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Morbid obesity influences the nocturnal electrocardiogram wave and interval durations among suspected sleep apnea patients

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Abstract

Background: Obesity is a global issue with a major impact on cardiovascular health. This study explores how obesity influences nocturnal cardiac electrophysiology in suspected obstructive sleep apnea (OSA) patients.

Methods: We randomly selected 12 patients from each of the five World Health Organization body mass index (BMI) classifications groups ($n_{total} = 60$) while keeping the group's age and sex matched. We evaluated 1965 nocturnal electrocardiography (ECG) samples (10 s) using modified lead II recorded during normal saturation conditions. R-wave peaks were detected and confirmed using dedicated software, with the exclusion of ventricular extrasystoles and artifacts. The duration of waves and intervals was manually marked. The average electric potential graphs were computed for each segment. Thresholds for abnormal ECG waveforms were P-wave > 120 ms, PQ interval > 200 ms, QRS complex > 120 ms for, and QTc > 440 ms.

Results: Obesity was significantly ($p < .05$) associated with prolonged conduction times. Compared to the normal weight ($18.5 \leq BMI < 25$) group, the morbidly obese patients ($BMI \geq 40$) had a significantly longer P-wave duration (101.7 vs. 117.2 ms), PQ interval (175.8 vs. 198.0 ms), QRS interval (89.9 vs. 97.7 ms), and QTc interval (402.8 vs. 421.2 ms). We further examined ECG waveform prolongations related to BMI. Compared to other patient groups, the morbidly obese patients had the highest

number of ECG segments with PQ interval (44% of the ECG samples), QRS duration (14%), and QTc duration (20%) above the normal limits.

Conclusions: Morbid obesity predisposes patients to prolongation of cardiac conduction times. This might increase the risk of arrhythmias, stroke, and even sudden cardiac death.

KEYWORDS
body mass index, electrocardiogram, interval duration, obesity, obstructive sleep apnea, wave duration

1 | INTRODUCTION

Obesity has become a major public health hazard with an epidemic proportion. Obesity is associated with many cardiovascular comorbidities, such as coronary artery disease (CAD) and sudden cardiac death (SCD) (Hubert et al., 1983). Furthermore, obesity and obstructive sleep apnea (OSA) are closely related. It is well known that obesity predisposes to OSA (Schwartz et al., 2008), which further exacerbates the cardiovascular consequences of obesity (Drager et al., 2013) and is an independent risk factor for cardiovascular diseases and SCD (Gami et al., 2013).

The pathophysiological cascade between OSA, obesity, and cardiovascular disease is multifactorial and partly unknown. In obese patients, upper airway collapsibility is often increased by underlying anatomic alterations and disturbances in upper airway neuromuscular control (Schwartz et al., 2008). This causes intermittent hypoxia and hypercapnia and upregulates the sympathetic nervous system, which is associated with increased cardiovascular morbidity (Malpas, 2010) and weight regulation (Guarino et al., 2017). The perivascular fat appears to be a source of pro-inflammatory and vasoactive factors that may contribute to endothelial and smooth muscle cell dysfunction and the pathogenesis of vascular diseases (Campia et al., 2012). Respiratory events cause pleural pressure swings, increasing heart rate, and blood pressure which can further lead to cardiopulmonary hyperreactivity to hypoxia, and cardiac anatomical remodeling (Sajkov & McEvoy, 2009). Moreover, obesity itself can result in cardiac remodeling, increased profibrotic stage, change in presentation of ion channels, leads to fibrosis, and predispose to arrhythmias (Mahajan et al., 2015; McCauley et al., 2020). The intrathoracic adipose tissue, comprising both mediastinal and epicardial elements, is situated adjacent to the heart and has the potential to infiltrate into the myocardium (Anumonwo & Herron, 2018). Research indicates a correlation between the quantity of pericardial adipose tissue and unfavorable LV remodeling as well as an adverse cardiovascular disease prognosis (Shah et al., 2017). Earlier research has also shown a connection between OSA and deviations in electrocardiography (ECG) waveform changes (Can et al., 2009; Gupta et al., 2012; Shi & Jiang, 2020). Collectively, these interrelated health conditions may increase the risk of conduction abnormalities and arrhythmias.

