Obstructive Sleep Apnoea: Longer Respiratory Event Lengths in Patients with Heart Failure

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Abbreviations:

AHI	apnoea-hypopnoea index
AI	apnoea index
AL	apnoea length
CD	circulatory delay (time from the end of an apnoea to the nadir of the following oxygen desaturation)
CI	cardiac index
CL	cycle length
CPAP	continuous positive airway pressure
CSA	central sleep apnoea
CSR	Cheyne-Stokes respiration
HF	heart failure
HI	hypopnoea index
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAP	mean arterial pressure
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
oAI	obstructive apnoea index
OSA	obstructive sleep apnoea
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PG	polygraphy
PSG	polysomnography
SDB	sleep-disordered breathing
TTPV	time to peak ventilation (time from the end of an apnoea to the peak of the following ventilation)
VL	ventilation length (duration of ventilation between two apnoeas)

Abstract:

This study investigated the effect of heart failure (HF) on respiratory patterns in patients with obstructive sleep apnoea (OSA).

Thirty-nine patients with established OSA (apnoea-hypopnoea index [AHI] > 10/h) and with HF (NYHA II+III, LVEF ≤40%; n=26, age 67±9 years) or without HF (LVEF ≥50%, NT-proBNP <400 pg/mL; n=13, age 73±6 years) underwent simultaneous right- and left-heart catheterization within 12h of cardiorespiratory polygraphy recording.

Respiratory patterns of OSA were significantly longer in OSA patients with versus without HF, including cycle length (CL; 46.0±10.0 vs 37.8±10.6 sec; p=0.024), ventilation length (VL; 25.4±6.3 vs 21.3±7.1 sec; p=0.044), apnoea length (AL; 20.5±4.9 vs 16.5±3.9 sec; p=0.013), time-to-peak ventilation (TTPV; 10.6±3.0 vs 8.3±2.5 sec; p=0.021) and circulatory delay (CD; 28.5±7.5 vs 22.6±3.7 sec; p=0.005). Positive and robust correlations were found between some of these parameters and the degree of congestion in HF; CL (r=0.53; p=0.006), VL (r=0.55; p=0.004) and TTPV (r=0.47; p=0.015) all increased with a rise in pulmonary capillary wedge pressure.

Respiratory patterns in OSA appear to be dependent on cardiac function, with an increase in event lengths as cardiac function decreases. In patients with HF, some of these events correlate with the degree of pulmonary congestion.

Introduction:

The Sleep Heart Health Study showed that obstructive sleep apnoea (OSA) was associated with an increased risk of incident heart failure (HF) [1]. In the presence of HF, untreated OSA represents an independent risk factor for the occurrence of malignant ventricular arrhythmias [2] and increased mortality [3], whereas continuous positive airway pressure (CPAP) therapy has been associated with decreased mortality and hospitalization in patients with HF and OSA [4].

Sleep-disordered breathing (SDB), and OSA in particular, is a common co-morbidity in HF patients [5-7]. The prevalence of OSA in patients with HF has been reported as being quite high, at 36% [5]. It is therefore becoming increasingly important to understand the potential link between HF and OSA, along with the pathophysiology of co-existing OSA and HF.

Anatomic predisposition alone is not the only factor contributing to collapsibility of the upper airway. Besides pharyngeal anatomy, fat distribution within the neck, upper airway muscle tone and responsiveness to various stimuli, like arousals from sleep or sex hormones, have been proposed [8, 9]. In patients with HF, an increased loop gain and rostral fluid shift might contribute to altered physiology [10, 11]. Another study suggested that rostral fluid shift from the periphery towards the neck might cause neck oedema with a resulting increase in upper airway resistance and development of obstruction, providing a unifying concept contributing to the pathogenesis of both OSA and central sleep apnoea (CSA) in patients with HF [12].

The occurrence of CSA with Cheyne-Stokes respiration (CSR) in patients with HF has been previously investigated in detail [5, 13 - 15]. To briefly summarise, the prevalence and severity of CSA-CSR increases in line with HF severity. On the other hand, SDB prevalence and severity may decrease when cardiac function improves [13, 15, 16].

