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SCIENTIFIC INVESTIGATIONS

Association between QRS Duration and Obstructive Sleep Apnea

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Background: Both obstructive sleep apnea (OSA) and prolonged QRS duration are associated with hypertension, heart failure, and sudden cardiac death. However, possible links between QRS duration and OSA have not been explored.

Methods: Cross-sectional study of 221 patients who underwent polysomnography at our center. Demographics, cardiovascular risk factors and ECG were collected to explore a relationship between OSA and QRS duration.

Results: The apnea-hypopnea index (AHI) was positively correlated with QRS duration (r = 0.141, p = 0.03). Patients were divided into 3 groups: AHI < 5 (61), AHI 5-29 (104), and AHI > 30 (55). The mean QRS duration prolonged significantly as OSA worsened (AHI < 5, 85 ± 9.5; AHI 5-29, 89 ± 11.9; and AHI > 30, 95 ± 19.9 ms, p = 0.001). QRS ≥ 100 ms was present in 12.7% of patients with severe OSA compared with 0% in the rest of the sample (p < 0.0001). After adjustment for age, race, and cardiovascular risk factors, this association remained significant in women but not in men.

Conclusion: QRS duration and OSA were significantly associated. Severity of OSA independently predicted prolonged QRS in women but not men. Nevertheless, prolongation of QRS duration in either sex may potentiate arrhythmic risks associated with OSA.

Keywords: Obstructive sleep apnea, electrocardiogram, QRS duration

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BRIEF SUMMARY

Current Knowledge/Study Rationale: QRS duration is an independent predictor of mortality. Obstructive sleep apnea produces structural changes of the heart which can lead to a widened QRS but this potential association has not been adequately explored.

Study Impact: QRS duration prolonged significantly as sleep apnea severity increased; however, on multivariate analysis the effect remained significant only in women. QRS widening could help explain associations between sleep apnea and cardiovascular events while the effect in women points to possible areas for future research.

Obstructive sleep apnea (OSA) has been associated with several cardiovascular conditions[1,2] including hypertension,[3] congestive heart failure,[4] and sudden cardiac death.[5] In fact, OSA has been associated with a 60% to 70% increased risk of cardiovascular morbidity and mortality.[6]

OSA is highly prevalent and underdiagnosed[7] in the general population. This problem may be worse in subjects with coronary artery disease, as recent studies have shown a 50% to 70% prevalence of OSA in such patients.[7,8] This high prevalence suggests that OSA may play a key role in the development of cardiovascular events.

Numerous studies have shown that OSA is associated with changes in cardiac structure, including left ventricular hypertrophy,[9-12]which can widen the QRS complex on the electrocardiogram (ECG).[13] QRS duration is an independent predictor of sudden cardiac death[15,16] and mortality[16,17] in conditions commonly associated with OSA, such as hypertension and heart failure. However, the relationship between OSA and QRS duration is unknown.

In this study we hypothesized that OSA severity, measured by the apnea-hypopnea index (AHI), is independently associated with QRS prolongation. If so, this could help explain any increased risk of sudden cardiac death in OSA.

METHODS

We conducted a retrospective cross-sectional study of consecutive patients who had a clinically indicated polysomnogram (PSG) study from January 2007 through July 2009 at Albert Einstein Medical Center, Philadelphia, PA. Inclusion criteria were age over 18 years and availability of a resting 12-lead ECG within the 6 months preceding polysomnography. Patients with known sleep apnea were excluded as were those with classic right or left bundle branch block or a ventricular paced rhythm. Patients with atrial fibrillation were included but other non-sinus rhythms were excluded. The final study population consisted of 221 subjects. This study was approved by the Albert Einstein Institutional Review Board.

Polysomnogram

All patients were initially evaluated by a certified sleep medicine certified physician. PSG recording and scoring were performed using the VIASYS SomnoStar Pro System. Electroencephalogram, electro-oculogram, and electromyogram were monitored for sleep staging. Nasal pressure monitoring, chest

Table 1—Baseline characteristics of the subjects included in the study

Variable n = 221	Mean ± SD or Number (%)
Age	51.9 ± 13.8
Gender (Female)	142 (64.2)
Race	
Caucasian	29 (13.1)
African American	170 (77)
Hispanic	19 (8.6)
Other (Asian)	3 (1.3)
No Obstructive sleep apnea	61 (27.6)
Obstructive sleep apnea	160 (72.3)
Mild-moderate	105 (47.5)
Severe	55 (24.8)
Obese (BMI > 30 kg/m^2)	187 (85)
Smoking	77 (34.8)
Diabetes mellitus type 2	75 (33.9)
Hypertension	140 (63.3)
Coronary artery disease	34 (15.3)
Congestive heart failure	19 (8.6)
Atrial fibrillation	8 (3.6)