In this study, we investigate whether a higher body mass index (BMI) is associated with prolonged conduction times (P-wave, PQ interval, QRS complex, and QTc interval) in suspected OSA patients. We hypothesized that the degree of obesity correlates with ECG conduction abnormalities in suspected OSA patients. This information might help in understanding the complex interplay between obesity, OSA, and cardiovascular disease.

2 | MATERIALS AND METHODS

2.1 | Study population

The dataset used in this study involved ($n = 916$) consecutive patients with suspected OSA. All patients had undergone full diagnostic polysomnography (PSG) at the Princess Alexandra Hospital (Brisbane, Australia) during 2015–2017. The PSG data were acquired with the Compumedics Grael acquisition system (Compumedics, Abbotsford, Australia). Approval for retrospective data collection was given by the Institutional Human Research Ethics Committee of the Princess Alexandra Hospital (HREC/16/QPAH/021 and LNR/2019/QMS/54313). Due to the retrospective nature of the study, no informed consent was needed from the patients according to the Metro South Human Research Ethics Committee.

Only patients with a total sleep time of ≥4 h in the PSG and without cardiac pacemakers were included. Patients were further divided into five groups (each $n = 12$) according to the World Health Organization BMI classification: normal weight (NW) group defined as $18.5 \leq \text{BMI} < 25$, preobesity (PO) group as $25 \leq \text{BMI} < 30$, a moderately obese group I (OGI) defined as $30 \leq \text{BMI} < 35$, severally obese group II (OGII) defined as $35 \leq \text{BMI} < 40$, and morbidly obese group III (OGIII) defined as BMI≥40 (WHO, 2000). After that, we sex and age matched the patients, and randomly selected 12 patients from the five different BMI groups.

2.2 | PSG analysis

The PSG recordings were scored manually following the prevalent American Academy of Sleep Medicine guidelines (Berry et al., 2012).

The scoring was performed by experienced sleep technicians in Princess Alexandra Hospital using Compumedics ProFusion PSG4 software (Compumedics). The scoring process has been described in more detail in a previous publication (Duce et al., 2016). The detailed information of each desaturation (e.g. start time and endpoint) was exported from ProFusion to Matlab (ver R2019b; Mathworks). All scored desaturations in which the patient was awake were excluded.

2.3 | ECG analysis

The patients had a total of 4571 baseline (pre-desaturation) ECG segments. Nocturnal ECGs (modified lead II) were recorded during the diagnostic PSG study, with a sampling frequency of 256 Hz. First, we excluded ECG segments originating less than 25 s after the end of the previous desaturation to avoid the possible influence of desaturation on the ECG (Sillanmäki et al., 2022). Second, 10-s ECG segments preceding desaturations events were extracted from the nocturnal ECG recording. After exclusions, a total of 1965 ECG segments were included in the further analysis. Peaks of the R-waves were detected using Kubios HRV Premium software (Kubios Oy) (Tarvainen et al., 2014), and detections were verified visually and manually corrected when necessary. Ventricular extrasystoles were excluded from the analyses by the software. After that, an average graph of electric potential during the ECG complex was computed for each 10-s segment and the duration of each wave and interval was manually marked (Sillanmäki et al., 2022). The T-wave endpoint was visually identified as an intersection between a tangent of the steepest part of the wave and the baseline and marked for each segment. The parameters studied were P-wave, PQ interval, QRS complex, and QTc interval. The heart rate corrected QT (QTc) intervals were calculated according to Bazett's formula (Bazett, 1997). The prevalence of prolonged ECG waveforms in different BMI groups was further studied. The upper normal thresholds for ECG waveform durations were 120 ms for P-wave, 200 ms for PQ interval, 120 ms for QRS complex, and 440 ms for QTc interval (Kusumoto et al., 2019; Rautaharju et al., 2009).

