Prolonged lung-to-finger circulation time indicates an increased risk of intermittent hypoxaemia in sleep apnoea patients

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Hypoxic severity is significantly higher with prolonged LFCt even with shorter respiratory events: considering proposed LFCt metrics could enable a more representative estimation of OSA severity and related cardiac impairments. https://bit.ly/4a67jh0

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Abstract

Introduction Intermittent hypoxaemia is closely associated with cardiovascular dysfunction and may be a more accurate indicator of obstructive sleep apnoea (OSA) severity than conventional metrics. Another key factor is the lung-to-finger circulation time (LFCt), defined as the duration from the cessation of a respiratory event to the lowest point of oxygen desaturation. LFCt serves as a surrogate marker for circulatory delay and is linked with cardiovascular function. Yet, the specific associations between respiratory and hypoxaemia characteristics and LFCt in patients with OSA remain unclear. This study aims to investigate these associations, ultimately contributing to a more nuanced understanding of OSA severity.

Methods The study comprised 878 in-lab polysomnographies of patients with suspected OSA. The conventional OSA metrics were computed along with nine hypoxaemia metrics and then divided into quartiles (Q1–Q4) based on respiratory event duration. In addition, these were further divided into subquartiles based on LFCt. The empirical cumulative distribution functions (CDFs) and linear regression models were used to investigate the association between desaturation metrics and LFCt.

Results The results showed that prolonged LFCt was associated with increased hypoxic severity. Based on CDFs, the hypoxic severity significantly increased with longer LFCt despite the duration of respiratory events. Furthermore, fall duration was elevated in patients with longer LFCt (Q1- desaturation fall duration (FallDur): 14.6 s; Q4-FallDur: 29.8 s; $p<0.0001$). The regression models also showed significant association between hypoxic severity and LFCt (Q1-desaturation fall slope (FallSlope): $\beta=-3.224$; Q4-FallSlope: $\beta=-6.178$; $p<0.0001$).

Discussion Considering LFCt along with desaturation metrics might be useful in estimating the association between the severity of OSA, physiological consequences of respiratory events and cardiac health.

Introduction

Obstructive sleep apnoea (OSA), characterised by nocturnal upper airway blockages, is a recognised chronic disorder and affects almost 1 billion adults worldwide [1]. In OSA, respiratory events (*i.e.* apnoeas and hypopnoeas) often cause recurrent episodes of intermittent hypoxaemia, leading to oxidative stress, increased sympathetic nerve activity, decreased stroke volume, and acute pulmonary and systemic hypertension [2, 3]. OSA is also a recognised risk factor for cardiovascular stress, coronary artery disease and heart failure [4, 5]. Moreover, the nocturnal chronic intermittent hypoxaemia induced by OSA can lead to an increased heart rate and, subsequently, cardiac arrhythmia [5–7].

Polysomnography (PSG) is the gold standard for diagnosing OSA and assessing its severity. In addition, several studies have demonstrated a correlation between circulation time, as derived from PSG and cardiac output, suggesting its potential as a marker for cardiovascular dysfunction. Despite this, circulation time is seldom utilised in sleep medicine [8–10]. Therefore, incorporating PSG-derived markers into the assessment of cardiac health could offer valuable insights into the prognosis of cardiovascular health in patients with OSA.

Typically, cardiac output is measured through nuclear medicine, ultrasound or magnetic resonance imaging techniques [11, 12]. However, cardiac output can also be easily estimated from PSG readings using the lung-to-finger circulation time (LFCt) of oxygen [8]. LFCt is a noninvasive physiological measure that indicates the traveling time of oxygenated blood from the lung to the fingertip [8], with longer LFCts indicating circulatory delay [9]. When LFCt is derived from a sleep study, it is calculated as the time from the end of a respiratory event to the nadir of the associated oxygen desaturation event [10]. Therefore, prolonged LFCt might be a novel marker to describe the physiological consequences of respiratory events and the severity of intermittent hypoxaemia [13].

The apnoea–hypopnoea index (AHI) is commonly used to quantify the severity of OSA [14] and the oxygen desaturation index (ODI) is used to quantify the hypoxic severity in patients with OSA. However, both AHI and ODI fail to account for the physiological consequences of individual respiratory events [15–17]. Conversely, detailed characterisation of the peripheral oxygen saturation (SpO_2) signal has been suggested to better describe the hypoxic severity and the association between cardiovascular disease and OSA [18–20]. Therefore, considering novel SpO_2-based metrics could prove a more representative estimation of the severity of OSA. For instance, calculating the area under the SpO_2 curve from a normal baseline reference (*i.e.* the onset of the desaturation event) or using 100% SpO_2 as a reference has shown promising results to determine the hypoxic severity in patients with OSA [21, 22] and has illustrated a strong connection with the cardiovascular consequences in patients with OSA [23].

Furthermore, previous studies showed that the PSG-derived LFCt can predict the cardiovascular mortality in patients with OSA [19, 24]. However, the specific associations between characteristics of respiratory events and desaturation events with LFCt remain unclear. Therefore, by investigating these less explored areas, we might find an additional utility of LFCt in sleep studies. In this study, the main hypothesis was that the increased severity of respiratory events and desaturation events are associated with longer LFCt. Hence, we aimed to investigate whether a prolonged LFCt describes the hypoxic severity and the severity of respiratory events.

Methods

Dataset

This retrospective study comprised 912 PSG recordings of patients with suspected OSA, conducted at the Sleep Disorders Centre, Princess Alexandra Hospital (Brisbane, Australia) between January 2011 and December 2017. The PSGs were conducted using the Compumedics Grael acquisition system and scored manually by experienced sleep technologists using Profusion PSG 4 software (Compumedics, Abbotsford, Australia). The arterial oxygen saturations were recorded using a transmissive Nonin Xpod 3011 (Minneapolis, USA) finger pulse oximeter. A respiratory event was scored as apnoea if the duration of $\geqslant$90% drop in peak signal in the thermal sensor was $\geqslant$10 seconds [14]. Hypopnoea was scored if the amplitude of the nasal pressure signal dropped $\geqslant$30% from the pre-event baseline for $\geqslant$10 seconds and was associated with $\geqslant$3% desaturation or arousal [14]. SpO_2 readings below 50% were not considered quantitatively reliable and were thus removed from the analyses as artifacts [25]. The Human Research Ethics Committee of the Princess Alexandra Hospital approved this retrospective data collection and analysis (HREC/16/QPAH/021 and LNR/2019/QMS/54313).