The severity of SDB is usually defined by counting the numbers of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index, AHI) [1, 3, 5 - 7]. However,

in HF patients with CSA-CSR, an increase in respiratory event lengths may limit the total AHI. Respiratory event lengths may therefore be a more appropriate way to describe the severity of CSA-CSR, and might also be useful as an indicator of cardiac function [14, 17, 18]. A prolonged circulation time (circulatory delay, CD) in HF could alter respiratory feedback mechanisms and cause an increase in the duration of CSA-CSR pattern with prolonged cycle length (CL), ventilation length (VL), apnoea length (AL), and time to peak ventilation (TTPV) [14, 19].

We therefore hypothesized that there might be a correlation between HF severity and the respiratory pattern in OSA, specifically respiratory event lengths. We investigated the possibility that deterioration of cardiac function with an increase in filling pressures might be linked with an increase in circulation time and changes in respiratory event lengths such as CL, VL, AL or TTPV.

Methods:

A total of 380 consecutive patients undergoing simultaneous right- and left-heart catheterization were prospectively screened for enrollment. The indication for cardiac catheterization was independent of this study. Forty patients refused to undergo cardiorespiratory polygraphy (PG) recordings the next night, 25 PG recordings were of insufficient quality and in 5 patients the insertion of the cardiac floating catheter failed respectively the graph for analysing was ambiguous.

Of the remaining 310 patients, 41% (127 patients) had CSA, 42% (130 patients) had OSA and 17% (53 patients) had no SDB. Of the 130 OSA patients, 39 had significant OSA (AHI >10/h, central respiratory events <25%) and were allocated in the HF or non-HF group. Patients with pretreated SDB, decompensated HF and/or any moderate to severe valvular heart disease (> grade II) were excluded from further analysis. Thirteen of those OSA patients had no clinical signs of HF and a preserved left ventricular function (left ventricular ejection fraction, LVEF ≥50%, N-terminal pro brain natriuretic peptide, NT-proBNP <400 pg/mL) [20] and 26 presented with symptomatic but stable HF due to impaired left ventricular systolic function (New York Heart Association [NYHA] class II + III, LVEF ≤40%). All patients gave written

informed consent to participate in the study, and the protocol was approved by the local ethics committee.

Cardiorespiratory PG recordings were performed as described earlier [5] using a 6-channel device (Embletta^{TM}, Embla, Amsterdam, Netherlands). Nasal airflow, chest and abdominal efforts, finger pulse oximetry (averaging time: 4 seconds; sampling frequency: 3 hertz), ECG, snoring and body position were recorded continuously. The temporary loss of one channel, except nasal airflow, was deemed acceptable. Recordings were analysed using Remlogic™ software (Embla, Amsterdam, Netherlands) and reviewed by two separate sleep specialists not involved in the study. Apnoea was defined as a drop in nasal airflow by ≥90% of baseline for ≥90% of the event´s duration and ≥10 seconds. This apnoea was specified to be obstructive if there was a continued or increased inspiratory effort throughout the entire period of absent airflow. Hypopnoea was defined as a ≥50% fall from baseline in airflow signal for ≥90% of the event´s duration, ≥10 seconds and a ≥3% desaturation from pre-event baseline [21].

Cycle length (CL) was defined as the time from the beginning of an obstructive apnoea to the end of the following ventilation (figure 1); CL therefore represents the sum of an obstructive apnoea (AL) and the following ventilation (VL). Time from resumption of airflow to the following peak in airflow was defined as time to peak ventilation (TTPV). Circulatory delay (CD) was the time from the first breath after apnoea to the following nadir of oxygen saturation. Data on respiratory event length shown represent an average of 24 separate measurements obtained throughout the night [14].

Statistics
Continuous data are expressed as median or mean value ± SD. Statistical analyses were performed using SigmaPlot software (Version 12.0, Systat, Germany). Pearson Product Moment Correlation was used for correlation analysis. Differences between groups were analyzed using Mann-Whitney Rank Sum Test, t-test or Fisher Exact Test. A value of $p<0.05$ was considered statistically significant.

Results:

Patient characteristics

Demographic and clinical parameters for the 39 patients included in the study are shown in table 1. Other than OSA patients with HF (n=26) being younger, and baseline parameters used as inclusion criteria (LVEF, NT-proBNP), there were no differences between groups in baseline parameters.