2.4 | Statistical analysis

The statistical significance of the differences between BMI groups was evaluated with the Wilcoxon rank-sum test, Wilcoxon signed rank-sum test, and chi-squared test. The limit for statistical significance was set to be $p < .05$ when comparing the PSG characteristics and prevalence of ECG waveform threshold exceedings. As every BMI category consists of samples from the same patients, the statistical significance of the difference between group medians was evaluated with the Wilcoxon signed-rank test. Moreover, as the categories contain a different number of samples and the Signed-rank works in a pair-wise manner, a total of 5000 iterations over all possible random permutations of the groups was conducted. This results in 5000 different p-values, and the median p-value was chosen to indicate the statistical significance. A $p < .01$ was set as a threshold based on Bonferroni correction to compensate multiple comparisons. Matlab 2019b (Mathworks Inc.) was used for the statistical analysis. The data are presented as means and cumulative distributions.

3 | RESULTS

Demographic information about the population is presented in Table 1. There were no statistically significant differences in PSG results between BMI groups (Table 1). The OGIII patients seemed to have more apnea/hypopnea-related findings compared to the NW group, yet the difference was not statistically significant. Even though the median apnea-hypopnea index was the highest in the OGII group, the OGIII group was more hypoxemic based on the desaturation severity.

In the OGIII group (consisting of morbidly obese patients), the medians of RR interval and all ECG waveform durations were significantly longer compared to the NW group (Table 2). The median RR interval in the OGIII group was longer compared to the NW group (905 vs. 844 ms, $p < .01$), respectively. The median P-wave duration of the OGIII group was 15.5 ms (15.2%) longer compared to the NW group (Table 2). The median PQ interval of the OGIII group was 22.2 ms (12.6%) longer compared to the NW group (Table 2). The difference between the OGIII group and other groups was prominent above the lower quartiles in the distribution chart (Figure 1b). The median QRS interval of the OGIII group was 7.8 ms (8.7%) longer compared to the NW group (Table 3). The difference between the OGIII group and other groups was the most prominent in the upper quartile (Figure 1c). The median QTc interval of the OGIII group was 18.4 ms (4.6%) longer compared to the NW group. Additionally, the median QTc interval of the OGII group was 15.0 ms (3.7%) longer compared to the NW group (Table 2). The differences between the groups were the most substantial in the interquartile range and disappeared at the extremes (Figure 1d).

We found that the OGIII group showed the most exceedings over normal threshold levels (Figure 1 and Table 3). Among OGIII patients, the PQ interval was prolonged in 44.0% of ECG samples, while in NW patients the prevalence of prolonged PQ interval samples was 4.7% (Table 3). Similarly, the QRS duration was prolonged in 13.6% of the OGIII samples, but no normal threshold exceeding durations over the threshold was seen in the NW group. The QTc duration was over the threshold in 20.2% of OGIII samples, and in the NW group, 14.0% of samples exceeded the threshold (Table 3). The P-wave threshold was exceeded in 39.9% of the NW group's ECG samples, while in OGIII 36.0% of samples were over the threshold (Table 3).

4 | DISCUSSION

4.1 | Principal findings

In this study, we investigated the impact of obesity on cardiac conduction in patients with suspected OSA. We observed significant differences in conduction times between normal weight and

TABLE 1 Clinical demographic and PSG (polysomnography) characteristics in different body mass index groups.