Respiratory event-specific LFCts were computed separately for apnoeas and hypopnoeas in MATLAB (R2022b, MathWorks, Natick, MA, USA). In both cases, respiratory event-associated LFCts were calculated from the point where a respiratory event ended to the lowest point of the accompanying desaturation event (figure 1). We observed a few negative LFCt events, *i.e.* an apnoea or hypopnoea that continued after the nadir of the associated desaturation event. Nevertheless, all LFCts were included in the analyses except nonphysiological outliers (n=3) where LFCts were >55 s. Patients with incomplete PSGs (n=34) were removed from further analysis (figure 2). The remaining 878 patients, with a total of 69 559 respiratory events and subsequent desaturation events, were included in the analysis. For clarity, the results related to apnoea events are presented in this paper and the results related to hypopnoea events are presented in the Supplementary material.

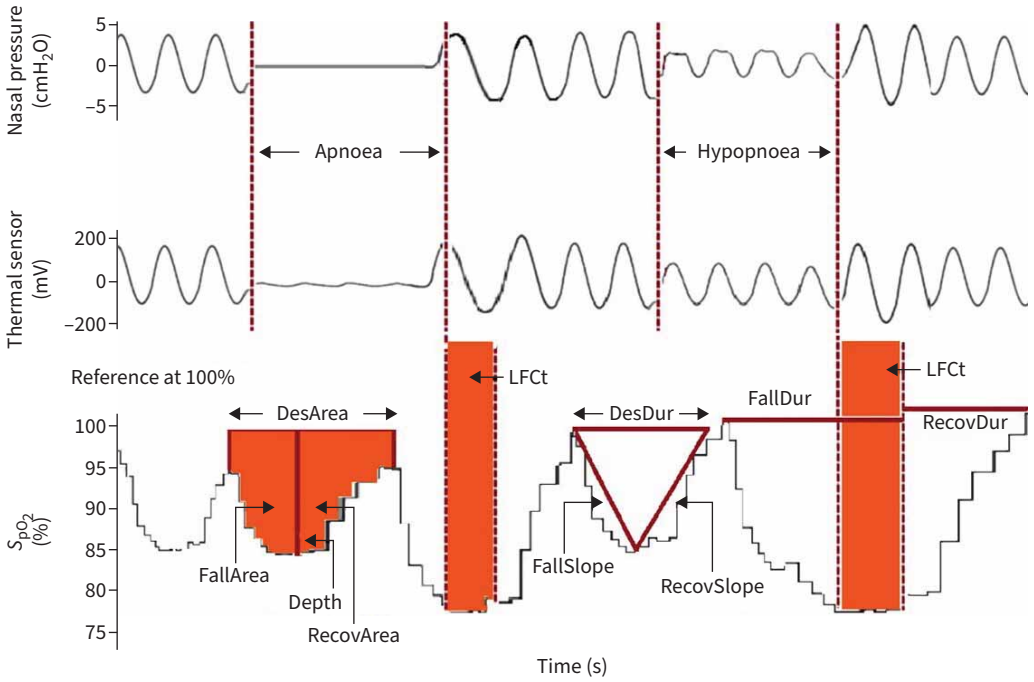

FIGURE 1 Schematic visualisation of computed peripheral oxygen saturation (SpO_2) signal-based parameters. Depth: desaturation depth from 100% reference; DesArea: desaturation area from 100% reference; DesDur: duration of an entire desaturation event; FallArea: fall area from 100% reference; FallDur: duration of the falling period of desaturation; FallSlope: desaturation fall slope; LFCt: lung-to-finger circulation time; RecovArea: recovery area from 100% reference; RecovDur: duration of the recovery period; RecovSlope: resaturation recovery slope.

Parameters

First, we calculated the conventional OSA metrics, *i.e.* AHI, ODI and arousal index (ArI), to describe the severity of OSA. Then, we calculated the following oxygen saturation-based parameters for all patients: average SpO_2, time spent below 90% SpO_2 ($T_{90\%}$) during sleep, median desaturation area, median fall area and median recovery area. In addition, we computed the following desaturation parameters event-wise: median desaturation area (DesArea), desaturation fall area (FallArea), desaturation recovery area (RecovArea), desaturation depth (Depth), desaturation duration (DesDur), desaturation fall duration (FallDur), desaturation fall slope (FallSlope), resaturation duration (RecovDur) and resaturation recovery slope (RecovSlope). For all event-wise desaturation parameters, a 100% SpO_2 level was used as a baseline (figure 1). DesArea, FallArea, RecovArea and Depth were calculated using the same method as in Pahari et al. [21]. DesDur describes the duration of an entire desaturation event while FallDur was the time difference from the onset of desaturation to the nadir, and the RecovDur from the nadir to the offset of a desaturation event. In addition, we also computed the desaturation, and resaturation differences and normalised them with FallDur and RecovDur to obtain FallSlope and RecovSlope, respectively. The calculations of the desaturation parameters are illustrated in figure 1.

Statistical analyses

In the first part of the analysis, the included 878 patients were divided into quartiles (Q1–Q4) based on the LFCt (figure 2). In the second part, all 18 752 apnoea events were pooled together and apnoea-related desaturation events were divided into quartiles (Q1–Q4) based on LFCts (figure 2). In the third part, apnoea-related desaturation events were first divided into quartiles (Q1–Q4) based on apnoea event duration. Then, the shortest and longest apnoeas (*i.e.* Q1 and Q4, respectively) were further divided into subquartiles based on LFCts (figure 2). In both patient-wise and event-wise analyses, the calculated parameters were compared between quartiles using the Wilcoxon rank sum test. Additionally, the empirical cumulative distribution functions (CDFs) were used to compare parameter values between quartiles, and the statistical significance of differences was evaluated with the Kolmogorov-Smirnov test. A p-value of <0.05 was used as the threshold for statistical significance.

