Respiratory Care Year in Review 2012: Asthma and Sleep-Disordered Breathing

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Introduction

Asthma

Objective Measures and Assessment of Lung Function

Environmental Control Measures to Avoid Allergens and Irritants

Pharmacology

Education

Sleep-Disordered Breathing

Sleep-Disordered Breathing and Mortality

Sleep-Disordered Breathing and Pre-diabetes

Sleep-Disordered Breathing and Portable Monitoring

Summary

Asthma has long been recognized as a common respiratory disease, and the recognition of sleep-disordered breathing is becoming more prevalent. Patients with these disorders are commonly seen by clinicians caring for patients with respiratory disease. There is also much academic interest in asthma and sleep-disordered breathing. The purpose of this paper is to review the recent literature related to asthma and sleep-disordered breathing in a manner that is most likely to have interest to the readers of *RESPIRATORY CARE*. *Key words:* asthma; lung function; pharmacology; diabetes; sleep-disordered breathing; patient education. [Respir Care 2013;58(5):874–883. © 2013 Daedalus Enterprises]

Introduction

It can be a challenge to review the literature relevant to one's practice and then update that practice based on the current evidence. At the 58th AARC Congress, *RESPIRATORY CARE* presented a series of lectures on the theme of

"Year in Review." Topics were chosen that are likely to have special interest to the readers of *RESPIRATORY CARE*. We previously reviewed invasive ventilation, noninvasive ventilation, and cystic fibrosis.¹ In this paper we publish topics related to asthma and sleep-disordered breathing (SDB).

Asthma

Asthma is defined as a chronic inflammatory disease of the airways and lungs that is frequently characterized by

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Table. Essential Components of Asthma Management

Objective measures and assessment of lung function
Environmental control measures to avoid allergens and irritants
Pharmacologic therapy
Patient education

airway hyper-reactivity and bronchoconstriction of the airways. Asthma is the most prevalent chronic respiratory disease within the United States today. The prevalence of asthma increased from 20.3 million persons in 2001 to 25.7 million persons in 2010 (2.9% each year), of whom 7 million were children under 18 years of age.²

Asthma is a multifactorial disease and hence much literature is published every year. A PubMed search with key words on the subject of asthma for 2012 yields thousands of publications, which further demonstrates the relevance and importance of this common disease. This review will focus on a selected number of 2012 publications based on the 4 essential components of asthma management as established by the National Health Lung Blood Institute Asthma Expert Panel Report Three (Table).³

Objective Measures and Assessment of Lung Function

As identified by the National Health Lung Blood Institute expert panel:

Diagnosing a patient as having asthma is only the first step in reducing the symptoms, functional limitations, impairment in quality of life, and risk of adverse events that are associated with the disease. The ultimate goal of treatment is to enable a patient to live with none of these manifestations of asthma, and an initial assessment of the severity of the disease allows an estimate of the type and intensity of treatment needed.

Diagnosis and monitoring are the main elements found within the first essential component of asthma management. From a diagnostic standpoint, spirometry has long been considered the gold standard of asthma diagnosis, and is recommended upon diagnosis and then annually or biannually thereafter. While not specific to asthma, a Journal Conference published 14 papers on pulmonary function testing in *RESPIRATORY CARE* in January 2012. In the summary of the conference, Ruppel and Enright⁴ state:

Pulmonary function testing is an important diagnostic specialty, particularly with regard to diseases such as COPD, asthma, and interstitial lung disease. As new and better therapies for a wide array of pulmonary disorders become available, pulmonary

function testing should play an increasing role in identifying and quantifying the physiologic changes attributable not just to the disease, but to the treatment as well.