	Normal weight	Preobesity	OCI	OCII	OCIII
Clinical characteristics					
COPD	0 (0)	0 (0)	2 (16.7)	0 (0)	0 (0)
Depression	2 (16.7)	2 (16.7)	1 (8.3)	4 (33.3)	4 (33.3)
Dyslipidemia	0 (0)	1 (8.3)	5 (41.6)	3 (25)	3 (25)
Hypertension	2 (16.7)	2 (16.7)	5 (41.6)	2 (16.7)	7 (58.3)
Hypothyroidism	0 (0)	4 (33.3)	0 (0)	2 (16.7)	0 (0)
Previous atrial arrhythmia	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)
Smoker	2 (16.7)	2 (16.7)	1 (8.3)	2 (16.7)	3 (25)
Type II diabetes	1 (8.3)	0 (0)	3 (25)	1 (8.3)	5 (41.6)
PSG results					
AHI (1/h)	10.1 (4.4–18.4)	5.0 (3.1–11.8)	14.6 (6.1–33.4)	17.2 (6.3–28.7)	15.7 (9.3–33.3)
Arousal index (1/h)	23.3 (17.5–33.3)	18.3 (11.6–26.3)	25.4 (13.5–30.6)	27.4 (18.3–40.5)	21.3 (16.7–26.9)
Desaturation severity (%)	0.07 (0.02–0.11)	0.03 (0.02–0.05)	0.34 (0.08–0.55)	0.15 (0.05–0.51)	0.36 (0.11–1.00)
ODI (1/h)	3.3 (1.2–5.2)	1.4 (1.1–2.5)	13.2 (3.5–27.1)	8.3 (2.7–18.6)	16.0 (6.6–20.3)
TST (h)	5.9 (4.6–6.6)	5.9 (5.3–6.4)	5.7 (5.4–6.8)	5.2 (4.5–5.6)	5.9 (5.7–6.1)
$t_{90\%}$ (s)	31.8 (8.1–60.8)	17.9 (3.7–144.3)	111.3 (48.7–495.7)	76.7 (8.7–545.6)	239.4 (37.4–2667.0)

Note: Values are presented as number (%) or median (interquartile range; IQR) where appropriate.

Abbreviations: COPD, chronic obstructive pulmonary disease; ODI, oxygen desaturation index; PSG, polysomnography; t90%, time with oxygen saturation below 90%; TST, total sleep time.

TABLE 2 Electrocardiography characteristics in different body mass index groups.

	Normal weight	Preobesity	OCI	OCII	OCIII
RR interval (ms)	844.1 (784.8–913.9)	828.3 (792.1–881.8)	**962.1 (836.2–1026.0)**	887.0 (776.8–990.5)	**904.9 (811.0–1080.6)**
P-wave duration (ms)	101.7 (85.9–125.6)	109.4 (101.6–115.7)	109.4 (98.1–114.3)	109.4 (99.4–118.2)	**117.2 (101.6–129.4)**
PQ interval (ms)	175.8 (152.3–183.6)	155.5 (148.4–171.9)	171.9 (160.2–184.4)	171.9 (152.3–191.4)	**198.0 (179.6–234.4)**
QRS interval (ms)	89.9 (78.1–101.6)	85.9 (78.1–93.8)	88.5 (82.0–98.5)	89.8 (82.0–101.3)	**97.7 (85.9–109.4)**
QT interval (ms)	375.0 (359.4–398.4)	359.4 (351.6–390.6)	398.4 (386.7–406.3)	**402.3 (343.8–421.9)**	**398.4 (378.9–425.8)**
QTc interval (ms)	402.8 (394.2–411.2)	399.5 (384.4–415.2)	404.7 (391.8–425.4)	**417.8 (403.9–428.5)**	**421.2 (402.4–436.8)**

Note: Values are presented as median (interquartile range). The bolded value indicates a significantly ($p < .01$) larger median compared to the normal weight group.

Abbreviations: OCI, obesity class I; OCII, obesity class II; OCIII, obesity class III.

morbidly obese patients across various ECG parameters. However, the differences were less pronounced among less obese patients.

4.2 | ECG changes in the context of the current literature

We discovered that higher BMI was associated with longer P-wave duration and longer PQ interval in suspect OSA patients. Moreover, the prevalence of first-degree atrioventricular block (PQ interval > 200 ms) seems to increase with BMI. The incidence of prolonged AV conduction was 4.7% in the NW group, whereas in the morbidly obese group, it was notably higher at 44%. This finding is in line with a previous study showing a link between BMI and the prevalence of AV block (Shan et al., 2021). The finding has clinical significance due to the established association between prolonged PQ intervals and an elevated risk of atrial fibrillation and even higher mortality rates (Shan et al., 2021). However, the association can be multifactorial since also age and gender can affect the risk (Gaisl et al., 2016; Maeno et al., 2013; Shan et al., 2021). Moreover, a previous study has shown that P-wave abnormalities are associated with OSA (Can et al., 2009), and simulated apneas cause acute prolongation of P-wave duration even in the healthy population (Gaisl et al., 2016; Maeno et al., 2013).