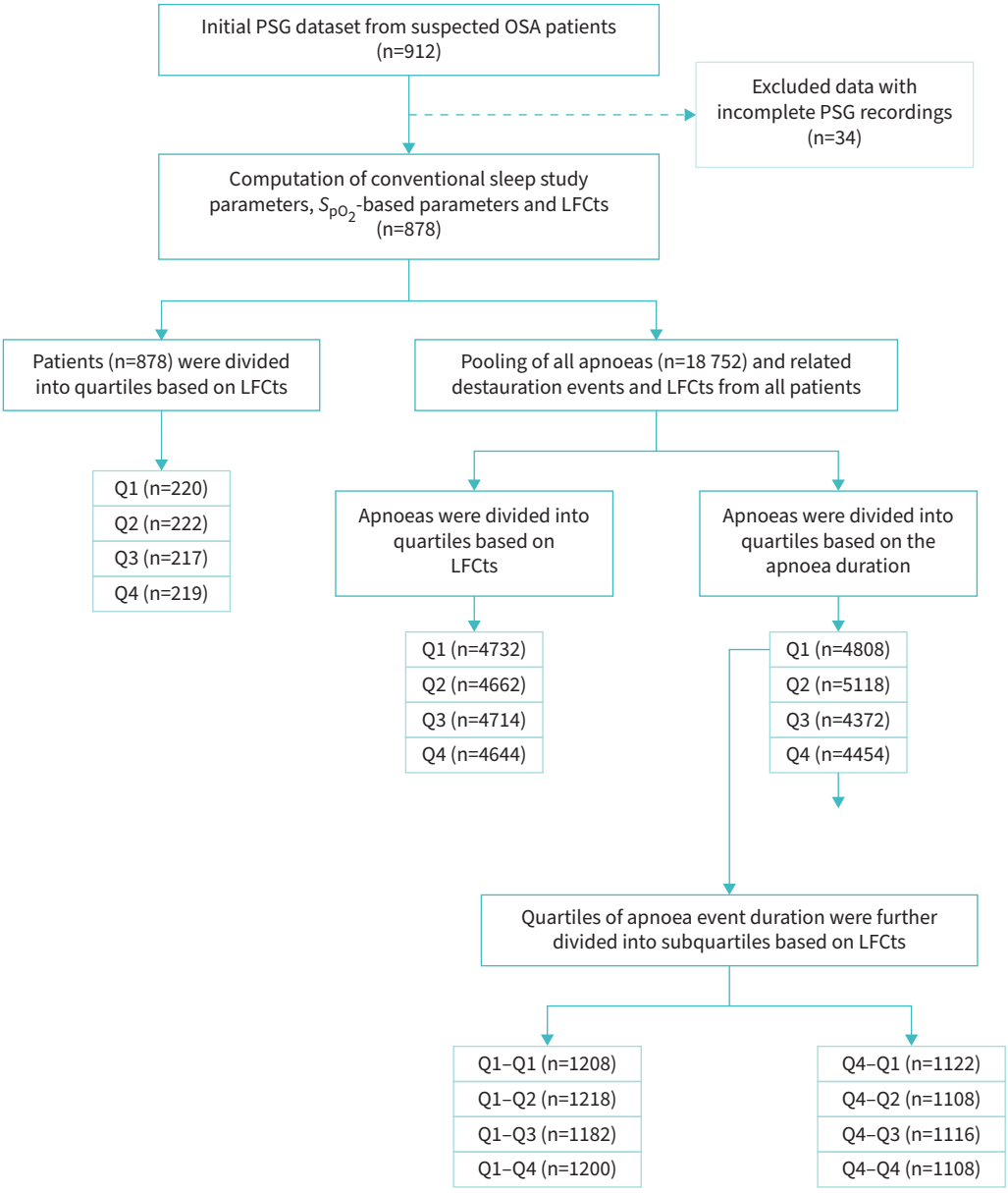

FIGURE 2 Flowchart of the analyses performed. LFCt: lung-to-finger circulation time; OSA: obstructive sleep apnoea; PSG: polysomnography; SpO_2: peripheral oxygen saturation.

Linear regression models were used to investigate the associations between desaturation parameters, respiratory events and LFCts. In these models, the LFCt was used as a continuous dependent variable. All predictive parameters were normalised by the maximum value of each parameter. Additionally, the regression coefficients (β-values) were further scaled to the 10% change in the parameter values. All parametric computations and statistical comparisons were performed with MATLAB (R2022b, MathWorks, Natick, MA, USA). Finally, a similar analysis was performed with hypopnoea-related events (Supplementary material).

Results

Patient-wise LFCt division

The study population was mostly middle-aged (median 55.9 yr.) and obese (median body mass index 34.4 $kg \cdot m^{-2}$). In patient-wise analyses, AHI, ODI and ArI were significantly higher in patients with longer LFCts. $T_{90\%}$ significantly decreased in Q4. Consequently, the hypoxic severity was also significantly higher and total sleep time lower in patients with longer LFCts (table 1). Atrial dysrhythmia, cerebral

TABLE 1 Demographic information, polysomnography and SpO_2-based parametric information presented as median (interquartile range)

Parameters	All (n=878)	Q1 (n=220) <11.0 s	Q2 (n=222) 11.0–14.6 s	Q3 (n=217) 14.6–18.9 s	Q4 (n=219) >18.9 s
Age (year)	55.9 (44.7–65.8)	48.0 (36.9–59.2)	55.0* (45.2–63.5)	56.7* (46.9–67.1)	61.8* (50.8–69.9)
BMI ($kg·m^{-2}$)	34.4 (29.3–40.4)	33.7 (27.7–40.2)	34.9 (29.8–41.3)	34.5 (29.3–40.7)	34.8 (30.1–39.6)
TST (min)	306 (252–360)	336 (276–384)	306* (252–354)	300* (252–360)	282* (240–342)
AHI ($events·h^{-1}$)	18.9 (8.4–39.8)	10.6 (4.7–23.3)	19.7* (10.1–48.6)	24.7* (10.8–48.6)	24.0* (12.0–42.6)
ODI ($events·h^{-1}$)	12.1 (3.6–29.1)	4.9 (1.4–14.8)	11.8* (4.1–29.6)	16.5* (5.3–30.8)	18.6* (6.7–32.7)
ArI ($events·h^{-1}$)	26.7 (18.0–41.9)	21.8 (15.1–32.4)	28.6* (19.2–41.3)	29.1* (20.7–48.1)	28.1* (18.6–45.9)
$T_{90\%}$ (s)	331.8 (30.8–2642.7)	68.3 (7.2–834.5)	317.4* (28.9–2533.4)	730.3* (83.7–4259.8)	578.0* (90.9–3462.8)
Average SpO_2 (%)	93.1 (90.4–95.2)	94.2 (91.6–96.0)	93.2* (90.6–95.2)	92.6* (89.6–94.9)	92.7* (89.8–94.8)
Smoking status and comorbidities					
Smoker, n (%)	141 (16.1%)	43 (19.5%)	44 (19.8%)	29 (13.4%)	25 (11.4%)*
Depression, n (%)	180 (20.5%)	55 (25.0%)	44 (19.8%)	44 (20.3%)	37 (16.9%)*
Anxiety, n (%)	72 (8.2%)	27 (12.3%)	17 (7.7%)	20 (9.2%)	8 (3.7%)*
Hypertension, n (%)	367 (41.8%)	70 (31.8%)	86 (38.7%)	99 (45.6%)*	112 (51.1%)*
Atrial dysrhythmia, n (%)	95 (10.8%)	14 (6.4%)	12 (5.4%)	30 (13.8%)*	39 (17.8%)*
CVA, n (%)	41 (4.7%)	8 (3.6%)	11 (4.9%)	8 (3.7%)	14 (6.4%)
Cardiac failure, n (%)	22 (2.5%)	3 (1.4%)	4 (1.8%)	8 (3.7%)	7 (3.2%)
Respiratory failure, n (%)	25 (2.8%)	4 (1.8%)	5 (2.3%)	9 (4.1%)	7 (3.2%)
COPD, n (%)	95 (10.8%)	18 (8.2%)	21 (9.5%)	26 (11.9%)	30 (13.7%)

The quartiles are formed patient-wise based on the median lung-to-finger circulation time (LFCt). The statistical comparison between continuous parameters was evaluated by the Wilcoxon rank sum test and between categorical variables using the chi-squared test. Q: quartile; BMI: body mass index; TST: total sleep time; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; ArI: arousal index; $T_{90\%}$: time spent under 90% oxygen saturation; SpO_2: average peripheral oxygen saturation; CVA: cerebral vascular accident. *: Statistically significant ($p<0.0001$) difference between quartiles (Q1 vs Q2, Q3, and Q4);

vascular accidents, cardiac failure, respiratory failure, hypertension and COPD were more common in patients with longer LFCts (table 1). In Q1, 31.8% of the population had hypertension while the prevalence increased to 51.1% ($p<0.05$) in the Q4 population. Similarly, only 6.4% of the population in Q1 had a history of atrial dysrhythmia while it significantly increased to 17.8% in Q4.