Two studies look at methodologies to assist in the diagnosis of asthma. Sumino et al⁵ looked at the ability of the methacholine challenge test to assist in the diagnosis of asthma in patients who were using controller medications. The study assessed 126 subjects with asthma receiving controller medication, versus 93 control subjects without asthma, to evaluate the sensitivity and specificity of the methacholine challenge test. The study found the sensitivity significantly lower in whites than in African-American participants, and in atopic subjects compared to non-atopic subjects. The authors concluded that the utility of the methacholine challenge test to rule out diagnosis of asthma depends on racial and topic characteristics. The study by Shi et al⁶ investigated impulse oscillometry as an objective and noninvasive measure of lung function to independently examine both smaller and larger airways. They compared impulse oscillometry in children with asthma, and in healthy children, for respiratory system resistance and reactance before and after a bronchodilator was administered. Small airway impulse oscillometry measurements that included the difference of resistance at 5 and 20 Hz, reactance at 5 Hz, resident frequency of reactants, and reactants area values were significantly different from those of children with controlled asthma and healthy children, especially before administering a bronchodilator. Receiver operating characteristic curve analysis showed cut points effectively discriminating controlled versus uncontrolled asthma, and correctly classifying more than 80% of the population.

Perhaps the biggest area of investigation in 2012 was in the utility of exhaled nitric oxide as a biomarker for asthma management. Three trials⁷⁻⁹ found that the utility of exhaled nitric oxide for the management of asthma was of questionable value. The meta-analysis by Jartti et al also questioned the utility of routine use of exhaled nitric oxide.¹⁰

While spirometry remains the gold standard, clinicians continue to seek better refinement of spirometry or other technologies to enhance the diagnosis and management of asthma. Ross et al¹¹ sought to examine the relationship among obesity and SDB in children with asthma. This prospective study of 108 children found obesity in 42.6% of the population, and SDB in 29.6% of the population. The study found that SDB had 3.62-fold increased odds of children having severe asthma, whereas obesity was not associated with asthma severity.

From a monitoring standpoint, many studies looked at a variety of different resources and tools to either assess patients or for self-assessment by patients for control of their asthma and symptoms. Gold and colleagues¹² high-

lighted the importance of asthma control in a retrospective analysis of the Asthma Insights and Management survey, enrolling 2,500 subjects with asthma older than 12 years of age. They found that subjects with lower income, lower educational status, and those who lacked health insurance were less likely to have well-controlled asthma. Subjects with uncontrolled asthma were more likely to report having used oral steroids and over-the-counter medications. Subjects with poorly controlled or uncontrolled asthma were also significantly more likely to report unscheduled physician visits, emergency department (ED) visits, or hospitalizations. Finally, subjects with uncontrolled asthma had increased odds of reporting limited activities of daily living. In another study of asthma control, Rudell and colleagues¹³ examined clinicians' ability to evaluate patient levels of asthma control, compared to the Global Initiative for Asthma Guidelines in 4 countries, by utilizing the Asthma Control Questionnaire in 55 subjects. They found that classification of asthma control was accurate in only 28 cases (51% of the time).

Two other studies in 2012 looked at the ability to monitor asthma and its impact on a geriatric population. A study by Crane and colleagues¹⁴ looked at the development and validation of a Patient Asthma Concerns Tool to identify the needs of older people with asthma. The tool was developed from a pool of 55 items from a comprehensive literature review and narrowed down, psychometrically tested, and refined to 14 items. In a sample of 193 subjects, the tool correlated well with the Juniper Asthma Control Questionnaire and Brooks' adherence score on related variables, and showed good reliability with good-to-excellent kappa and intraclass correlation coefficient scores. The internal consistency of factors was high, and the overall Cronbach factor was 0.70. Further investigation is necessary.

Smith et al¹⁵ evaluated characteristics of older subjects with asthma, versus controls, to determine overall differences and impact on quality of life. This study consisted of 77 subjects with a mean age of 68.7 ± 7.2 years (77% female). In subjects with asthma, a higher rate of positive skin prick tests were found in 88.9% of the subject compared to their controls ($P = .007$). The mean percent of predicted FEV₁ at baseline was lower in the asthma group compared with controls ($P = .007$). For quality of life assessment they used version 2 of the 36-item Medical Outcomes Study Short Form questionnaire, and subjects with asthma reported worse general health, increased body pain, and worse overall physical health, compared with controls ($P = .02$, $P = .02$, and $P = .01$, respectively).