Haemodynamic parameters

While cardiac index (CI) and aortic oxygen saturation were not statistically different between the two patient groups, those with HF had elevated mean arterial pressure (MAP), mean pulmonary artery pressure (PAP) and mean pulmonary capillary wedge pressure (PCWP), and lower mixed venous oxygen saturation compared with patients without HF (table 2).

Respiratory parameters

The total AHI and obstructive apnoea index (oAI) were comparable in both groups. There were no differences between those with and without HF in mean oxygen desaturations at night (table 2). All measured respiratory parameters were prolonged in patients with versus without HF: CL 37.8 ± 10.6 sec vs 46.0 ± 10.0 sec, p=0.024; VL 21.3 ± 7.1 sec vs 25.4 ± 6.3 sec, p=0.044; AL 16.5 ± 3.9 sec vs 20.5 ± 4.9 sec, p=0.013; TTPV 8.3 ± 2.5 sec vs 10.6 ± 3.0 sec, p=0.021 and CD 22.6 ± 3.7 sec vs 28.5 ± 7.5 sec, p=0.005 (figure 2).

Statistically significant correlations between CD and CL (r=0.531, p=0.005), VL (r=0.503, p=0.009), AL (r=0.434, p=0.027) and TTPV (r=0.576, p=0.002) were documented in patients with OSA and HF (OSA+HF); with increase in CD, respiratory event lengths prolonged (figure 3). Correlations between AL and the following ventilation period (VL) were significant in both patient groups (OSA−HF, r=0.863, p<0.001; OSA+HF, r=0.581, p=0.002); as apnoea duration increased, the following ventilation time was prolonged (figure 4).

Correlation between haemodynamic and respiratory parameters

There were no correlations between left ventricular function and respiratory parameters in OSA patients without HF. In contrast, significant and robust

correlations between respiratory and haemodynamic parameters were documented in OSA patients with HF; CL, VL and TTPV increased as pulmonary congestion (PCWP) worsened: CL r=0.53, p=0.006; VL r=0.55, p=0.004; TTPV r=0.47, p=0.015 (figure 5). Correlations between PCWP and AL (r=0.37, p=0.63) or CD (r=0.36, p=0.072) were not statistically significant.

Discussion:

The main findings of this study were a difference in OSA-related respiratory patterns (respiratory event lengths) in patients with and without HF, and a significant positive correlation between pulmonary congestion and respiratory event lengths in OSA patients with HF.

In general, respiratory event lengths were prolonged in HF patients compared to OSA patients without subjective and objective signs of HF. These differences in OSA respiratory patterns between patients with and without HF are consistent with the findings of Ryan et al [18] who investigated respiratory event lengths in 40 OSA patients with (n=22) or without (n=18) HF. However, the correlations between CD and other respiratory event lengths identified in our trial go beyond the results of the previous study [18]. With deterioration of cardiac function, as indicated by a lengthening in CD, respiratory event lengths like CL, VL, AL and TTPV were prolonged. Two other studies have reported different respiratory patterns in the presence and absence of HF in patients with CSA [17, 19].

HF itself is associated with an increase in circulation time and in the context of apnoeas with an increase in CD. Our results showed a progressive delay, with an increase in peripheral oxygen exhaustion indicated by lower mixed venous saturation.

The correlation between prolonged CD and TTPV as well as VL can be explained by the dynamic response to asphyxia in OSA patients [22] and the finding that CD results in hyperventilation [23]. The amplified response of peripheral chemoreceptors to a high carbon dioxide level causes hyperventilation. In patients without SDB, the

response of peripheral chemoreceptors to changes in blood gas tensions may not be as dynamic as that in patients with CSA or OSA.

The current study showed that longer VL is associated with a comparable lengthening of AL. This correlation between VL and AL may be interpreted in two different ways. Firstly, it might be due to changes in chemical control in OSA patients. The results of two previous studies showed that patients with untreated OSA have greater ventilatory instability and therefore a higher AHI [24, 25]. The chemical control system might be unstable in patients with OSA, probably because of altered sensitivity in the feedback loop (loop gain). Alternatively, the explanation may be the prolonged circulation time and higher carbon dioxide levels in HF patients. The longer circulation time leads to a delayed report of gas tensions and this contributes to a longer AL with associated increases in carbon dioxide levels and a prolonged time until reaching the apnoea threshold. A longer AL causes a longer VL, without a change in loop gain.

