Do Rheumatoid Arthritis Patients Have a Higher Risk for Sleep Apnea?

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ABSTRACT. ***Objective***. Patients with rheumatoid arthritis (RA) have an increased risk for developing cardiovascular disease (CVD) compared to subjects in the general population. The development of CVD has also been linked to chronic sleep apnea. The purpose of this study was to examine the risk for sleep apnea in patients with RA compared to subjects without RA.

Methods. We recruited RA patients and non-RA subjects who were age and sex matched from the same population. These persons completed the Berlin Sleep Questionnaire, which evaluated their level of risk (high or low) for sleep apnea. In addition, there were 3 subscales evaluating snoring, fatigue, and relevant comorbidities [i.e., high blood pressure and obesity [body mass index (BMI) ≥ 30 kg/m^2)]. Chi-squared tests were used for comparisons.

Results. The study population consisted of 164 patients with RA and 328 patients without RA. Age, sex and BMI were similar for both groups. There was no difference in snoring ($p = 0.31$) or in the comorbidities subscale ($p = 0.37$). However, RA patients reported more fatigue (38%) than subjects without RA (13%; $p < 0.001$). Overall, the risk for sleep apnea was significantly higher for the RA patients (50%) than the non-RA subjects (31%; $p < 0.001$).

Conclusion. Patients with RA may be at a higher risk for sleep apnea compared to non-RA subjects. This apparent risk difference may be attributed to reports of fatigue in RA patients, which may be associated with sleep apnea or RA disease itself. (J Rheumatol First Release Aug 1 2009; doi:10.3899/ jrheum.081335)

Key Indexing Terms:
SLEEP APNEA RHEUMATOID ARTHRITIS CARDIOVASCULAR DISEASE

Patients with rheumatoid arthritis (RA) have an increased risk for developing cardiovascular disease (CVD) compared to subjects in the general population[1,2]. Development of CVD has also been linked to chronic obstructive sleep apnea (OSA)[3]. OSA is defined as an apnea-hypopnea index (AHI) of > 5.0 events per hour and estimated to occur in up to 25% of adult men and women in the general population[4,5]. OSA is strongly associated with obesity, diabetes, and dyslipidemia and is highly prevalent in patients with hypertension, stroke, coronary artery disease, and heart failure. OSA itself may lead to incident cardiovascular disease whereas treatment with continuous positive airway pressure (CPAP) eliminates much of the increased CVD risk[3,6].

One area not yet fully explored is the relationship between CVD, RA, and OSA[7]. It has been shown that RA, like other pain conditions, chronic illnesses, and mood disorders, is associated with disturbed sleep[8]. Very little is known about the frequency of sleep disturbances and OSA in patients with autoimmune diseases, including RA, and whether OSA in RA patients is associated with risk of CVD[7,8]. As recently reviewed by Holman, there are a number of potential mechanisms through which OSA may contribute to CVD in patients with RA. Our group's findings regarding increased risk of sudden death in RA raises the possibility that unrecognized OSA may contribute to increased CV risk through autonomic abnormalities and arrhythmias[1]. We therefore examined risk for sleep apnea in patients with RA compared to subjects without RA.

MATERIALS AND METHODS

The study population for this cross-sectional study comprised 164 patients

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Supported in part by grants from the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS, R01 AR46849) and NHLBI (R01 HL55502); and made possible by the Rochester Epidemiology Project (Grant R01-AR30582 from NIAMS).

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Accepted for publication April 30, 2009.

with RA and 328 subjects without RA ascertained among adult residents (≥ 18 years) of Olmsted County, Minnesota using the population-based resources of the Rochester Epidemiology Project, a population-based medical records linkage system that allows ready access to complete inpatient and outpatient medical records from all community medical providers[9]. RA subjects fulfilled the 1987 American College of Rheumatology (ACR) classification criteria for RA between 1980 and 2006[10]. Age and sex matched non-RA subjects were ascertained from a population-based cohort of subjects[11]. This study was approved by the Institutional Review Boards at Mayo Clinic and Olmsted Medical Center.

Study participants in both groups completed a physical examination (including measurement of height and weight) and the Berlin Sleep Questionnaire, which is frequently used to evaluate risk for sleep apnea[12]. The Berlin questionnaire consists of questions relating to 3 categories of known risk factors for sleep apnea: snoring, fatigue, and comorbidities [i.e., high blood pressure and obesity (BMI ≥ 30 kg/m^2)]. It was developed in Berlin, Germany, in April 1996 by the Conference on Sleep in Primary Care. The responses to each category of questions are scored to produce an indicator of high/low risk for each category, and the scores for the 3 categories are combined to obtain the overall indicator of high or low risk for sleep apnea. Chi-squared tests were used to compare the RA patients and the non-RA subjects. Logistic regression models were used to assess the association between RA and risk for sleep apnea after adjusting for potential confounders.