In earlier investigations, QRS prolongation is shown to be relatively prevalent in OSA patients (Gupta et al., 2012). In our study, we found that intraventricular conduction duration (the mean QRS interval) was longer in morbidly obese patients compared to the normal-weight population, and the number of prolonged QRS samples is higher in obese patients. This implies a relationship

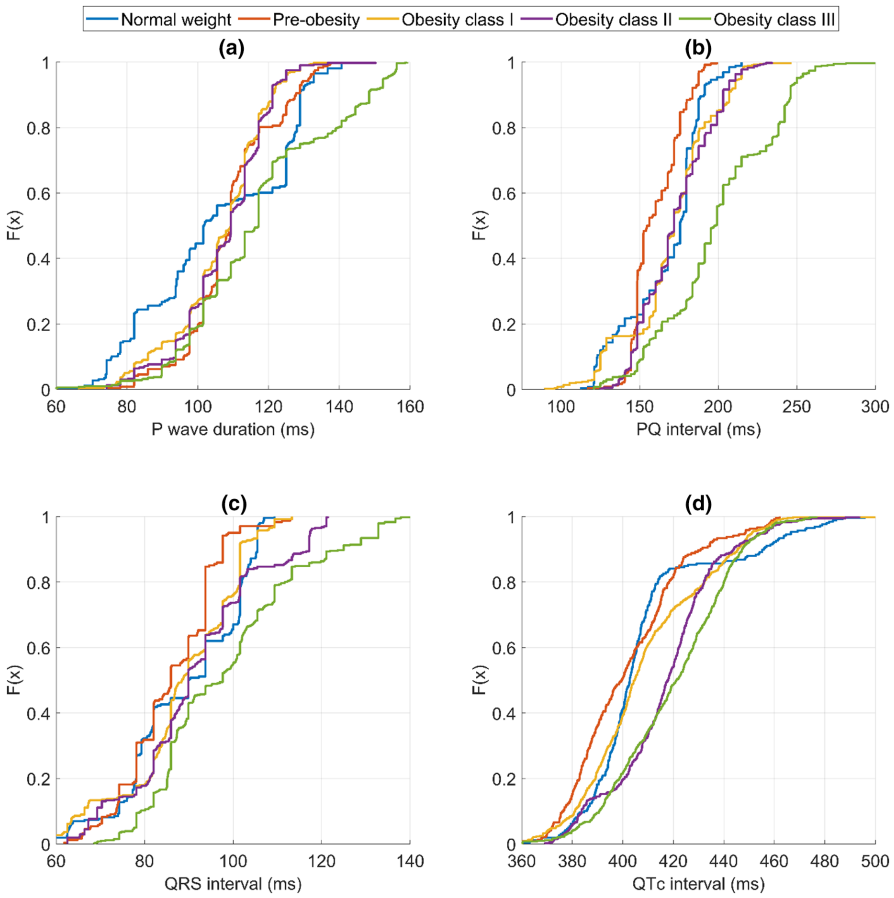

FIGURE 1 Cumulative distributions of baseline electrocardiogram waveforms for different body mass index groups. (a) P-wave duration, (b) PQ intervals, (c) QT intervals, and (d) QTc intervals.

TABLE 3 Prevalence on prolonged ECG waveforms in different body mass index (BMI) classes.

