI < 5/hr . Yet, Azarbarzin et al. again, did not find significance in AHI and incidence of HF [24]. In our study, the AHI was higher in those with EF ≤45% compared to those with normal EF (40.8 vs 20.7). It has also been shown that sleep hypoxic burden predicts incidence of HF in men [20]. Yuksel et al found an association between hypoxic burden and major cardiovascular and cerebrovascular events in sleep apnea patients [25]. Additionally, Khouzani et al showed that oxygen saturation < 85% was a better predictor of mortality than AHI in OSA [10]. In our study, there was a trend of longer hypoxic time in those with EF ≤ 45% vs those with normal ejection fraction, but this did not reach statistical significance. However, hypoxic time in our study was determined by oxygen saturation < 88%. It is likely that AHI and hypoxic time with oxygen saturation < 88% do not always capture the degree of

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heart failure. Therefore, using other markers such as Tcirc that correlate with hypoxic burden may help identify those with HF and higher mortality risk.

4.2. Circulation Time and Cardiac Output

In 2015, Hosokawa et al. [26] also demonstrated cardiac output and cardiac index measured by right heart catheterization significantly correlate with the LFCT measured by overnight PSG. We confirmed this in our study in which Tcirc during sleep is longer in patients who have EF ≤45%. All subjects with EF≤45% had prolonged circulation time (median of 27.8 seconds) in comparison to those with EF ≥50%. This implies that Tcirc may be used to identify the presence of heart failure and perhaps Tcirc should be reported as part of the PSG measurements. It is further confirmed in multivariable analysis as the use of beta blocker is generally associated with presence of heart failure, and those who are taking beta blockers are more likely to have prolonged Tcirc.

4.3. Circulation Time Predicting HFrEF

Recently, Bitter et al used cycle length in the diagnosis of central and obstructive sleep apnea (CSA/OSA). Circulatory delay (CD) was measured the same way as Tcirc in our study, and they found that in HFrEF, CD cut off for CSA/OSA patients was 26.4 seconds with AUC = 0.79 [20]. This may be compared to our optimal cut-off point of 28.6 sec (AUC = 0.60) with OR = 2.56 for low EF ≤ 45%. This indicates that patients with high circulation time above the optimal cut-off point should have an echocardiogram to rule out presence of HF.

4.4. Study Limitations

Our study has several limitations. First, this is a retrospective study. We did not exclude subjects with BMI >40 kg/m^2, and morbidly obese subjects may constitute a distinct type of hypopnea-dominant SDB and may have concomitant obesity hypoventilation syndrome and/or a distinct hypopnea-dominant OSA [27]. We also noted a wide range of Tcirc amongst the patients, which may affect the data. This might be explained by various degree of severity in patient's HF for those EF ≤45%. We chose median instead of mean data to account for the degree of variation in Tcirc. In addition, EF can be dependent on the echocardiographer's interpretation. To avoid such bias, we choose EF ≥50% and EF≤45% to avoid the discrepancies. Further, the use of beta blocker could bias the study as HF patients tend to be on beta blockers which has been shown to be associated with prolonged circulation time [28]. Finally, we did not exclude smokers or those with elevated carboxyhemoglobin, which may reflect the accuracy pf pulse oximetry [29]. Despite our limitation, we believe that Tcirc during PSG is a good indicator of cardiac function.

4.5. Future Direction

A future prospective study with PSG and pulse oximetry and TTE days apart can provide the most accurate results for optimal cut off points for predicting HFrEF. We can also further stratify patients between OSA and CSA to see if there are additional differences. It is also reasonable to suspect that the Tcirc estimated by our method should also be valid using a home sleep apnea test (HSAT) rather than in-lab PSG. Future evaluation of Tcirc via HSAT will be forthcoming in view of the increasing utilization of HSATs in the medical community.

5. Conclusion

Our findings demonstrate that those with low EF have prolonged sleep circulation time, which can be estimated during PSG with pulse oximetry. Our analysis shows that those with sleep circulation time over 28.6 seconds on PSG should have an evaluation of cardiac function.

Author Contributions: B.C was responsible for acquisition of the data, J.R was responsible for analysis of the data, W.J.H Was responsible for acquisition of the data, edition and manuscript preparation, and R.J.C. made

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substantial contributions to the conception and design of the work, and manuscript preparation. All of the co-authors approved the final version submitted for publication and agree to be accountable for all aspects of the work.

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Data Availability: Data from this project will be made available upon request to the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

AHI	Apnea-Hypopnea Index
BMI	Body mass index
CD	Circulatory delay
CSR	Cheyne-Stokes respiration
EF	Ejection fraction
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HSAT	Home sleep apnea test
LECT	Lung-to-ear circulation time
LFCT	Lung to finger circulation time
OSA	Obstructive sleep apnea
PSG	Polysomnogram
SDB	Sleep-disordered breathing
Sec	seconds
Tcirc	Circulation time
TTE	Transthoracic echocardiogram

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