SD, standard deviation; BMI, body mass index.

wall movement, abdominal movement, snoring, and oxygen saturation were monitored for respiratory assessment. Electrocardiogram and tibial electromyogram were monitored for cardiac arrhythmias and nocturnal limb movements, respectively. The AHI, defined as the sum of apneas and hypopneas per hour of sleep, was recorded from the PSG report. OSA severity was defined by AHI according to recommendations from the Sleep Task Force of the American Academy of Sleep Medicine (no OSA when AHI < 5, mild-moderate OSA with AHI 5-30, and severe OSA with AHI > 30).[17]

Electrocardiogram

The resting 12-lead ECGs of these patients were accessed from their electronic medical records. Heart rate, QRS duration, PR interval, and corrected QT interval (QTc) were abstracted from the computerized ECG interpretation (Marquette 12SL ECG Analysis Program run on the MUSE ECG system). The onset of QRS is detected first because it is the easiest; the slope change is usually very rapid and in great contrast to the other slopes in the median. This is followed by QRS offset. The onsets and offsets are determined by an analysis of simultaneous slopes in all 12 leads. Onsets are defined as the earliest deflection in any lead, and offsets as the latest deflection in any lead. Thus, the QRS duration is measured from the earliest onset in any lead to the latest deflection in any lead. Similarly, the QT interval is measured from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead. The PR interval is measured form the earliest detection of atrial depolarization in any lead to the earliest detection of ventricular depolarization in any lead (the QRS onset). The QT is corrected for heart rate using Bazett's formula. The values of these intervals were recorded in milliseconds (ms).

Data Collection and Cardiovascular Risk Factors

PSG, ECG, and demographic data including age, gender, and race were collected from electronic medical records. Cardiovascular risk factors—namely hypertension, diabetes, coronary artery disease, congestive heart failure, atrial fibrillation, obesity (BMI ≥ 30 kg/m^2), and smoking status—were noted from the records. Recording of these variables were done blinded to the OSA status or severity.

Statistical Methods

Data were summarized by calculating mean ± SD for continuous variables, and numbers and percentages for categorical variables. Due to non-linearity of the variables analyzed we used Spearman correlation coefficients to explore the association as continuous variables between AHI, mean and minimum oxygen saturation during sleep, with QRS and other ECG intervals. We performed one-way ANOVA and independent *t*-tests to assess differences between cardiovascular risk factors and ECG intervals by presence or absence of OSA and by its severity (AHI < 5; no OSA, AHI 5-29; mild-to-moderate OSA and AHI ≥ 30; severe OSA) and by mean oxygen saturation < 88 % (cut-off used by Medicare for home oxygen) and minimum oxygen saturation < 94% (lowest quartile) during sleep. We then assessed whether severity of OSA was associated with a prolonged QRS (≥ 100 ms). Finally, we performed regression analyses to identify significant univariate predictors for QRS duration (p-value ≤ 0.10). To assess the independent effect of OSA on AHI and mean and minimum oxygen saturation during sleep, we performed multivariate analyses adjusting for age, sex, and cardiovascular risk factors (p-value < 0.05). Due to significant differences in QRS duration between men and women previously reported[18,19] and noted in our study, we performed analyses stratified by gender, and therefore no adjustment for gender was needed. All analyses were performed using JMP 8.0 (SAS Institute; Cary, NC) and 2-tailed p values < 0.05 were considered significant in advance.

RESULTS

Baseline characteristics of the 221 participants (64.2% female) are shown in **Table 1**. Characteristics of the subjects and prevalence of cardiovascular risk factors according to the presence or absence of OSA and its severity are shown in **Table 2**. Overall, subjects with OSA tended to be older and male. Subjects with mild to moderate OSA had a higher prevalence of congestive heart failure and subjects with severe OSA tended to be more obese and hypertensive. Because there were no significant differences between the mild and moderate OSA groups, we decided to cluster them in a single group.

QRS and AHI showed a weak but significant and positive correlation (rho = 0.14, p = 0.03). **Table 3** displays ECG intervals by presence or absence of OSA and by its severity. QRS was significantly wider as OSA severity increased (**Figure 1**). Furthermore, QRS ≥ 100 ms was present in 12.7% of those with severe OSA compared with 0% of patients in the mild to moderate OSA group, and 0% in those without OSA, p < 0.0001 (**Figure 2**). PR and QTc intervals were not significantly correlated with AHI (rho = -0.03, p = 0.58 and rho = -0.02, p = 0.75, respectively) and were not significantly different among groups.

