Considering cardiovascular mortality in patients with rheumatoid arthritis from a different perspective: a role for autonomic dysregulation and obstructive sleep apnea.

Andrew J Holman

J Rheumatol 2007;34;671-673
http://www.jrheum.org/content/34/4/671.citation

1. Sign up for TOCs and other alerts
   http://www.jrheum.org/alerts

2. Information on Subscriptions
   http://jrheum.com/faq

3. Information on permissions/orders of reprints
   http://jrheum.com/reprints_permissions

*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Considering Cardiovascular Mortality in Patients with Rheumatoid Arthritis from a Different Perspective: A Role for Autonomic Dysregulation and Obstructive Sleep Apnea

Increased cardiovascular morbidity and mortality has been described among patients with rheumatoid arthritis (RA)\(^1\). The leading cause of death (42\%) among patients with RA is of cardiac origin\(^2\). Ironically, just when normal or near normal lives are within reach for many of our patients, they are faced with increased mortality from cardiovascular disease (CVD).

As rheumatologists, we are considering the causes of increased CVD among our patients with autoimmune disease\(^3\). But as immunologists, we have a penchant for analysis of medical disorders from an immunologic perspective. Considering this important issue from a different point of view may be worthwhile. Many clinicians are concerned about the impact of endothelial inflammation in atherosclerotic cardiovascular disease. Following this lead, some rheumatologists have also embraced the concept that our primary nemesis, inflammation, plays a greater role in this cardiovascular process than previously recognized. Also, our use of corticosteroids to treat rheumatic diseases raises the specter of our complicity to an even greater level. All signs seem to point to us. Intuitively, corticosteroid treatment and the underlying inflammatory disease seem to be responsible. However, there may be other reasonable rationales for increased CVD risk among patients with RA that arise from a different perspective.

Fibromyalgia research has broadened our understanding of human physiology to include concepts of neuroregulation and especially autonomic regulation\(^4\). Also, to study fibromyalgia, one must frequent the sleep and neurology literature. The effect of common sleep disorders, particularly obstructive sleep apnea and narcolepsy, creep into one’s schematic view of the universe. Consequently, those interested in the fibromyalgia enigma have found their lexicon expanding into regions not traditionally of interest to the rheumatology community. Study of sleep disordered breathing may offer additional insight into why patients with RA are more apt to develop CVD.

The increased rate of CAD in patients with inflammatory disease is inadequately explained by traditional risk factors\(^5\). The duration of disease in RA corrected for age only partially explains an increased risk, and evidence for corticosteroid use is mixed\(^6\). However, radiographic intensity of RA does appear to correlate with increased CVD. What unforeseen comorbidity could account for both increased CVD and increased autoimmune disease activity? Obstructive sleep apnea (OSA).

OSA is defined as an apnea-hypopnea index (AHI) of > 5.0 events per hour. Mild disease is defined as 5–15, moderate as 15–30 and severe as an AHI > 30\(^7\). Based on 4 large studies, OSA, including mild OSA, occurs in 17–26\% of men and 9–28\% of women older than 20\(^8\)-\(^11\). Apnea may be central, obstructive, or both. Traditional risk factors assessed by a rheumatologist, such as body mass index (BMI), shirt collar size, a history of hypertension, snoring, daytime somnolence, morning headache, or witnessed apnea are important clinical features of this syndrome. Due to the time, labor, and cost burden associated with formal polysomnography (PSG), ambulatory overnight oximetry has also been proposed as a tool to triage patients\(^12\). With PSG facilities in high demand and long delays for referrals, this technique is a cost effective modality for screening moderate to severe OSA\(^13\).

The impact of OSA on CVD has been thoroughly reviewed by Parish and Somers\(^14\). The Sleep Health Heart Study used PSG to evaluate 6426 patients already enrolled in cardiovascular risk trials to confirm OSA as a significant risk factor for coronary artery disease, hypertension (HTN), congestive heart failure (CHF), and stroke. The age-adjusted odds of vascular mortality of untreated OSA at 5 years is increased 4.7 fold\(^15\) compared those with aggressively treated OSA, but treatment with continuous positive airway pressure (CPAP) abrogates much of this increased risk\(^16\). This treatment benefit may be even more significant for CHF.

OSA is also a potent and often forgotten cause of autonomic arousal\(^17\). In the past, increased risk of HTN and stroke associated with OSA was thought to be due to a plethora of disparate events, including cumulative hypoxic injury of endothelium. Recent studies have proposed that it is the autonomic response to chronic OSA that accounts for much of the increased CVD risk\(^18\). Noradrenergic activation during hypoxia and apnea may affect systemic vascu-
lar tone through central and peripheral mechanisms. These autonomic abnormalities occur even when patients are awake and not hypoxic. An increased risk of sudden death in RA also raises concern for untreated OSA due to the impact of dysautonomia on arrhythmia. OSA has also been linked to inflammatory, coagulation, and endothelial changes, which should pique the interest of rheumatologists (Table 1)\textsuperscript{14}.