Two other asthma scores were evaluated in studies published in 2012: one in the pediatric population, and one in the adult population. In a multicenter study by Wildfire and colleagues,¹⁶ investigators sought to develop and validate a new instrument, the Composite Asthma Severity

Index (CASI). This instrument was intended to qualify disease severity in children by taking into account impairment, risk, and the amount of medication needed to maintain control. The CASI scores included 5 domains: daytime symptoms with albuterol use, nighttime symptoms with albuterol use, controller treatment, lung function measures, and exacerbations. The CASI score ranges from 0 to 17, with the mean of 6.2. CASI was stable, with minimal change in variance after 1 year of treatment. The investigators found that CASI retained its discriminatory ability even with minimal symptoms after months of guideline-based care. CASI has the ability to determine levels of asthma severity and provide a composite clinical characteristic of asthma.

In the study enrolling adults,¹⁷ the Asthma Symptom Utility Index was developed to assess the frequency and severity of asthma symptoms, and was determined to have internal consistency reliability, with a Cronbach alpha of 0.74. Test-retest reliability was 0.76. Construct validity was demonstrated by significant correlations between Asthma Symptom Utility Index scores and Asthma Control Questionnaire and Mini Asthma Quality-of-Life Questionnaire scores ($P < .001$). Bime et al¹⁷ concluded that the Asthma Symptom Utility Index is reliable, valid, and responsive to changes and asthma control over time.

Environmental Control Measures to Avoid Allergens and Irritants

In a study that looked at environmental aspects and the control of asthma, Oh et al¹⁸ examined the association between poor asthma control with in utero smoking and secondhand smoke exposure among Latino black children with asthma. Poor asthma control among children 8–17 years of age was independently associated with in utero smoking, with an odds ratio of 1.5. In utero smoking by the mother was associated with secondary asthma outcomes, including early-onset asthma (odds ratio 1.7), daytime symptoms (odds ratio 1.6), and asthma related limitation of activities (odds ratio 1.6).

Pharmacology

Pharmacology as a component of rescue, and control of asthma exacerbations is an important aspect of asthma management. There are many studies published each year that deal with general pharmacology, controller medications, combination therapy, and adherence to asthma medications under various conditions.

A study by Rank and colleagues¹⁹ determined the change in asthma controller medication use as measured by the controller-to-total asthma medication ratio and its association with changes in asthma exacerbation rates between 1997–1998 and 2004–2005. They found that the propor-

tion of individuals with controller-to-total asthma medication ratio has improved by 16.1%. Annual exacerbation rates did not change significantly in any group during the study period. While not statistically significant, African-American and Hispanic individuals with asthma had higher exacerbation rates and a lower proportion with a controller-to-total asthma medication ratio in this trial.

A study by Schilling et al²⁰ looked at controller medications to determine whether physiological pulmonary measures are superior to other measures for evaluating outcomes and determining whether children with asthma have a higher risk of serious adverse events than adults. They found that the frequency of successfully demonstrating efficacy was far superior using physiologic pulmonary measures, such as FEV₁ and peak flow, compared to other asthma symptom measures. While the frequency of serious asthma exacerbations was higher in children than adults, it was not statistically significant and was less than 1% in the study population. These results suggest that physiologic pulmonary function measures should be used in evaluating the efficacy of asthma controller medications.

A study by Anderson and Lipworth²¹ looked at the ability to assess dose-response of inhaled budesonide on outcome measures of asthma between overweight and normal weight subjects with persistent asthma. Subjects were divided into 2 groups: overweight with a body mass index (BMI) ≥ 25 kg/m², and controls with BMI < 25 kg/m². Each cohort was treated with low-dose 200 μ g per day and high-dose 800 μ g per day of the budesonide. The study demonstrated significant improvements in the control group for both fraction of exhaled nitric oxide and symptom response at both low and high-dose budesonide ($P < .001$). A trend toward attenuated cortisol suppression in overweight subjects was seen with the low-dose and high-dose budesonide. There was no significant difference seen at either dose in FEV₁ or methacholine challenge between weight groups.