Apnoea-wise LFCt division

The apnoea duration increased with prolonged LFCts in Q4 compared with Q1. The longer LFCts were also associated with a greater desaturation area and fall area due to a significantly longer fall duration (table 2). In addition, fall slopes were significantly more gentle and recovery areas were smaller in Q4 compared with Q1; indicating deeper and longer desaturation events and a faster recovery period in Q4 compared with Q1 (table 2).

TABLE 2 Apnoea-related oxygen saturation signal-based parameters presented as median (interquartile range)

Parameters	All events (n=18 752)	Q1 (n=4732) <12.9 s	Q2 (n=4662) 12.9–17.8 s	Q3 (n=4714) 17.8–22.9 s	Q4 (n=4644) >22.9 s
LFCt (s)	17.8 (12.9–22.9)	9.1 (3.7–11.2)	15.5* (14.3–16.7)	20.3* (19.1–21.5)	27.2* (24.8–31.7)
ApnoeaDur (s)	25.0 (18.0–33.0)	26.0 (18.0–35.0)	22.0* (17.0–29.0)	24.0* (19.0–31.0)	28.0* (21.0–35.0)
DesDur (s)	28.0 (21.0–35.0)	27.0 (20.0–36.0)	29.0* (23.0–37.0)	33.0* (27.0–41.0)	41.0* (31.0–51.0)
FallDur (s)	21.4 (14.3–30.2)	14.6 (9.9–21.9)	18.1* (13.1–25.4)	23.7* (18.2–30.6)	29.8* (22.0–39.1)
RecovDur (s)	9.9 (7.8–12.6)	10.8 (8.2–14.6)	10.1* (8.2–12.3)	9.0* (7.4–11.4)	10.1* (7.9–12.5)
DesArea (s%)	281.9 (180.8–435.4)	227.7 (142.9–356.2)	274.7* (178.4–414.8)	294.5* (191.9–456.4)	334.2* (225.4–489.4)
FallArea (s%)	181.4 (107.4–303.4)	121.7 (71.8–208.9)	164.4* (104.4–276.8)	205.1* (128.6–329.1)	246.3* (156.0–371.4)
RecovArea (s%)	90.4 (58.8–135.5)	97.6 (60.9–148.7)	99.7 (64.5–143.9)	82.3* (53.9–125.6)	84.9* (58.6–121.6)
Depth (%)	13.1 (9.4–19.4)	11.9 (8.6–17.8)	14.3* (9.7–20.3)	13.4* (9.5–19.8)	13.1* (9.8–19.1)
FallSlope ($s·\%^{-1}$)	0.43 (0.27–0.66)	0.48 (0.32–0.75)	0.52* (0.34–0.79)	0.41* (0.27–0.61)	0.32* (0.22–0.51)
RecovSlope ($s·\%^{-1}$)	0.86 (0.50–1.43)	0.66 (0.37–1.12)	0.91* (0.54–1.51)	1.01* (0.62–1.61)	0.88* (0.53–1.46)

The quartiles are formed based on lung-to-finger circulation time (LFCt). Q: quartile; LFCt: lung-to-finger circulation time; ApnoeaDur: duration of an apnoea event; DesDur: duration of an entire desaturation event; FallDur: duration of the falling period of desaturation; RecovDur: duration of the recovery period; DesArea: desaturation area from 100% reference; FallArea: fall area from 100% reference; RecovArea: recovery area from 100% reference. Depth: desaturation depth from 100% reference; FallSlope: desaturation fall slope; RecovSlope: resaturation recovery slope. *: Statistically significant ($p<0.0001$) difference between quartiles (Q1 vs Q2, Q3 and Q4); the statistical comparison was done by the Wilcoxon rank sum test.

TABLE 3 Oxygen saturation signal-based parameters for shortest apnoea events (Q1 apnoea duration <18.0 s) presented as median (interquartile range)

Parameters	All events (n=4808)	Q1–Q1 (n=1208) LFCt <12.9 s	Q1–Q2 (n=1218) LFCt 12.9–16.4 s	Q1–Q3 (n=1182) LFCt 16.4–20.7 s	Q1–Q4 (n=1200) LFCt >20.7 s
LFCt (s)	16.4 (12.9–20.7)	10.3 (7.9–11.8)	14.7* (13.9–15.6)	18.5* (17.4–19.5)	24.9* (22.3–30.4)
ApnoeaDur (s)	15.0 (13.0–17.0)	15.0 (13.0–17.0)	15.0 (13.0–17.0)	16.0* (14.0–17.0)	16.0* (14.0–17.0)
DesDur (s)	24.0 (19.0–28.0)	21.0 (16.0–24.0)	22.0* (19.0–26.0)	25.0* (22.0–28.0)	28.0* (23.0–35.0)
FallDur (s)	13.7 (9.9–18.3)	10.1 (7.7–12.9)	12.1* (9.8–14.8)	15.8* (12.9–18.9)	19.1* (145.3–23.8)
RecovDur (s)	9.0 (7.3–11.4)	9.5 (7.5–11.9)	9.5 (7.8–11.8)	8.4* (7.2–10.6)	8.5* (6.9–11.0)
DesArea (s%)	206.6 (136.4–299.2)	195.9 (121.4–291.6)	222.6* (138.6–302.8)	192.8 (133.7–281.6)	218.4* (154.0–319.2)
FallArea (s%)	118.7 (76.1–178.1)	96.6 (58.5–151.1)	117.9* (72.3–167.6)	117.7* (83.6–174.9)	146.9* (95.6–215.6)
RecovArea (s%)	80.1 (49.9–126.6)	93.6 (57.1–138.9)	99.5 (61.2–139.7)	65.9* (44.1–107.9)	68.6* (45.4–107.9)
Depth (%)	12.1 (8.7–17.6)	12.9 (9.0–19.8)	14.1 (9.3–18.7)	10.9* (8.2–15.5)	11.1 (8.4–15.7)
FallSlope (s·%$^{-1}$)	0.52 (0.34–0.84)	0.68 (0.45–1.23)	0.65* (0.44–1.04)	0.45* (0.31–0.65)	0.37* (0.25–0.57)
RecovSlope (s·%$^{-1}$)	0.77 (0.47–1.20)	0.76 (0.44–1.33)	0.80 (0.48–1.16)	0.78 (0.52–1.19)	0.74 (0.43–1.19)