RESULTS

The 164 RA patients and 328 non-RA subjects had the same gender distribution, with 28% males and 72% females in both groups (Table 1). Age was similar in both groups, with an average age of 62.9 ± 12.2 years for the RA patients and 64.0 ± 10.5 years for the non-RA subjects. The 2 groups had comparable BMI, with RA patients having an average BMI of 28.4 (SD 5.5 kg/m^2) and non-RA subjects having an average BMI of 28.2 (SD 5.5 kg/m^2).

The Berlin Sleep Questionnaire, which was completed by all study participants, showed that 82 (50%) of the RA patients and 101 (31%; p < 0.001) of the non-RA subjects were at a high risk of having sleep apnea. Within the questionnaire, no difference was found in the snoring subscale (48% for the RA patients and 44% for the non-RA subjects; p = 0.31) or in the co-morbidities subscale (59% for the RA patients and 54% for the non-RA subjects, p = 0.37). However, there was a significant difference between the 2 groups in the fatigue subscale (38% for the RA patients and 13% for the non-RA subjects; p < 0.001). This difference persisted after adjustment for smoking status, BMI, and high blood pressure (adjusted OR: 4.58; 95% CI: 2.83, 7.41; p < 0.001).

Patients with RA were more likely to have a diagnosis of obstructive sleep apnea (14%) than subjects without RA (9%), but this difference was not statistically significant (p = 0.13). Adjustment for smoking status, BMI, and high blood pressure did not change this association (adjusted OR: 1.59; 95% CI: 0.84, 2.99; p = 0.15).

Among 164 RA patients, 110 (67%) were rheumatoid factor positive, 23 (14%) had a prior diagnosis of sleep apnea, and 8 (5%) were being treated with continuous positive airway pressure (CPAP, Table 2). These 23 patients represent only 20% of RA patients at high risk for OSA. Subjects at a high risk of sleep apnea were more likely to be male (39% vs 17%; p = 0.002), have a higher average BMI (mean 30.2 kg/m^2 vs 26.7 kg/m^2; p < 0.001), have a BMI classified as obese (57% vs 22%; p < 0.001), and have high blood pressure (52% vs 22%; p < 0.001) compared to those at a low risk of sleep apnea.

DISCUSSION

Based on the Berlin Sleep Questionnaire, the percentage of subjects at high risk for sleep apnea is higher among RA patients than non-RA subjects, with a statistically significant higher frequency of fatigue. Subjects at high risk for sleep apnea are also more likely to be male, have high blood pressure, and have a higher average BMI, with more individuals in the BMI classification of obese than those in the low risk of sleep apnea category. In addition, the relatively small per-

Table 1. Characteristics of study subjects with and without RA, and risk of sleep apnea. Values are number (%) unless otherwise indicated.

	Subjects		
	Non-RA, n = 328	RA, n = 164	p
Female	236 (72)	118 (72)	1.00
Age years, mean ± SD	64.0 ± 10.5	62.9 ± 12.2	0.31
Body mass index, kg/m^2, mean ± SD	28.2 ± 5.5	28.4 ± 5.5	0.62
High blood pressure	136 (42)	61 (37)	0.17
Smoking, current or former	138 (44)	76 (46)	0.64
Diagnosed with obstructive sleep apnea	31 (9)	23 (14)	0.13
Berlin Questionnaire Score			
High risk of sleep apnea	101 (31)	82 (50)	< 0.001
Low risk of sleep apnea	227 (69)	82 (50)	
Berlin Questionnaire Subscales			
Category 1: Snoring	144 (44)	80 (48)	0.31
Category 2: Fatigue	41 (13)	63 (38)	< 0.001
Category 3: Comorbidities	178 (54)	97 (59)	0.37

Table 2. Characteristics and risk factors according to risk of obstructive sleep apnea (OSA) in patients with RA. Values are number of patients (%) unless otherwise noted.

	Low Risk of Sleep Apnea, n = 82	High Risk of Sleep Apnea, n = 82	p
Female	68 (83)	50 (61)	0.002
Age, years, mean ± SD	62.6 ± 11.7	63.2 ± 12.8	0.74
High blood pressure	18 (22)	43 (52)	< 0.001
Smoking, current or former	33 (40)	43 (52)	0.12
Rheumatoid factor positive	55 (67)	55 (67)	1.00
Diagnosed with OSA	7 (9)	16 (20)	0.04
Treatment of OSA with CPAP	3 (4)	5 (6)	0.46
Body mass index (BMI)	26.7 ± 5.0	30.2 ± 5.4	< 0.001
Underweight, BMI ≤ 18.5 kg/m^2	3 (4)	4 (5)	0.70
Overweight, BMI ≥ 25 kg/m^2	45 (55)	63 (77)	0.003
Obese, BMI ≥ 30 kg/m^2	18 (22)	47 (57)	< 0.001

CPAP: continuous positive airway pressure.

centage (20%) of RA patients with a clinical diagnosis of OSA suggests that OSA may be under recognized in RA patients. Alternatively, the Berlin Sleep questionnaire may be less sensitive in this patient population.