The use of inhaled corticosteroids (ICS) after an asthma exacerbation that results in an ED visit has always been an area of high interest. There were 3 studies published during 2012 that looked at various aspects in both the adult and pediatric population dealing with ICS after ED discharge. The study by Andrews and colleagues²² sought to determine what proportion of pediatric patients seen in the ED for asthma exacerbations received ICS or attended follow-up appointments, in a cohort of 3,435 subjects. Those with severe asthma were more likely to receive ICS and attend a follow-up appointment (odds ratio 2.9 and 2.0, respectively). Subjects between 2 and 6 years of age and > 12 years were less likely to attend follow-up ($P < .001$).

A second study by Andrews et al²³ sought to determine the clinical effectiveness and cost-effectiveness of 3 ICS options for children with asthma. They conducted a cost-

effective analysis using a decision tree to compare 3 ED-based ICS delivery options: usual care (follow-up care only); prescribing (uniform ICS prescribing); and dispensing (uniform dispensing ICS). The decision tree analysis model suggested that uniform prescribing or dispensing of ICS at the time of ED visits for asthma may lead to decrease in the number of ED visits and hospitalizations within 1 month of the ED sentinel event and provides a substantial cost savings.

The study by Stanford and colleagues²⁴ sought to assess whether receiving a controller medication at discharge affected the risk of reoccurrence or whether delaying controller initiation alters this risk. The study retrospectively reviewed 6,139 subjects. The investigators found the adjusted hazard ratio associated with not having a controller medication at discharge was 1.79. The controller-by-time interaction was significant ($P < .001$), with hazard rising as time-to-control initiation increased. Delaying initiation by 1 day approximately tripled the risk of relapse.

The dilemma of when to initiate ICS alone or ICS with long-acting β agonist (LABA) is always an area of interest when utilizing asthma guidelines management strategies. Wells and colleagues²⁵ estimated the effect of ICS therapy and fixed-dose ICS/LABA combination therapy on severe asthma exacerbations in a racially diverse population through database modeling: 1,828 subjects met the inclusion criteria, 37% were African-American, 46% were treated with ICS therapy alone, and 54% were treated with an ICS/LABA combination. The modeling demonstrated that treatment with ICS/LABA fixed-dose combination therapy appeared to perform as well as or better than ICS treatment alone in reducing severe asthma exacerbations, including multiple high-risk subgroups.

Due to the black box warning, LABA use is always a concern in the African-American population. This warning is listed both for LABA alone and for when combined with ICS. A study by Brown and colleagues²⁶ assessed safety and asthma control within budesonide/formoterol pressurized metered-dose inhaler versus the budesonide over a 1-year period in an African-American population. The study was in subjects ≥ 12 years of age with moderate to severe asthma previously receiving medium to high-dose ICS. The investigators determined that both treatments were well tolerated. Asthma exacerbation incidence and rate were lower with the budesonide/formoterol, versus budesonide alone ($P = .006$). Time to first asthma exacerbation was longer with the budesonide/formoterol versus budesonide alone ($P = .02$). Serious adverse events occurred in 12 and 15 subjects, respectively, none considered drug-related. The authors concluded that, in this population, budesonide/formoterol with the pressurized metered-dose inhaler was well tolerated over 12 months, with a safety profile similar to that of budesonide alone. The asthma

exacerbation rate was reduced by 38.5%, versus budesonide alone.

Perhaps the best review of current asthma pharmacology and the future of asthma pharmacology is by Barnes.²⁷ Barnes stressed the need and future of single inhaler maintenance and reliever therapy. This approach attempts to reduce the likelihood of confusion and misaligned therapies and approaches, and potentially decreases adherence issues in the patients being prescribed asthma medications. Barnes reviewed new medications under development, which include β agonist, ICS, long-acting muscarinic agents, and anti-IgE (immunoglobulin) medications. Barnes also discussed targeting inflammatory mediators such as lipid mediator blockade, cytokine blockade, inhibiting TH2 cytokines, and chemokine receptor antagonist. Barnes concludes by discussing broad-spectrum anti-inflammatories such as phosphodiesterase (PDE4) inhibitors and kinase inhibitors, as well as the future role of macrolides.