The subquartiles are formed based on lung-to-finger circulation time (LFCt). Q: quartile; LFCt: lung-to-finger circulation time; ApnoeaDur: duration of an apnoea event; DesDur: duration of an entire desaturation event; FallDur: duration of the falling period of desaturation; RecovDur: duration of the recovery period; DesArea: desaturation area from 100% reference; FallArea: fall area from 100% reference; RecovArea: recovery area from 100% reference; Depth: desaturation depth from 100% reference; FallSlope: desaturation fall slope; RecovSlope: resaturation recovery slope. *: Statistically significant (p<0.0001) difference between quartiles (*i.e.* Q1–Q1 vs Q1–Q2, Q1–Q3, Q1–Q4 and Q4–Q1 vs Q4–Q2, Q4–Q3, Q4–Q4); the statistical comparison was evaluated by the Wilcoxon rank sum test.

Apnoea-wise duration and LFCt division

Apnoeas were significantly longer in Q4 compared with Q1 in apnoea-based quartiles. When the apnoea event duration-based quartiles Q1 and Q4 were further divided into subquartiles based on LFCts; the hypoxic severity was higher in Q1–Q4 compared with Q1–Q1 and in Q4–Q4 compared with Q4–Q1. Although the apnoea durations were similar in the different LFCt-based subquartiles, DesDur and FallDur were significantly elevated when LFCt increased (table 3 and table 4). Consequently, DesArea, FallArea and RecovSlope increased while RecovArea and FallSlope decreased as a function of LFCt (table 3 and table 4, figure 3 and figure 4).

Cumulative distribution function and regression analyses

Based on CDFs, DesDur, FallDur, DesArea and FallArea were significantly higher, and FallSlope was more gentle in Q1–Q4 and Q4–Q4 compared with Q1–Q1 and Q4–Q1, respectively (figure 5). The CDF results also illustrated that even short apnoea events can cause severe desaturation and this phenomenon can be captured by LFCt (figure 5).

TABLE 4 Oxygen saturation signal-based parameters for longest apnoea events (Q4 apnoea duration >33.0 s) presented as median (interquartile range)

Parameters	All events (n=4454)	Q4–Q1 (n=1122) LFCt <11.5 s	Q4–Q2 (n=1108) LFCt 11.5–18.4 s	Q4–Q3 (n=1116) LFCt=18.4–24.6 s	Q4–Q4 (n=1108) LFCt >24.6 s
LFCt (s)	18.4 (11.6–24.6)	6.4 (−5.9–9.5)	15.2* (13.4–16.9)	21.4* (19.9–22.8)	29.4* (26.5–33.3)
ApnoeaDur (s)	40.0 (36.0–47.0)	41.0 (37.0–49.0)	40.0 (36.0–47.0)	40.0 (36.0–48.0)	40.0 (37.0–46.0)
DesDur (s)	47.0 (38.0–56.0)	39.5 (27.0–50.0)	46.0* (39.0–54.0)	48.0* (41.0–56.0)	53.0* (46.0–60.0)
FallDur (s)	35.2 (26.3–43.8)	23.9 (14.6–33.0)	33.8* (27.7–41.6)	37.9* (31.6–44.8)	41.7* (34.6–48.6)
RecovDur (s)	10.9 (8.7–14.1)	12.7 (9.4–17.9)	10.9* (9.1–14.1)	9.5* (7.3–12.6)	10.9* (9.3–12.9)
DesArea (s%)	408.4 (277.3–632.4)	306.5 (187.0–511.4)	422.5* (305.1–686.4)	468.1* (319.9–705.5)	427.5* (315.9–610.2)
FallArea (s%)	296.2 (185.7–477.9)	180.4 (101.9–290.6)	312.8* (209.6–521.9)	354.4* (244.7–562.8)	330.1* (236.3–493.4)
RecovArea (s%)	103.6 (71.6–156.5)	113.5 (72.2–179.9)	117.2 (82.9–169.2)	100.3* (66.9–150.8)	92.7* (69.4–128.6)
Depth (%)	14.5 (10.5–21.6)	11.9 (8.9–17.3)	16.3* (11.0–23.9)	16.9* (11.6–23.9)	14.1* (10.9–19.7)
FallSlope (s·%$^{-1}$)	0.34 (0.22–0.50)	0.36 (0.24–0.54)	0.39* (0.26–0.57)	0.36 (0.24–0.51)	0.27* (0.20–0.40)
RecovSlope (s·%$^{-1}$)	0.94 (0.53–1.57)	0.57 (0.33–0.99)	1.13* (0.60–1.81)	1.18* (0.73–1.97)	0.95* (0.62–1.45)

The subquartiles are formed based on lung-to-finger circulation time (LFCt). Q: quartile; LFCt: lung-to-finger circulation time; ApnoeaDur: duration of an apnoea event; DesDur: duration of an entire desaturation event; FallDur: duration of the falling period of desaturation; RecovDur: duration of the recovery period; DesArea: desaturation area from 100% reference; FallArea: fall area from 100% reference; RecovArea: recovery area from 100% reference; Depth: desaturation depth from 100% reference; FallSlope: desaturation fall slope; RecovSlope: resaturation recovery slope. *: Statistically significant (p<0.0001) difference between quartiles (*i.e.* Q1–Q1 vs Q1–Q2, Q1–Q3, Q1–Q4 and Q4–Q1 vs Q4–Q2, Q4–Q3, Q4–Q4); the statistical comparison was evaluated by the Wilcoxon rank sum test.