Another important finding of this study was documentation of a correlation between pulmonary congestion and respiratory event lengths. This is the first time that an interaction between HF severity and respiratory patterns in OSA has been reported. Despite these results, we were unable to demonstrate any correlations between PCWP and AHI, oAI or hypopnoea index (HI). An earlier study by our group also showed no correlations between PCWP or PAP and AHI, apnoea index (AI) or oAI in OSA patients (AHI >5/h) with HF [26]. In contrast, there were correlations between all these parameters for HF patients with CSA. Respiratory event lengths were not investigated. A correlation between PCWP and AHI was detected in 33 additional patients with CSA and HF [15].

Taken together, these results call the suitability of AHI as a marker of SDB severity into question. In HF patients, respiratory event lengths may provide a more precise estimate of disease severity in OSA. Furthermore, the conclusion that OSA is not dependent on HF severity is potentially unreliable [26].

In a recent study, Jafari and coworkers confirmed a fluid shift from the periphery towards the neck in patients with OSA. Because the AHI did not change, they

concluded that this rostral fluid shift had no significant impact on the severity of OSA [10]. Our previous [26] and current results show that AHI is not a good measure of OSA severity, at least in patients with HF. Routine measurements of respiratory event lengths could provide more insight into severity of SDB, regardless of whether the aetiology is being primarily obstructive or central.

The potential for HF to have an influence on OSA severity was shown in this study. Patterns of OSA depend on the degree of pulmonary congestion. Two other studies have also discussed links between OSA and HF. Cioffi and coworkers investigated the prevalence of left ventricular systolic dysfunction (LVSD) and OSA in 300 patients [27]. LVSD was significantly more prevalent in patients with OSA of any severity compared with those who did not have SDB. Although these results do not provide causative evidence, they do indicate a relationship of some sort. It has also been shown that OSA can impair left ventricular diastolic function, irrespective of other possible factors [28]. In combination, the findings of these different studies highlight the presence of a reciprocal relationship between OSA und HF.

Male gender also appears to be an independent risk factor for the development of OSA in younger adults [29, 30]. The results of the current study agree with these previous findings, with the group of patients having HF and OSA being significantly younger, and more likely to be male than those who have OSA without HF.

There are a number of limitations of this study. Multi-channel cardiorespiratory PG recordings were used and there was no polysomnography (PSG). Therefore, data on sleep, sleep quality and arousals are not available. This means that total AHI could be underestimated because total sleep time might be shorter than total recording time. In addition, because we could not detect arousal, hypopnoea scoring was only possible using airflow and oxygen saturation data. Nevertheless, for the purpose of measuring obstructive respiratory patterns, high quality PG recordings provide all the important information required. We tried to perform PG studies as close as possible to the time of invasive haemodynamic measurements. It is probably not feasible to perform a full PSG study in a sleep lab while a patient is awaiting or has just had cardiac catheterization. The small sample size is another limiting factor. Inclusion of 39 patients means that our study is similar to previous trials, but multivariate analysis

is not possible with this number of patients and potential confounding factors cannot be definitely ruled out. Therefore, further studies are required to more fully and accurately determine respiratory event lengths in patients with OSA and HF. Finally, follow-up (longitudinal) studies are required to investigate a potential dependency of respiratory event lengths and other respiratory or SDB parameters on cardiac function. How these parameters (type of SDB, graduation, event lengths etc) might change with deterioration or recovery of cardiac function is unclear and needs to be determined. This might open a possibility to monitor cardiac function in HF patients.

Conclusions:

We have shown that respiratory patterns in OSA are dependent on cardiac function. Impaired cardiac function is associated with an increase in respiratory event lengths. In patients with HF, some of these events correlate with the degree of pulmonary congestion. In light of these results, the AHI does not appear to be a good measure of SDB severity and respiratory impairment in patients with OSA and HF.