The paper by Krishnan and colleagues²⁸ compared subjective and objective measurements of children's adherence to ICS or placebo to determine whether adherence to study medications modified treatment related differences and outcomes. An adherence rate of $< 80\%$ was seen in 75% of the 140 children when adherence was measured objectively, but only in 6% of children when measured by means of self-report. There was poor agreement between objective and subjective measurements of adherence of $> 80\%$. Self-reported adherence over the 4-year period generally overestimated objectively measured adherence. This suggests that objective rather than self-report adherence data to identify low levels of adherence to asthma medications.

The paper by Moullec et al²⁹ is a systematic review of the efficacy of interventions to improve ICS adherence among adult asthmatics to determine whether the use of chronic care model components (ie, teaching of management skills, providing decision-support, delivery system design, and clinical information systems) resulted in greater adherence. The systematic review included 18 studies that demonstrated that inclusion of a greater number of chronic care model components with an intervention was associated with stronger effects on ICS adherence outcomes. The interventions featured 1, 2, and 4 chronic care model components having medium (effect size = 0.29), large (effect size = 0.53), and very large (effect size = 0.83) effects, respectively.

Education

The reviews here deal with asthma follow-up visits, the importance of device education, use of asthma action plans, literary and language proficiencies, and new concepts in delivering asthma education that may or may not be successful.

Li and colleagues³⁰ described the follow-up care within 28 days of ED visits for asthma and determined the association of 28 days follow-up visits with ED revisits and hospitalizations in the subsequent year. This was a population-based, retrospective cohort study of 29,391 children with asthma, between the ages of 2 and 17 years, treated in an ED in Ontario, Canada. Results demonstrated 32.8% had follow-up, 6,496 (2.1%) had an ED revisit, and 801 (2.7%) had a hospital readmission. Having a follow-up visit was not associated with ED revisit or hospitalization (hazard ratios of 0.98 and 1.06, respectively). Younger children and those with indices of more severe acute or chronic asthma were more likely to have ED revisits and hospitalizations.

A study published in *RESPIRATORY CARE* in late 2011 by Basheti et al³¹ demonstrates the importance and difficulty of proper education on aerosol delivery devices technique. The study evaluated the most problematic steps in the use of the Diskus and Turbuhaler for both pharmacists and patients in Jordan and Australia. While there was a significant difference in that pharmacists in Australia received inhaler technique education more recently than those in Jordan ($P = .03$), they often made the same mistakes. The pharmacists in both countries showed inability to follow the correct steps for exhaling to residual volume or exhaling away from the device. With the Turbuhaler there were significant differences between pharmacists from Australia and Jordan in holding the device upright while loading (45% vs 2%, $P < .001$). As would be expected, the patients made errors similar to those of the pharmacist with individual steps with both the Diskus and Turbuhaler.

Gupta and colleagues³² looked at the use of asthma action plans, which have been strongly recommended for the use of asthma self-management by all asthma guidelines. Studies in the past have demonstrated both positive and negative benefits to asthma action plans. This study sought to characterize the variability in both the content and format of existing plans, and the extent to which the format conforms to evidence-based visual design recommendations. Investigators collected 69 English or French language adult out-patient plans from around the world. They found large variability in format, and the plans fulfilled a mean of only 3.5 out of 8 evidence-based visual design recommendations. Content was also variable, including different descriptions of the baseline clinical state and descriptions of instructions at each action point. The authors concluded that these results suggest that evidence-based visual design has not been adequately addressed in most plans, and design evidence and experts should be included in future development.