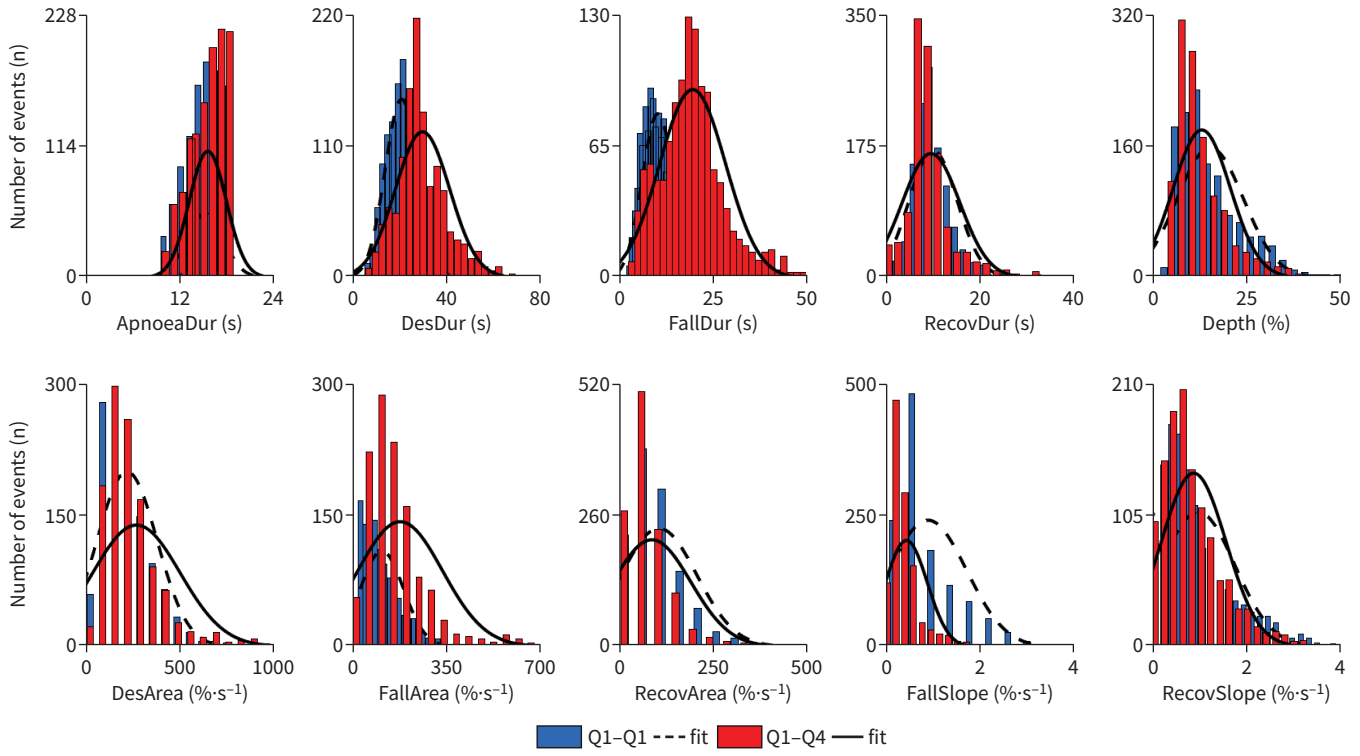

FIGURE 3 Histogram of apnoea-related oxygen saturation signal parameters related to all shortest (Q1 <18.0 s) apnoeas and related desaturation events. The events were divided into quartiles (Q1–Q4) based on apnoea duration, where Q1 was the shortest and Q4 the longest duration. The shortest apnoea duration-related events, *i.e.* Q1, were further divided into subquartiles based on lung-to-finger circulation times (LFCts) (Q1–Q4). Only the shortest and longest LFCt-based subquartiles, *i.e.* Q1–Q1 and Q1–Q4, are included here. Please note the different scales used for each parameter. ApnoeaDur: duration of an apnoea event; Depth: desaturation depth from 100% reference; DesArea: desaturation area from 100% reference; DesDur: duration of an entire desaturation event; FallArea: fall area from 100% reference; FallDur: duration of the falling period of desaturation; FallSlope: desaturation fall slope; fit: histogram plot with a distribution fit; LFCt: lung-to-finger circulation time; Q1–Q1: quartiles with the shortest apnoea duration and the shortest LFCt; Q1–Q4: quartiles with the shortest apnoea duration and the longest LFCt; RecovArea: recovery area from 100% reference; RecovDur: duration of the recovery period; RecovSlope: resaturation recovery slope.

The regression analyses also showed that hypoxic severity is strongly associated with LFCt. FallDur had a significant association with prolonged LFCt, and LFCt was elevated up to 0.5 s when the longest apnoea-related desaturation events (Q4-apnoea) were investigated separately with regression models (table 5). A 10% decrease in FallSlope increased the LFCt up to 3.22 s. When only the longest apnoea-related events were included in the models, the 10% decrease in FallSlope elevated the LFCt up to 6.17 s (table 5). A decrease in apnoea duration was also significantly associated with longer LFCts; however, we consider this change in LFCt (<0.01 s) to be clinically insignificant.

Hypopnoea analyses

The observations related to hypopnoeas were in line with those of apnoeas (see Supplementary material). Longer LFCts were associated with more severe desaturation events, even in the case of short hypopnoea events (Supplementary Tables S1 and S2; Supplementary Figures S2, S3 and S4). In contrast, LFCt increased up to 1.91 s when the RecovSlope increased by 10% in hypopnoea-related desaturation events and elevated up to 5.08 s when only the longest hypopnoea-related desaturation events were considered in the models (Table S3). In general, we observed that hypoxic severity was higher with a similar length of apnoeas in apnoea-related desaturation events compared with hypopnoea-related desaturation events (table 3, table 4 and Table S2).

Discussion

In this study, we investigated whether there is an association between LFCt, hypoxic severity and duration of respiratory events. The results revealed a strong association of hypoxic severity with LFCt length. Prolonged LFCt was significantly linked with increased desaturation duration and fall duration; and