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Table 1: Demographic and clinical parameters

	OSA–HF (n = 13)	OSA+HF (n = 26)	P-value
Age (years)	72.7 ± 5.8	67.2 ± 9.4	0.019
Gender, male	6	18	n.s.
BMI (kg/m^2)	31.7 ± 6.6	30.6 ± 4.6	n.s.
NYHA class	2.5 ± 0.5	2.7 ± 0.5	n.s.
Systolic BP (mmHg)	136 ± 26	123 ± 14	n.s.
Diastolic BP (mmHg)	79 ± 12	73 ± 10	n.s.
Heart rate (bpm)	70 ± 8	71 ± 11	n.s.
LVEF (%)	55 ± 1	32 ± 6	<0.001
Medication (%)			
ACEI/ARB	77	96	n.s.
Diuretics	38	92	<0.001
Aldosterone antagonists	8	62	0.002
β-blockers	46	96	<0.001
Digitalis	0	8	n.s.
Amiodarone	0	8	n.s.
Statins	38	38	n.s.
CV risk factors (%)			
CAD	38	58	n.s.
Hypertension	85	73	n.s.
Diabetes	23	27	n.s.
Smoking (current, former)	15, 23	8, 38	n.s.
Laboratory findings			
NT-proBNP (pg/mL)	167 ± 106	1999 ± 1696	<0.001
Haemoglobin (g/dL)	14.0 ± 1.3	13.5 ± 1.6	n.s.
Haematocrit (%)	41.0 ± 4.0	40.1 ± 4.2	n.s.
Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	n.s.
hsCRP (mg/dL)	0.0 ± 0.4	0.7 ± 1.5	n.s.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; OSA–HF, obstructive sleep apnoea without heart failure (LVEF ≥50%, NT-proBNP <400 pg/mL); OSA+HF, obstructive sleep apnoea with heart failure (NYHA class II+III, LVEF ≤40%).

Table 2: Haemodynamic and respiratory results

|	OSA–HF (n=13)	OSA+HF (n=26)	P-value
Cardiac index (L/min/m^2)	2.3 ± 0.4	2.2 ± 0.6	n.s.
mRAP (mmHg)	3.9 ± 3.4	7.3 ± 5.4	n.s.
RVEDP (mmHg)	5.2 ± 3.4	7.6 ± 4.4	n.s.
PAP (mmHg)	18.8 ± 3.9	27.1 ± 10.4	0.011
mPCWP (mmHg)	9.5 ± 3.5	17.7 ± 8.5	0.003
MAP (mmHg)	102 ±14	90 ± 15	0.02
AO SaO$_2$ (%)	95.0 ± 2	95.5 ± 3	n.s.
PA SaO$_2$ (%)	72.0 ± 4	66.3 ± 7	0.012
AHI (h^{-1})	34.3 ± 27	32.3 ± 18	n.s.
oAI (h^{-1})	8.5 ± 8	10.0 ± 11	n.s.
HI (h^{-1})	21.6 ± 23	18.3 ± 9	n.s.
Mean SaO$_2$ (%)	90.0 ± 4.2	91.8 ± 2.4	0.041
Minimum SaO$_2$ (%)	78.0 ± 8.7	79.8 ± 6.4	n.s.
Mean desaturation (%)	6.0 ± 1.7	5.7 ± 1.6	n.s.

AHI, apnoea-hypopnoea index; AO SaO$_2$, aortic oxygen saturation; HI, hypopnoea index; MAP, mean arterial pressure; mPCWP, pulmonary capillary wedge pressure; mRAP, right atrial pressure; oAI, obstructive apnoea index; OSA–HF, obstructive sleep apnoea without heart failure (LVEF ≥50%, NT-proBNP <400 pg/mL); OSA+HF, obstructive sleep apnoea with heart failure (NYHA class II+III, LVEF ≤40%); PA SaO$_2$, oxygen saturation in the pulmonary artery; PAP, pulmonary artery pressure; RVEDP, right ventricular end-diastolic pressure; SaO$_2$, arterial oxygen saturation.