	Normal weight % (*n*)	Preobesity % (*n*)	OCI % (*n*)	OCII % (*n*)	OCIII % (*n*)
P-wave duration >120 ms	39.9 (103)	19.8 (48)[a]	12.4 (65)[a]	15.2 (62)[a]	36.0 (193)
Prolonged PQ interval >200 ms	4.7 (12)	0 (0)[a]	14.9 (78)[a]	15.3 (62)[a]	**44.0 (236)**[a]
Prolonged QRS 110–119 ms	0 (0)	1.7 (4)[a]	0.7 (4)	**11.3 (46)**[a]	**7.3 (39)**[a]
Prolonged QRS ≥120 ms	0 (0)	0 (0)	0 (0)	**3.5 (14)**[a]	**13.6 (73)**[a]
Prolonged QTc ≥440 ms	14.0 (36)	6.6 (16)[a]	13.8 (72)	11.8 (48)	**20.2 (108)**[a]

Note: Statistical significance of differences was assessed using chi-squared test. A bolded value indicates a significant ($p < .05$) difference with all groups.

Abbreviations: ECG, electrocardiography; OCI, obesity class I; OCII, obesity class II; OCIII, obesity class III.

[a]Significant difference between the corresponding group and normal weight group.

between obesity and modifications in cardiac electrical conduction that go beyond the impact solely attributed to OSA. The QRS prolongation might stem, at least in part, from analogous factors akin to those noted in AV block, such as cardiac remodeling, among others. Sobhani et al. recently showed that not only BMI but also hypertension and increased lipide levels were associated with prolonged QRS duration (Sobhani et al., 2022). Furthermore, both obesity and OSA are known to associate with ventricular hypertrophy (LVH) (Cuspidi et al., 2014; Noda et al., 1995), which itself is connected with QRS prolongation. LVH is further associated with an increased prevalence of heart failure, lethal ventricular arrhythmias, and even SCD (Cavalera et al., 2014; Cuspidi et al., 2014; Kahan & Bergfeldt, 2005). Hence, the prolonged QRS duration observed in morbidly obese patients might indirectly point toward increased myocardial fibrosis, fatty infiltration of the myocardium, and LV wall thickening.

The QT interval reflects the total duration of ventricular myocardial depolarization and repolarization. Several studies have explored

the correlation between repolarization parameters and diverse cardiac conditions. For example, QT dispersion (QTd), which measures the variation in recovery time across different regions of the heart, has been found to correlate with the severity of CAD (Helmy et al., 2017). Furthermore, the QT interval length itself is found to be independently associated with the emergence of malignant ventricular arrhythmias in patients with CAD (de Carvalho et al., 2022). De Carvalho et al. showed a 7% rise in malignant ventricular arrhythmias for every 10 ms increase in the QT interval (de Carvalho et al., 2022). Most notably, both prolonged QTc and heightened QTd serve as significant predictors of overall and cardiovascular mortality, likely attributed to an increased susceptibility to arrhythmias. (Okin et al., 2000). Interestingly, it has been established in previous research that delays in repolarization are seen also in OSA patients (Shi & Jiang, 2020). In morbidly obese patients, the median QTc duration was found to be nearly 20 ms longer than in the normal weight group. Consequently, individuals afflicted by morbid obesity might encounter a heightened health risk in comparison to those with a normal weight. Interestingly, this phenomenon appears to be reversible, at least to some extent, as weight loss has been shown to be associated with a shortening of the QTc interval (Papaioannou et al., 2004).