Our findings are consistent with the results of the 2005 National Sleep Foundation poll, which showed that 26% of the individuals in the general population meet the Berlin Sleep Questionnaire criteria for high risk of sleep apnea[13]. Among those at high risk of sleep apnea, there was a statistically significant difference between sexes, with more men (31%) in the high risk of sleep apnea category than women (21%; $p \leq 0.001$). Our study showed similar results, with 69% of the male RA patients in the high risk of sleep apnea category compared to only 42% of the female RA patients. The National Sleep Foundation poll also found the Berlin Sleep Questionnaire to be strongly associated with obesity. Among obese individuals, 58% had a high-risk Berlin questionnaire score compared to only 2% of the individuals with low BMI. Our results showed the same trend with 72% of the obese individuals having a high-risk Berlin questionnaire score compared to only 6% of the low BMI individuals. Further, sleepiness symptoms were previously found to be common in the general population, with 26% reporting feeling tired or fatigued on ≥ 3 days of the week. This symptom was much more common in the high-risk group determined by the Berlin questionnaire results, having been reported by 63% in this group. It was also found that persons reporting a chronic medical illness were more likely to have a high-risk Berlin questionnaire score (35%) than a low-risk Berlin questionnaire score (11%).

Apart from these findings in the general population, only 2 studies (reported as abstracts) examined the risk of OSA in RA patients[14,15]. Holman, *et al* reported 45% prevalence of OSA in men with connective tissue diseases, including RA[15]. The prevalence of OSA was high regardless of BMI or type of inflammatory disease. It is intriguing that the percentage of RA patients at high risk for sleep apnea is high despite the paradoxical relationship between BMI and CVD in patients with RA[16]. In another study from Japan, more than half the 96 RA patients (mostly female) had OSA[14]. Among patients who were treated with CPAP, the investigators observed a 40% reduction in RA disease activity and CRP values at 6 months. More recently, a small study provided convincing evidence regarding inflammatory etiology of OSA. Eight obese male patients with OSA (but no RA) experienced a significant decline in OSA symptoms[17]. The effect was not only significant but about 3-fold higher than effects of CPAP, which is the standard therapy for OSA.

These findings have implications regarding the potential contribution of OSA to CVD in RA patients. OSA has been linked to inflammatory, coagulation, and endothelial changes, which can also be found in patients with RA and possibly suggest common underlying pathological mechanisms[3]. Recent studies suggest that the autonomic response to chronic OSA accounts for much of the increased CVD risk[18]. The autonomic nervous system influences inflammatory disease activity and autoimmunity through a variety of mechanisms[19]. In patients with RA, autonomic status, as measured by rapid heart rate variability, predicts therapeutic response to anti-tumor necrosis factor (anti-TNF) therapy, suggesting the possibility that OSA in patients with RA may contribute to poor response to anti-TNF therapy and perhaps even increased risk of CVD[20]. Finally, OSA is associated with increased risk of nocturnal sudden cardiac deaths[21], and the increased risk of sudden deaths in patients with RA raises concerns for untreated OSA due to its impact on dysautonomia or arrhythmia[1].

Some potential limitations should be taken into consideration when interpreting our results. First, our findings may not be generalizable to non-white individuals because our study population was entirely white. Not all of the participants in this study, if any, were medically evaluated for OSA, although some participants were already undergoing treatment for OSA with CPAP. It is unknown whether or not the fatigue reported by the Berlin Sleep Questionnaire was due to the RA disease itself, comorbid conditions such as fibromyalgia[22], or to potential undiagnosed OSA. Finally, participation bias is a possibility if subjects at high or low risk of sleep apnea were more likely to participate in this study. However, this is unlikely because subjects completed the Berlin questionnaire as part of another study aiming to examine the risk of heart disease in RA. RA subjects in this study were mostly in good health with normal to high BMI compared to a typical prevalent RA cohort, with many in the low BMI category. The strengths of our study include its population-based design with extensive medical record and questionnaire based information on all subjects and systematic assessment of sleep apnea and related conditions using a well-established assessment tool. Although cost considerations may limit evaluation of OSA using in-laboratory polysomnography in RA patients, a variety of low cost alternatives exist and may prove cost effective in selected patient groups[23].

In conclusion, patients with RA may be at a higher risk for sleep apnea compared to non-RA subjects. This apparent risk difference may be attributed to reports of fatigue in the RA patients, which may be associated with sleep apnea or the RA disease itself. Further research including formal sleep evaluation is needed to determine the extent of sleep apnea in patients with RA and its impact on the increased risk of CVD.

ACKNOWLEDGMENT

We are grateful to Cynthia Stoppel for her patient recruiting efforts and Sherry Kallies for manuscript preparation.

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