Table 2—Characteristics by presence or absence of obstructive sleep apnea and by its severity

Variable	No OSA (n = 61)	Mild-moderate OSA (n = 105)	Severe OSA (n = 54)	p-value
Age	47.3 ± 14.3	54.2 ± 11.5#	52.9 ± 16.1+&	0.0900
Sex (female)	50 (81.9)	63 (60)*	29 (52.7)^	0.0020
Race				
Caucasian	7 (11.5)	15 (14.3)	7 (12.7)	
African American	45 (73.7)	79 (75.2)	46 (83.6)	
Hispanic	8 (13.1)	10 (9.5)	1 (1.8)	
Other (Asian)	1 (1.64)	1 (0.95)	1 (1.8)	0.51
Obese (BMI > 30 kg/m^2)	48 (78.7)	90 (85.7)	49 (90.7)&	0.1800
Smoker	23 (37.7)	35 (33.3)	19 (34.5)	0.8400
Diabetes mellitus type 2	19 (31.1)	34 (32.4)	22 (40)	0.5400
Hypertension	34 (55.7)	67 (63.8)	39 (70.9)&	0.2300
Coronary artery disease	8 (13.1)	20 (19)	6 (10.9)	0.3300
Congestive heart Failure	2 (3.3)	12 (11.4)#	5 (9.1)	0.1900
Atrial fibrillation	1 (1.6)	3 (2.8)	4 (7.2)	0.2200

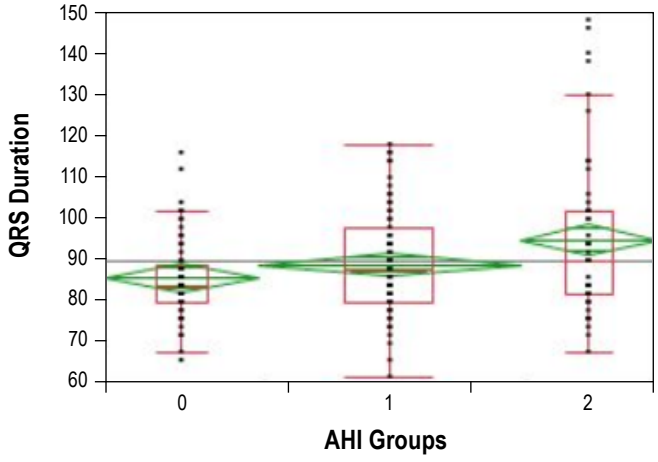
*p-value ≤ 0.05 for no OSA vs. mild-moderate OSA, #p-value ≤ 0.001 for no OSA vs. mild-moderate OSA, &p-value ≤ 0.07 for no OSA vs. severe OSA, +p-value ≤ 0.05 for moderate vs. severe OSA, ^p-value ≤ 0.001 for no OSA vs. severe OSA. BMI, body mass index.

Table 3—ECG intervals by presence or absence of OSA and by its severity

Variable	No OSA (n = 61)	Mild-moderate OSA (n = 105)	Severe OSA (n = 54)	p-value
PR interval	159.01 ± 26.7	163.09 ± 24.9	158.23 ± 27.2	0.4500
QRS interval	85.80 ± 9.5	89.19 ± 11.9*	95.20 ± 19.9^	0.0014
QT interval	386.01 ± 39.8	390.30 ± 35.43	390.47 ± 42.4	0.7500

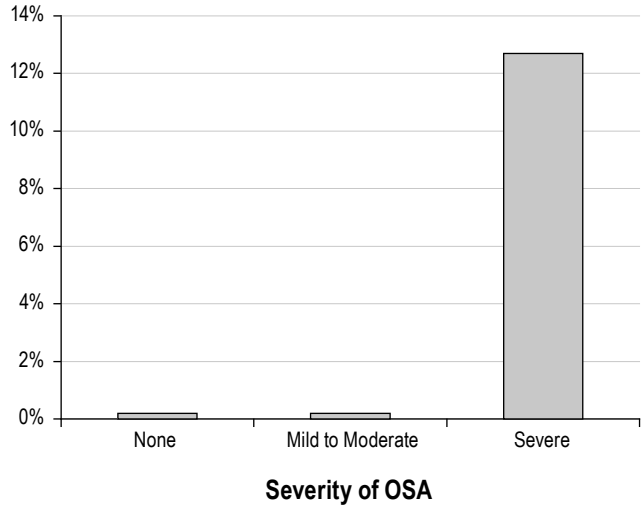
*p-value 0.01 for no OSA vs. mild-moderate OSA, ^p-value 0.0003 for no OSA vs. severe OSA. ECG, electrocardiogram; OSA, obstructive sleep apnea.