4.3 | Potential mechanisms

The mechanisms driving electrophysiological changes associated with obesity encompass a range of factors. Both obesity and OSA can disturb the autonomic nervous system, characterized by heightened sympathetic activity and diminished parasympathetic tone may impact ECG (Guarino et al., 2017). Additionally, obesity exerts mechanical stress on the heart, which lead to structural adaptations such as hypertrophy and changes in cardiac mechanics. For example, obesity is associated with left atrial enlargement that leads also changes in electrophysiology (Lin et al., 2011; Wang et al., 2004). The presence of oxidative stress and mitochondrial dysfunction within the context of obesity may further disrupt intracellular signaling pathways that hold relevance for cardiac electrophysiology (Cojocaru et al., 2023). It is also known that obesity-related chronic inflammation predisposes to myocardial fibrosis (Cavalera et al., 2014). The fibrotic remodeling alters the heart's microstructure and disrupts the normal electrical pathways, thereby resulting in prolonged conduction (Verheule & Schotten, 2021). The presence of excessive adipose tissue around the heart and infiltrating the myocardium may influence the propagation of electrical signals across the cardiac system (Anumonwo & Herron, 2018). Moreover, morbidly obese individuals may have comorbidities requiring medications, some of which, such as certain antiarrhythmics and antidepressants, have the potential to prolong the QT interval (Van Noord et al., 2010). Furthermore, obesity-related metabolic disturbances can lead to electrolyte imbalances, further contributing to the prolongation of the repolarization (Van Noord et al., 2010).

4.4 | Strengths and limitations

Our research sets itself apart from numerous prior studies that relied on isolated ECG recordings. In our study, we explore multiple time points and various ECG parameters associated with cardiac conduction. This approach provides a comprehensive evaluation over an extended duration, capturing potential changes not apparent during waking hours. Analyzing ECG samples during sleep further offers information under real-life conditions, free from the potential influence of stress or other factors present during awake ECG recordings. Furthermore, we combined research focusing on both OSA and obesity. For this reason, these findings have potential implications for improving risk assessment within this particular patient cohort. Moreover, it is worth noting that several studies on OSA tend to focus solely on male participants. In our study, both sexes were included. However, it is important to acknowledge certain limitations within our study. Both OSA and obesity are associated with other comorbidities and cardiovascular disease risk factors, including diabetes, hypertension, and dyslipidemia. These underlying conditions might influence the results. Moreover, the ECG samples were relatively short (10 s). The segment duration was selected as a compromise between a sufficiently long segment to obtain a reliable representation and to not exclude too many samples in patients with frequent desaturations. The ECGs of some samples were subject to interpretation because of the power line interference that had not been corrected by the recorder. Additionally, we only compared the groups with the normal weight group. No further statistical comparisons were made between OP, OGI, and OGII patients. This, though, should not be a big defect as the medians of other groups were positioned most in the middle of the medians of the NW group and OGIII group. Furthermore, the relatively small number of subjects in each BMI group is a limitation of this study. This limitation arises from the retrospective nature of our study design, which presented challenges in forming matched groups based on age and sex. Yet, our study advances beyond previous research on obesity and cardiovascular changes by focusing on specific ECG wavelength and interval alterations in morbidly obese patients. ECG segments that coincided with nocturnal desaturations were excluded from the study. This decision was made because previous research has established that nocturnal desaturations can influence the ECG (Sillanmäki et al., 2022). By excluding these segments, the study aims to focus solely on the impact of obesity on ECG waveform and interval alterations, without the potential confounding effects of desaturations. While acknowledging limitations, our study contributes valuable insights into the intricate relationship between OSA, obesity, and cardiovascular health.

5 | CONCLUSIONS

We found that morbid obesity is especially associated with prolonged conduction times. This predisposes obese patients to

cardiac conduction disorders and possibly also to arrhythmias. The mechanisms underlying the development of electrophysiological changes in morbidly obese patients are complex and multifactorial. Understanding these mechanisms is crucial for improved risk assessment and the development of targeted interventions to mitigate the cardiac consequences of obesity in clinical practice.

AUTHOR CONTRIBUTIONS

J.A.L. provided the Kubios software. B.D. provided the patient data. A.S., S.S., and S.K. analyzed the patient data. All authors interpreted the patient data and contributed to writing the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Lipponen JA is a shareholder of a company (Kubios) that designs ECG analysis and heart rate variability analysis software. Other co-authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are not publicly available due to privacy policy but are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Approval for retrospective data collection was obtained from the Institutional Human Research Ethics Committee of the Princess Alexandra Hospital (HREC/16/QPAH/021 and LNR/2019/QMS/54313). The need for informed consent was waived by the Metro South Human Research Ethics Committee due to the retrospective nature of the study.

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