Figure legends

Figure 1. Scheme of respiratory event lengths in obstructive sleep apnoea (CD, circulatory delay; CL, cycle length; AL, apnoea length; VL, ventilation length; TTPV, time to peak ventilation).
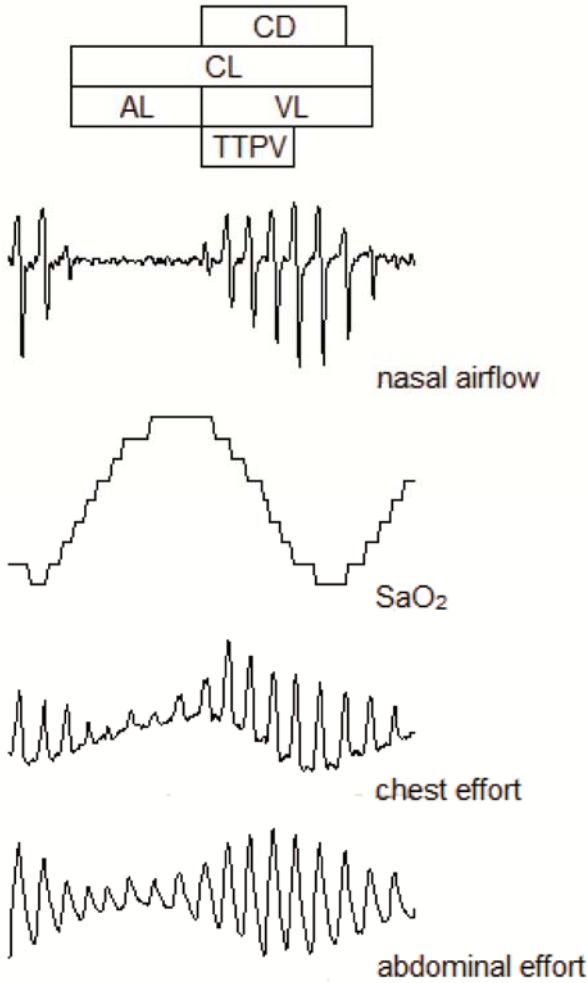
Figure 2. Differences in respiratory event lengths between obstructive sleep apnoea patients with (OSA+HF) and without (OSA–HF) heart failure.
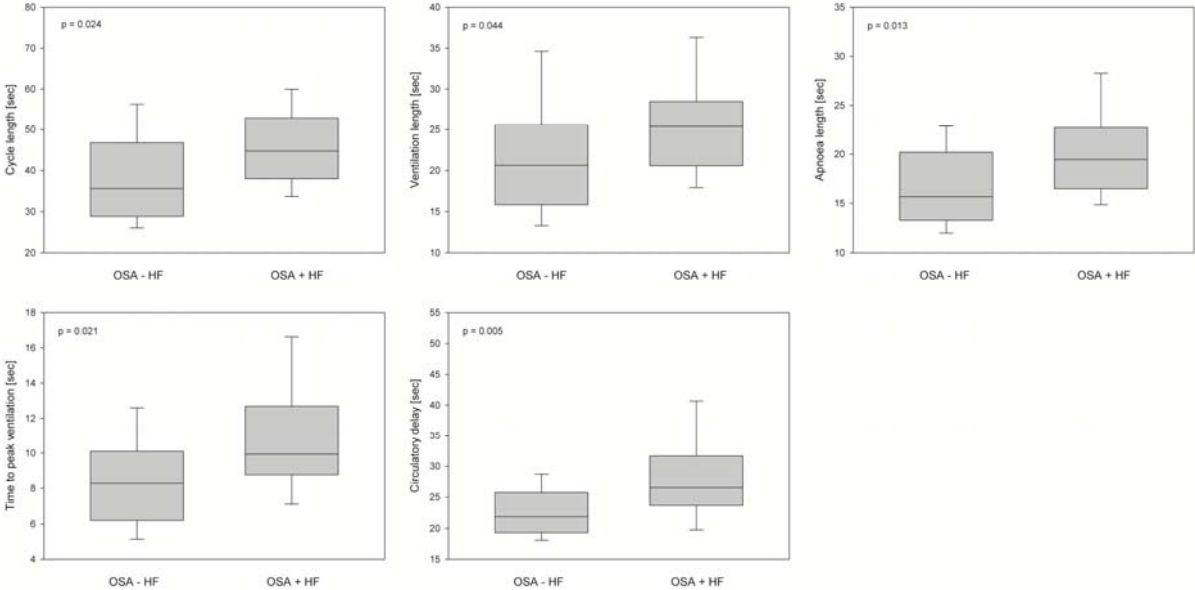