A study by Rosas-Salazar et al³³ highlighted the following about health literacy in asthma. Understanding of health literacy and asthma has markedly improved. Current evi-

dence of children and adults suggests that poor health literacy is an important key barrier to asthma knowledge. There is an incomplete understanding of the relationship between low health literacy and other asthma outcomes at this time. Clinical trials are needed to assess effective interventions in subjects with asthma and low health literacy. Wisnivesky et al³⁴ looked at the association between language proficiency and outcomes in elderly subjects with asthma. The authors determined that, when adjusted for health literacy proficiency, those who actually demonstrated lower proficiency realized and reported an overall lower quality of life and worse adherence to medications.

A paper by Backer et al³⁵ studied the level of disease control in adults with asthma managed by their general practitioners and a dedicated nurse when using a systematic asthma consultation based on the Global Initiative for Asthma guidelines. At the baseline visit, 684 subjects (36.8%) were classified as well controlled, 740 (39.8%) as partially controlled, and 434 (23.4%) as uncontrolled. After the intervention a higher level of asthma control was found at the follow-up visit, compared to baseline visits (uncontrolled asthma 29.7% and 16.5%, respectively, $P < .001$). At the time of the follow-up visit, changes in treatment strategies were found ($P < .01$), and the level of lung function improved at follow-up.

Eakin et al³⁶ evaluated the effects of providing mobile Breathmobile services only, a facilitated asthma communication intervention only, or both the Breathmobile and a facilitated asthma communication intervention on asthma outcomes relative to standard care in children. Other than a slight improvement in symptom-free days at 6-months in the Breathmobile plus facilitated-asthma-communication-intervention group, the intervention components did not result in any significant improvements in asthma management or asthma morbidity.

Education and modification of the patient's environment are important aspects of asthma management. Schatz and Zeiger³⁷ determined what environmental changes subjects with allergic asthma say they would be willing to make, and what changes they had actually made. This study looked at subjects with asthma and known perennial aeroallergens sensitization who were asked by telephone to rate on a 1 to 5 point Likert scale their willingness to make specific changes. The intervention showed that 60 stage-1 subjects were willing to institute 14 of the 18 proposed allergen specific recommendations. Of the 36 stage-2 subjects who were allergic to mites, mold, and/or dander, 29 (80.6%) reported that they had implemented at least 1 of the recommendations made in the study. Subjects who owned their homes were significantly more likely to make at least 1 change than were subjects who rented their homes.

Sleep-Disordered Breathing

In 1997, Young et al estimated that 4% of men and 2% of women have obstructive sleep apnea (OSA), 50% of men and 25% of women snore, and up to 24% of middle-age men and 9% of middle-age women have SDB.³⁸ In a recent update, Young et al combined the results from 3 large population-based studies, including the 1997 Wisconsin study, and estimated that approximately 20% of adults had at least mild OSA, and 7% have moderate OSA.³⁹ The presence of SDB increases with age, and numerous studies have shown that OSA is linked to a number of cardiovascular diseases (CVDs), including hypertension, heart failure, atrial fibrillation, metabolic syndrome, myocardial infarction, diabetes, stroke, and transient ischemic attacks.⁴⁰⁻⁴²

The incidence of CVD and metabolic conditions such as type-2 diabetes, glucose intolerance, and insulin resistance has increased dramatically over the past 20 years. Indeed, the literature is relatively robust in outlining the potential importance of evaluating individuals with CVD and diabetes for the typical signs and symptoms of SDB, so that appropriate care can be prescribed. Many of the risk factors for the development of diabetes, such as obesity and hypertension, are also known to be risk factors associated with SDB. In addition to screening individuals with CVD and diabetes for signs and symptoms of SDB, there is an effort to identify individuals who are at high risk for the development of CVD and diabetes before the full onset of the disease.