Figure 1—QRS duration by obstructive sleep apnea severity measured by apnea-hypopnea index



0 = No OSA; 1 = Mild-moderate OSA; 2 = Severe OSA.

Figure 2—QRS > 100 ms by presence or absence of OSA and by its severity



To examine a possible relationship between nocturnal hypoxemia and QRS duration, we also looked at mean oxygen saturation and minimal oxygen saturation. Mean QRS duration was 93.4 ± 16.4 ms for the lowest quartile of mean oxygen saturation (< 94%) versus 88.9 ± 14.3 ms for those with mean oxygen saturation ≥ 94% (p = 0.049). We next divided patients into those with minimum oxygen saturation of ≤ 88% (current Medicare criteria for home oxygen prescription) and those with minimum oxygen saturation > 88%. Mean QRS duration for patients with nocturnal hypoxemia as defined above was 91.6 ± 16.0 ms compared to 86.1 ± 10.3 ms for those without (p = 0.005). After stratifying by sex, the difference in QRS duration remained significant in women (88.6 ± 14.3 ms vs. 83.5 ± 8.3 ms in patients with and without nocturnal hypoxemia), but

not in men (96.1 ± 17.5 ms vs. 96.4 ± 11.5 ms in patients with and without nocturnal hypoxemia).

Sex, race, hypertension, coronary artery disease, congestive heart failure, and AHI were significant univariate predictors for QRS duration (**Table 4**). After stratifying by sex, women had a shorter QRS duration than men (86.8 ± 12.7 vs. 94.9 ± 15.1 ms), consistent with previous studies.[18,19] In multivariate analyses, in men, atrial fibrillation, congestive heart failure, and race remained significant predictors of QRS duration after adjustments, while in women, atrial fibrillation, congestive heart failure, and AHI remained as significant predictors (**Table 5**). Minimal oxygen saturation was not a significant predictor of QRS duration on multivariate analyses.

DISCUSSION

Our major finding is that QRS duration and OSA are significantly associated. This was particularly true for patients with severe OSA (AHI > 30), where 12.7% had a QRS ≥ 100 ms compared to 0% of patients without OSA or with only mild to moderate OSA. After multivariate analyses, AHI remained a significant predictor of prolonged QRS in women but not in men.

Previous Studies

Previous small studies have looked for a possible association between QRS duration and OSA. Andreas et al.[20] found a mean QRS duration of 96 ± 9 ms in OSA, similar to the 95.20 ± 19.9 ms found in our study. Their control subjects had similar QRS duration (96 ± 10 ms) and the authors concluded that OSA was not associated with QRS prolongation. In our study, subjects without OSA had a more normal QRS duration (85.8 ± 9.5 ms). This difference may relate to the fact that their controls were snorers with an AHI up to 10, while in our study controls had an AHI < 5 as suggested by the American Academy of Sleep Medicine Task Force.[17] Furthermore, their sample size was small (n = 47). In another study, Steiner et al.[21] studied 12 patients with congestive heart failure and compared ECG parameters by presence or absence of OSA. Although they noted no statistically significant changes in QRS duration between OSA groups, the mean QRS was 99 ± 13 ms in controls and 144 ± 43 ms in patients with OSA. This study is limited by small sample size (6 patients in each group) and by the mean AHI of the OSA group being only 17.8; therefore few conclusions can be drawn from these results.

In previous studies, QRS ≥ 120 ms has been independently associated with all-cause mortality[15,16] and sudden death.[14-16] Though mean QRS duration in our patients with severe OSA was < 120 ms, it is notable that only severe OSA subjects had a QRS ≥ 100 ms while this finding was absent in others. We can speculate that changes in QRS duration occur slowly and move in only one direction (wider). In addition OSA probably worsens over time. Therefore our patients might, over time, develop additional QRS widening. Further study is needed to investigate this possibility.

One of the interesting findings in this study is that AHI was independently associated with QRS duration in women but not in men. There are several possible ways to explain this. Prior studies have noted shorter QRS duration in women, as we also found. Any increase in QRS duration in response to OSA would produce a greater percentage change in women versus men, making it easier to detect statistically. On the other hand, there may be a true difference between men and women in response of the left ventricle to the afterload burden imposed by OSA. Animal studies have shown differences in gene expression between males and females in response to pressure overload.[22] In addition, women appear to have greater wall thickening in response to aortic stenosis than do men.[23] Among hypertensive patients followed by the LIFE study, women had reduced regression of electrocardiographic hypertrophy after 5 years of therapy versus men.[24] Given these findings, it may be that women develop greater left ventricular hypertrophy in response to OSA, leading to greater QRS prolongation. Wall thickness tends to be slightly less in women than men; thus the female heart might experience greater wall stress from the high negative intrathoracic pressure produced by obstructive apneas.