As essentially a drowning reflex response to inadequate respiration and transient hypoxia, a chronically heightened dysautonomic state results with excessive sympathetic tone affecting vascular, metabolic, and immunologic homeostasis. OSA adversely affects diabetic care and metabolic rate affecting vascular, metabolic, and immunologic homeostasis. OSA adversely affects diabetic care and metabolic rate. These dysautonomic abnormalities occur even when patients are awake and not hypoxic. An increased risk of sudden death in RA also raises concern for untreated OSA due to the impact of dysautonomia on arrhythmia.

OSA is associated with insulin resistance and increased oxidative stress. Insulin resistance related to systemic inflammation or glucosecorticoid use has been proposed as an explanation of increased CVD risk in patients with RA, but the effect of OSA on insulin resistance was not considered\textsuperscript{6}. Effective treatment of OSA with CPAP in patients with type 2 diabetes improves HbA\textsubscript{1c} and nocturnal frequency, and even improves nocturnal blood glucose levels in non-diabetic individuals\textsuperscript{20}. OSA is also an independent cause of weight gain\textsuperscript{21}, which, in turn, directly influences OSA.

No information is currently available describing the incidence of OSA in patients with autoimmune disease, but 2 small pilot studies have begun to explore this important question. In 2003, Shimizu, \textit{et al} conducted PSG evaluations in 96 consecutive Japanese patients (84\% women) with RA\textsuperscript{22}. Remarkably, 53\% of this cohort were found to have OSA by international standards of AHI > 5.0. Patients of Asian heritage have a higher rate of OSA, possibly due to cephalometric characteristics, but the expected prevalence in Japan would not be 53\%\textsuperscript{23}. A pilot study in Seattle also reported a prevalence of OSA in 45\% of men with a connective tissue disease [RA, systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), psoriatic arthritis]\textsuperscript{24}. Obesity by BMI and Epworth sleepiness scale were poor predictors of OSA in these men. Only 40\% with OSA were obese by BMI, and 20\% had either normal or low BMI. The prevalence of OSA was high regardless of inflammatory disease, including the AS group who had the lowest mean BMI. Therefore, without this assessment, as supported by diagnostic PSG, their ultimate increased prevalence of CVD to be recognized in years to come would have remained mysterious. As a subgroup prevalence of untreated OSA over the general population increases, as may be the case for those with inflammatory arthritis, an increased risk of CVD should accompany it.

Some of our assumptions must be questioned, since often only those with high BMI are referred for PSG. A curious inverse relationship of BMI to CVD mortality in patients with RA has already been reported\textsuperscript{25}. But high BMI was protective only if erythrocyte sedimentation rate was low. Consequently, our traditional view of BMI and OSA, at least in patients with RA, requires some reconsideration. Whether effective treatment of their OSA with CPAP will partially or completely abrogate an increased risk of CVD in the setting of an autoimmune disease remains to be determined. But, looking for this CVD risk factor in our patients is an option currently available by simply ordering a PSG or screening with ambulatory pulse oximetry.

The systemic inflammatory consequences of untreated OSA include endothelial dysfunction, reduced fibrinolytic activity, and increased serum levels of interleukin 6 (IL-6), C-reactive protein, tumor necrosis factor-\textalpha, IL-1\beta, leptin, reactive oxygen species, adhesion molecules, fibrinogen, and plasminogen activator inhibitor\textsuperscript{26}. Treatment with CPAP reduces TNF-\textalpha and CD40L expression and decreases CD8 T cell cytotoxicity\textsuperscript{27}. Immunoology is clearly influenced by the central nervous system and autonomic tone, and these principles require more attention.

At least with regard to CVD mortality in our patients, it would be of considerable interest to conclusively document the incidence of OSA in RA, SLE, and other autoimmune diseases. Assessing whether treatment of OSA with CPAP decreases CVD risk in this subset of patients would also be worthwhile. Sleep specialists are already interested in autonomic tone, hypoxia, and therapeutic intervention to reduce CVD risk. Perhaps we should be as well.

Rheumatologists are trained to deal with complex and deceptive diseases. In many multisystem disorders, such as systemic sclerosis, systemic lupus, and vasculitis, our effort to look at the bigger picture of multiple organ involvement is somewhat unique among consultative physicians. We are considered “arthritis specialists” by many colleagues and patients, but we are concerned by much more than simply joint pathology. It is that broader view that needs to be present.
rekindled in this debate over the cause of increased cardiovascular mortality in patients with inflammatory disease.

ANDREW J. HOLMAN, MD,
Assistant Clinical Professor of Medicine,
University of Washington,
Pacific Rheumatology Research Inc.,
4300 Talbot Road South, Suite 101,
Renton, Washington 98055,
USA.

Address reprint requests to Dr. Holman.
E-mail: AJHSeattle@aol.com

REFERENCES