Sleep-Disordered Breathing and Mortality

Findings from the Wisconsin Sleep Cohort⁴³ and the Sleep Heart Health Study⁴⁴ established that SDB was not only associated with CVD and other morbidities, but could also be linked to high mortality risk if left untreated. The Wisconsin Sleep Cohort⁴³ revealed an adjusted hazard ratio of 3.8 for all-cause mortality in the participants with severe SDB, as compared to those without SDB, whereas the Sleep Heart Health Study resulted in an adjusted hazard ratio of 2.09 for all-cause mortality in participants with severe SDB.⁴⁰ Interestingly in Punjabi's report,⁴⁴ SDB was not associated with increased mortality in men over the age of 70 years, but in men between the ages of 40 and 70 years with severe SDB, the risk of dying from any cause was twice that of comparable participants without SDB.

A study published in 2012 provides us with additional analysis of the incidence of SDB and how it is affected by, and how it in turn affects CVD.⁴⁵ The purpose of the study was to identify demographic and clinical variables found in patients with OSA that could be associated with the incidence of various adverse outcomes. The 8-year longi-

tudinal study analyzed all causes of mortality and outcomes of myocardial infarction, cerebrovascular accident, and pulmonary embolus. It was conducted at the Henry Ford Sleep Disorders and Research Center on 1,691 subjects diagnosed with either primary snoring or OSA. Of the subjects, 1,025 were positive for OSA and 494 were diagnosed as non-apneic snorers. The non-apneic snorers were used as the control group. Of the participants diagnosed with OSA, 42% had severe OSA, defined as an apnea-hypopnea index (AHI) ≥ 30 events/h. The subjects with severe OSA were relatively young (< 50 years of age), quite obese, predominantly male, and there was a very high proportion of African Americans.

The Henry Ford study was different from the previous studies in that prior medical history of cardiovascular risk factors or CVD did not eliminate subjects from the final analysis of those diseases or outcomes in follow-up. The authors felt that this would help to evaluate the impact of medical history on outcomes and allow for the results to have enhanced clinical relevance. The authors listed 5 key findings:

- All-cause mortality and outcomes of myocardial infarction, cerebrovascular accident, and pulmonary embolus were predicted by age and sex.
- Mortality and CVD outcomes were predicted by histories of CVD, not by OSA severity.
- Severe OSA was a significant, independent predictor of mortality for OSA in those < 50 years of age and in male subjects.
- Use of CPAP > 4 hours per night was associated with lower mortality in the severe OSA group and within the subgroups of male and older age with severe OSA.
- Severe OSA and male sex predicted mortality. Severe OSA, age, and HTN history predicted myocardial infarction.

To summarize the results of this study, the occurrence of significant cardiovascular outcomes and events was predicted by the history of cardiovascular risk factors and demographics, more so than by the severity of the OSA. However, males < 50 years of age with severe OSA were at particular risk of adverse cardiovascular events and mortality. Another key finding in this study is that the use of CPAP therapy, of at least 4 hours per night, was associated with lower mortality in subjects with severe OSA, though this benefit was not seen in subjects with less severe OSA in this study.

Sleep-Disordered Breathing and Pre-diabetes

The incidence of diabetes has increased to 8.3% of the United States population, and currently it is estimated that

there are 79 million American adults in a pre-diabetic condition characterized by glucose intolerance and insulin resistance.⁴⁶ It is known that individuals normally transition to full diabetes within 3 years of developing the pre-diabetic condition. Because of the high association of SDB, CVD, and diabetes, a recently published study looked at known markers of SDB and attempted to correlate them with individuals in a pre-diabetic state.⁴⁷ It was theorized that SDB markers might also be associated with pre-diabetes and could then be used to identify not only patients with SDB but also those in danger for the development of pre-diabetes.

This study published in 2012 looked at the general markers of SDB, in particular snoring and snorting, along with awakening gasping and witnessed apneas, and whether or not those same markers could be applied to a population of adults in a pre-diabetic state. According to the authors, the purpose of this study was to determine if the markers of SDB could also be associated with pre-diabetes so that intervention and the treatment of SDB could be used as a novel strategy to prevent the development of pre-diabetes and diabetes. Data from the National Health and Nutrition Evaluation Study from 2005–2008 on 5,685 participants were utilized, with approximately 50% of the participants being women, about 74% of participants being white, and with variable weight ranges.