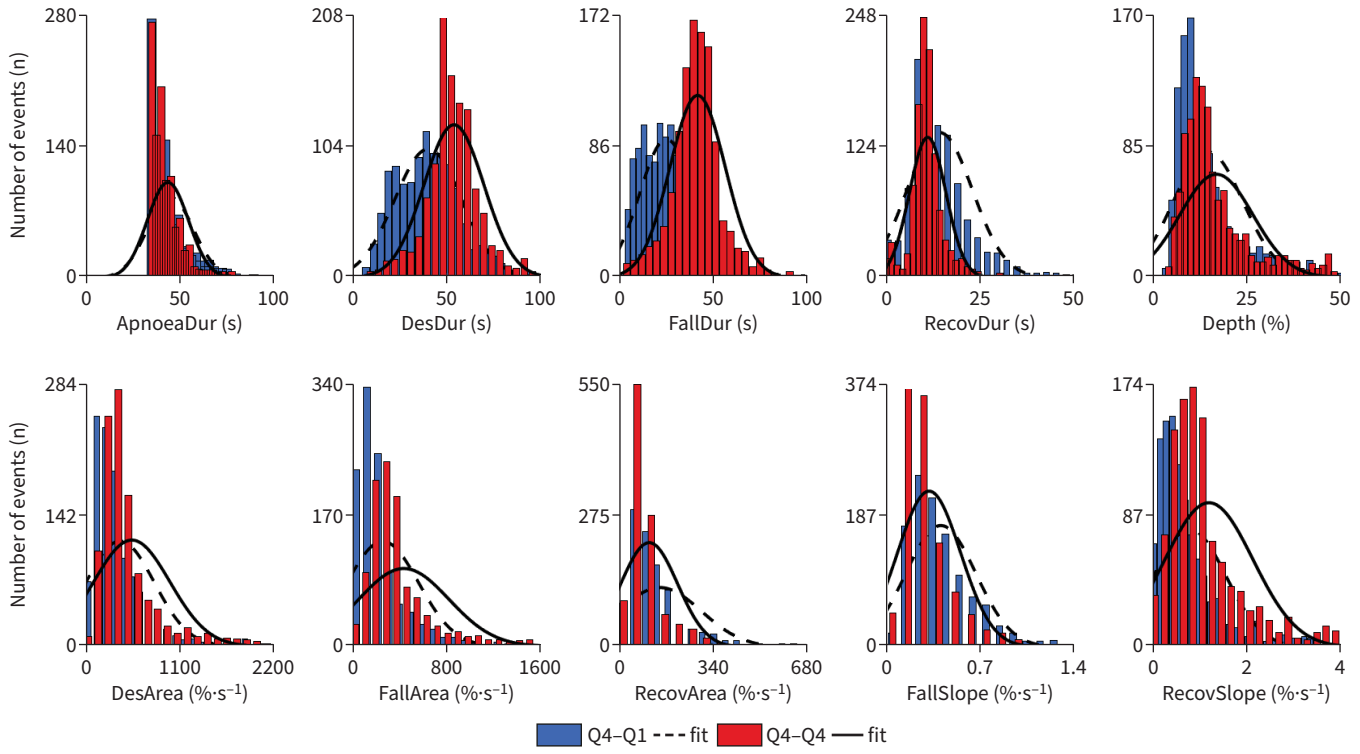

FIGURE 4 Histogram of apnoea-related oxygen saturation signal parameters related to all longest (Q4 >33.0 s) apnoeas and related desaturation events. The events were divided into quartiles (Q1–Q4) based on apnoea duration. The longest apnoea duration-related events, *i.e.* Q4, were further divided into subquartiles based on lung-to-finger circulation times (LFCts) (Q1–Q4). Only the shortest and longest LFCt-based subquartiles, *i.e.* Q4–Q1 and Q4–Q4, are included here. Please note the different scales used for each parameter. ApnoeaDur: duration of an apnoea event; DesDur: duration of an entire desaturation event; FallDur: duration of the falling period of desaturation; fit: histogram plot with a distribution fit; RecovDur: duration of the recovery period; Depth: desaturation depth from 100% reference; DesArea: desaturation area from 100% reference; FallArea: fall area from 100% reference; Q4–Q1: quartiles with the longest apnoea duration and the shortest LFCt; Q4–Q4: quartiles with the longest apnoea duration and the longest LFCt; RecovArea: recovery area from 100% reference; FallSlope: desaturation fall slope; LFCt: lung-to-finger circulation time; RecovSlope: resaturation recovery slope.

therefore increased DesArea and FallArea, too. Furthermore, when events were divided into quartiles based on respiratory event duration and further into subquartiles based on LFCt, the fall duration increased with longer LFCt independent of respiratory event duration. The fall slope decreased significantly when LFCt increased. In addition, the desaturation area and fall area elevated significantly as a function of LFCt when they were related to the short apnoeas quartile (Q1) and the long apnoeas quartile (Q4).

The longer respiratory events were also associated with shorter LFCts, which is in line with a previous study where a 1 s increase in respiratory event duration was associated with a 0.06 s decrease in LFCts [24]. However, the decrease in LFCt was very small in our study, *i.e.* around 0.02 s for a 10% increase in apnoea duration; therefore, this small variation in LFCt might be clinically insignificant. The relationship between LFCt and hypoxic severity was independent of the respiratory event duration. In general, longer respiratory events are associated with severe hypoxaemia; however, this study revealed that the depth of desaturation events was longer and deeper even with shorter apnoea events, reflecting a higher hypoxic severity. We had similar observations with shorter hypopnoea events as well, where prolonged LFCts were linked to higher hypoxic severity with a similar length of hypopnoeas. This result indicates that it is highly likely that patients with OSA might have different levels of hypoxic severity regardless of the length of respiratory events, and therefore prolonged LFCt might be useful to capture this variation. Importantly, previous studies have reported that LFCt and hypoxic burden can be used as significant predictors for cardiovascular disease and mortality [19, 24]. Furthermore, we observed a trend of prolonged LFCt in obese and older patients, which is also consistent with previous findings [10, 24, 26]. It is known that obesity is directly associated with haemodynamic overload and a decrease in cardiac output occurs with age, which might explain the trend of prolonged LFCt in obese and older patients [27, 28].