Figure 3. Correlations between circulatory delay and cycle length (A) or ventilation length (B) in obstructive sleep apnoea patients with heart failure.
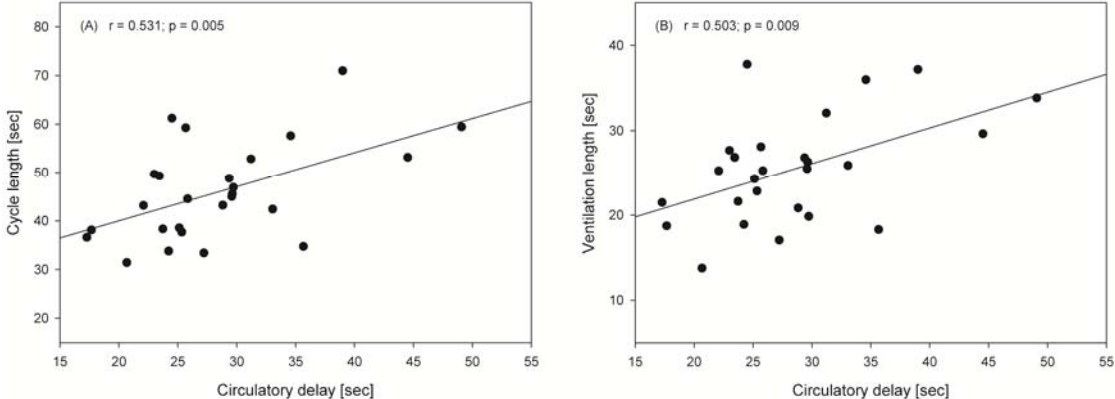
Figure 4. Correlations between ventilation lengths and apnoea lengths.
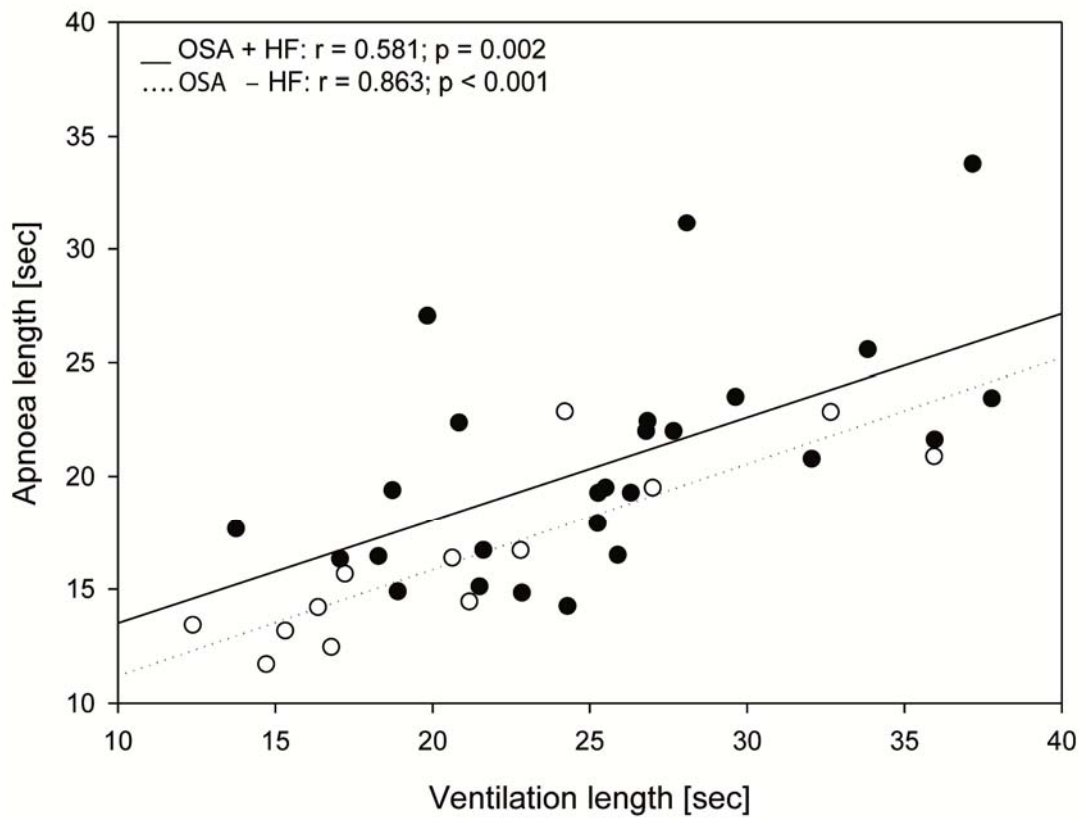
Figure 5. Correlations between pulmonary congestion (pulmonary capillary wedge pressure; PCWP) and respiratory event lengths.