Regarding the relationship between QT duration and OSA, previous studies have reported conflicting findings. Smith et al.[25] measured QT and PR interval changes associated with spontaneous and respiratory-related arousals in OSA patients, finding a shortening of the QT during arousal. However, that study included only 20 OSA patients and lacked a control group. In another study, Lue et al.[26] reported opposite find-

Table 4—Univariate predictors for QRS duration

Predictor	ß-Estimate (SE)	p-value
Gender (Female)	-4.0230 (0.96)	< 0.0001
Race	-1.876 (0.97)	0.0600
Hypertension	-1.7988 (0.98)	0.0700
Coronary artery disease	-2.8586 (1.31)	0.0308
Congestive heart failure	-6.1830 (1.65)	0.0002
Atrial fibrillation	-11.5424 (2.44)	< 0.0001
Apnea hypopnea index	0.0705 (0.03)	0.0540

All variables in Table 1 were analyzed. Significant predictors were considered if p-value ≤ 0.10.

Table 5—Multivariate predictors for QRS duration stratified by sex

	Males		Females	
Predictor	ß-Estimate (SE)	p-value	ß-Estimate (SE)	p-value
Race	-6.5369 (3.02)	0.0343	-1.3668 (1.94)	0.4840
Congestive heart failure	15.1239 (5.32)	0.0059	8.4250 (4.11)	0.0426
Atrial fibrillation	24.7257 (6.64)	0.0004	16.7225 (7.46)	0.0260
Apnea-hypopnea index	-0.0257 (0.05)	0.6409	0.1055 (0.05)	0.0565

All variables listed in Table 1 were included in the model.

ings with prolongation of the QT and corrected QT intervals in the OSA group compared to controls. In our study, we did not find an association between OSA and QTc interval. These conflicting results might be explained by the multiple factors that influence QT duration, and the fact that it can change very rapidly.

Mechanistic Considerations

Prolonged QRS and OSA can each be seen in various cardiovascular conditions with important clinical implications.[1,2] Both have been associated with increased left ventricle mass, hypertension,[3] congestive heart failure,[4] and ventricular arrhythmias.[27,28] Several pathophysiologic mechanisms can explain these associations. In OSA, breathing against a closed upper airway generates high negative intrathoracic pressure, which increases left ventricular transmural pressure and afterload, contributing to left ventricular hypertrophy.[29] Furthermore, OSA is an accepted causal factor for the development of hypertension, which also contributes to left ventricular hypertrophy. Other possible mechanisms by which OSA might contribute to QRS widening include endothelial dysfunction,[29] systemic inflammation, sympathetic activation, blood pressure surges, and oxidative stress, all of which contribute to increased arterial stiffness[9] and increased afterload stress on the left ventricle.

Strengths and Limitations

Our study has a large sample size in comparison with most OSA studies. All of our patients underwent polysomnography study, the gold standard test to define this condition; this allowed us to assess OSA severity. We performed multivariate analyses to control for many of the clinical factors that could confound our results. Our study has some limitations. Given the cross-sectional nature of the study we cannot determine causality, as we cannot assess if prolonged QRS duration preceded or followed development of OSA. Our sample population was mainly African American, limiting generalizability of these results to other populations. In the multivariate analysis QRS prolongation was independently associated with OSA in women, but not in men, which could be due to overadjustment (example: hypertension and obesity, conditions commonly found in OSA) or insufficient power, as the majority of our population sample were women. Lead time bias is likely present in our study, as the onset of OSA in our population is not well established. However, in theory the longer the disease has been present, the greater the impact on cardiovascular disease, in our case the greater the QRS prolongation.

CONCLUSIONS

This is the first study linking increased QRS duration with OSA and may help explain the increased risk of sudden cardiac death in both conditions. For the overall sample, increased QRS duration was significantly associated with OSA, particularly in those with severe OSA (AHI > 30). After multivariate analyses severe OSA remained a significant independent predictor of prolonged QRS in women but not in men, while congestive heart failure and atrial fibrillation remained independent predictors in both men and women. Nevertheless, prolongation of QRS duration in either sex may potentiate arrhythmic risk associated with OSA. Mechanisms underlying the gender effects of the QRS-OSA interaction remain to be determined.

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