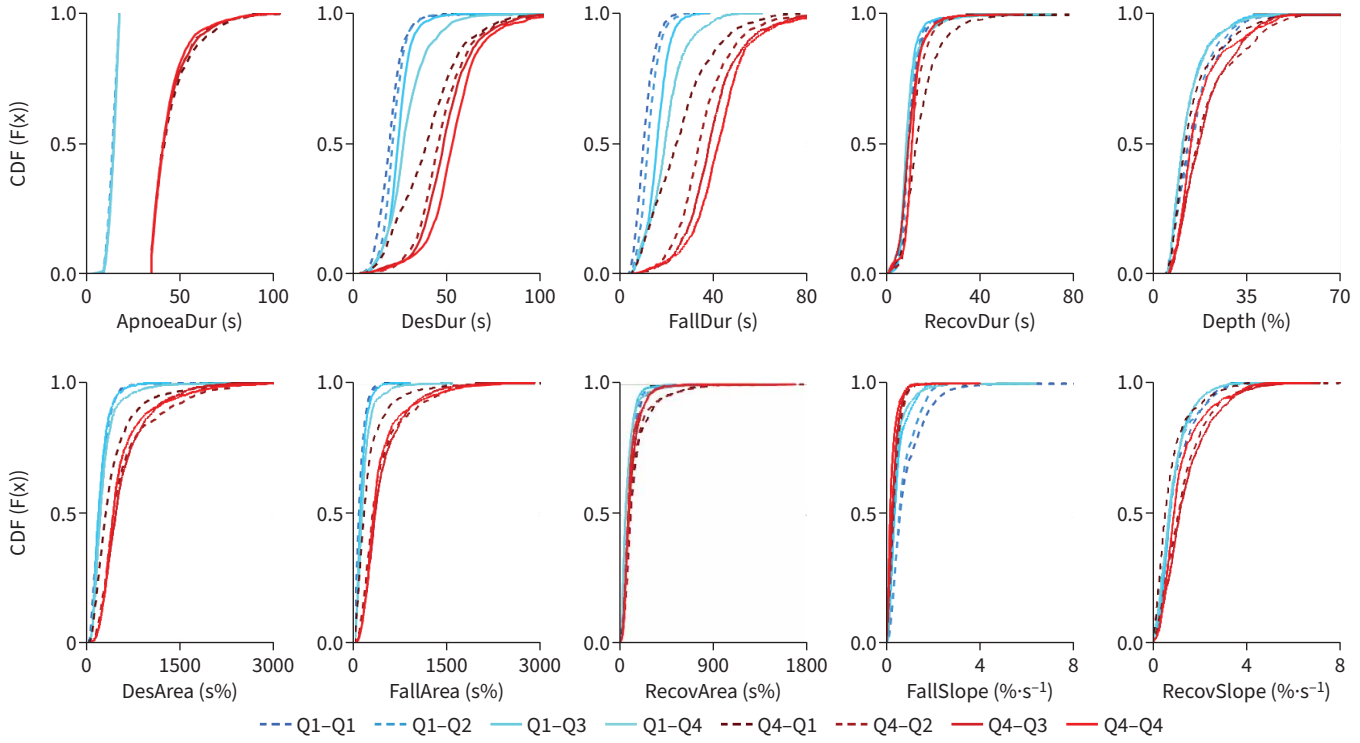

FIGURE 5 Empirical cumulative distribution functions (CDFs) of all shortest (Q1) and longest (Q4) apnoea-related oxygen saturation signal-based parameters between different lung-to-finger circulation time (LFCt)-based subquartiles. The events were divided into quartiles (Q1–Q4) based on apnoea duration. The shortest and longest apnoea duration-related events, *i.e.* Q1 and Q4, were further divided into subquartiles based on LFCts (Q1–Q4). All LFCt-based subquartiles, *i.e.* Q1–Q1 to Q1–Q4 and Q4–Q1 to Q4–Q4 are included in this figure. The Kolmogorov-Smirnov test was used to determine the significance of the differences ($p<0.0001$) between the CDFs. Please note the different scales used for each parameter. ApnoeaDur: duration of an apnoea event; CDF: cumulative distribution functions; Depth: desaturation depth from 100% reference; DesArea: desaturation area from 100% reference; DesDur: duration of an entire desaturation event; FallArea: fall area from 100% reference; FallDur: duration of the falling period of desaturation; LFCt: lung-to-finger circulation time; Q1–Q1: quartiles with the shortest apnoea duration and the shortest lung-to-finger circulation time (LFCt); Q1–Q2: quartiles with the shortest apnoea duration and the second shortest LFCt; Q1–Q3: quartiles with the shortest apnoea duration and the second longest LFCt; Q1–Q4: quartiles with the shortest apnoea duration and the longest LFCt; Q4–Q1: quartiles with the longest apnoea duration and the shortest LFCt; Q4–Q2: quartiles with the longest apnoea duration and the second shortest of LFCt; Q4–Q3: quartiles with the longest apnoea duration and the second longest LFCt; Q4–Q4: quartiles with the longest apnoea duration and the longest LFCt; RecovArea: recovery area from 100% reference. FallSlope: desaturation fall slope; RecovDur: duration of the recovery period; RecovSlope: resaturation recovery slope.

In addition, we observed that hypertension was more common in patients with longer LFCts than in patients with shorter LFCts. It has been shown that the haemodynamic stress during apnoeas correlates with hypoxic ventilatory response and increased blood pressure [29]. Additionally, another clinical study reported that a higher degree of vasoconstriction in patients with OSA leads to blood pressure surges and hypoxia [30]. Thus, haemodynamic stress, such as activation of the sympathetic nervous system and a higher degree of vasoconstriction, might increase LFCts. Additionally, severe hypoxaemia in patients with OSA has also been associated with increased heart rate, cardiac response and severe cardiovascular diseases [16, 20]. Moreover, previous studies have demonstrated that LFCt has the potential to be used as a marker for cardiovascular health and comorbidities in sleep studies [8, 24, 26]. Therefore, although our study alone does not suffice to fully determining the clinical utility of LFCt with respect to cardiac impairment; the LFCt distribution reported in the present study showed that hypoxic severity can be significantly elevated even with short apnoeas, which has considerable implications for cardiac health prognosis in patients with OSA.

We acknowledge that the study has some limitations. We computed LFCts from the end of the respiratory event to the time when the accompanying desaturation event reached nadir. Thus, the computed LFCt includes the inherent instrumental delay of the pulse oximeter. However, the same type of oximetry devices were used for all patients, therefore, the delay is similar for each patient and therefore has a limited

TABLE 5 Linear regression models investigating the connection between apnoea-related oxygen saturation signal-based parameters and LFCt

Parameters	All apnoeas, β	Shortest apnoeas (Q1), β	Longest apnoeas (Q4), β
ApnoeaDur (s)	−0.027*	0.012	−0.038
DesDur (s)	0.365*	0.409*	0.481*
FallDur (s)	0.451*	0.386*	0.574*
RecovDur (s)	−0.094*	0.006	−0.251*
DesArea (s%)	0.208*	0.189*	0.194*
FallArea (s%)	0.327*	0.339*	0.287*
RecovArea (s%)	−0.074*	−0.046*	−0.132*
Depth (%)	0.086*	−0.041*	0.161*
FallSlope ($s \cdot \%^{-1}$)	−3.224*	−2.886*	−6.178*
RecovSlope ($s \cdot \%^{-1}$)	1.348*	0.050	2.300*

The regression results are presented by considering all apnoeas, shortest apnoeas (apnoea Q1) and longest apnoeas (apnoea Q4). β values correspond to the change in LFCt (in seconds) associated with a 10% change in parameter value. Q: quartile; ApnoeaDur: duration of an apnoea event; DesDur: duration of an entire desaturation event; FallDur: duration of the falling period of desaturation; RecovDur: duration of the recovery period; DesArea: desaturation area from 100% reference; FallArea: fall area from 100% reference; RecovArea: recovery area from 100% reference. Depth: desaturation depth from 100% reference; FallSlope: desaturation fall slope; RecovSlope: resaturation recovery slope; LFCt: lung-to-finger circulation time. *: Statistically significant ($p<0.0001$) in the regression model.

impact on the results. Furthermore, sleep stages and sleeping position were not included while evaluating LFCt and oxygen saturation characteristics. Sleep stages affect intermittent hypoxaemia [31] and cardiovascular functioning [3], while sleeping position impacts the respiratory event lengths [32, 33]. Therefore, including sleep stages and sleeping position could bring additional information to the present study, outlining an area for future research. In addition, we had limited information about medication history and cardiovascular disease outcomes that might have slight impact on our present analysis. Furthermore, this study is only from a one-night study and night-to-night variability could affect the results. Thus adding a multiple-night study might bring additional information to the research.

Conclusions

This study revealed that prolonged LFCt is related to severe hypoxic load independent of the duration of respiratory events. Therefore, LFCt might be used as an additional PSG-based metric in clinical practice to represent the hypoxic severity in patients with OSA and to further study the cardiac health of patients with OSA.

Provenance: Submitted article, peer reviewed.

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Ethics statement: The Human Research Ethics Committee of the Princess Alexandra Hospital approved this retrospective data collection and analysis (HREC/16/QPAH/021 and LNR/2019/QMS/54313).

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