The markers that were attributed to SDB were short sleep duration of < 6 hours, occasional or frequent snoring by the subject's report, occasional or frequent observations of snorting, and excessive daytime sleepiness. On initial analysis, all 4 of these markers of SDB were associated with the individuals with pre-diabetes. About 31% of the participants were diagnosed with a pre-diabetic condition, so there appeared to be a significant correlation between the markers of SDB and pre-diabetes. After correction for some of the confounders (male sex, weight, obesity), the final analysis revealed that only snoring and snorting were associated with the pre-diabetic condition. There was a stronger association between the markers of snorting and snoring among women, non-Hispanic whites, and Mexican Americans. Specifically, in the non-Hispanic black population, there was no significant correlation between these markers of SDB and pre-diabetes. This finding points out how different population groups may exhibit different signs, symptoms, and markers that need to be appreciated in clinical practice.

A second study⁴⁸ that dealt with metabolic control and diabetes in individuals with sleep apnea used a controlled trial of CPAP to determine whether adequate treatment of SDB could influence pre-diabetes and diabetic control. The purpose of the study was to determine if treatment of sleep apnea could improve glucose intolerance. This was a small study, with only 50 subjects, but, more importantly, it was a randomized double-blind crossover study. Each

group that was in one treatment arm of the study crossed over and also completed the opposite treatment. The 50 participants had moderate to severe sleep apnea, defined as an AHI of > 15 events/h. The study was limited to individuals with moderate to severe sleep apnea because, according to the authors, a number of previous studies have shown that individuals with mild to moderate disease do not have good outcomes even with therapy. Forty-two percent of the participants were men, the mean age of participants was 54 years, the BMI averaged 39 kg/m^2 , and the average AHI was 44 events/h. The participants were put on either CPAP or sham CPAP therapy for a period of 2 months, at which time they had a washout period of 1 week and then crossed over to the other treatment arm. The study showed that 8 weeks of CPAP therapy was unlikely to improve glucose metabolism in subjects who were obese with moderate OSA. However, for subjects who had severe OSA there was significant improvement in insulin sensitivity index. A second notable finding from this study was that, in those individuals who did find benefit from the use of CPAP therapy, each additional hour of CPAP above the requisite 4 hours was associated with significant further improvement in their insulin index. The results of this study suggest that careful attention to patient adherence to CPAP therapy is key to ensuring maximal benefit. A final point of interest in this study was that obese subjects with severe OSA were at particular risk for the development of not only type-2 diabetes but also CVD. This is not a surprising finding, but, again, it underscores the point that certain subsets of the population need not only our clinical diagnostic skills, but also our help in adhering to appropriate therapy.

Sleep-Disordered Breathing and Portable Monitoring

In 2008, the Centers for Medicare and Medicaid Services (CMS) ruled that portable monitoring or home sleep testing was an acceptable method for the diagnosis and establishment of the medical necessity for CPAP therapy. Since that ruling the number of portable monitors (PM) available has increased substantially, and technological advances have occurred to make PMs an attractive option for certain select patients and markets. The cost of providing standard in-laboratory polysomnography (PSG) diagnostic testing is often cited as a deterrent to sleep apnea evaluation, and, in addition, the issue of accessibility for certain subsets of patients due to geographical location or inability to travel is a consideration. It has been somewhat unclear how to determine the optimal treatment plan for the patient who was diagnosed with OSA via a PM. Just prior to release of the CMS decision on PMs, the American Academy of Sleep Medicine (AASM) published clinical guidelines on the use of PM in the diagnosis of OSA.⁴⁹ Included in the AASM clinical guidelines was a reference to data

suggesting that a protocol using PM and autoPAP (APAP) could be used to diagnose and treat carefully selected patients.

In 2012, Rosen et al published the results of a multi-site randomized trial (HomePAP study) comparing the use of PMs and APAP versus laboratory-based PSG and PAP titration.⁵⁰ Seven sleep centers participated in the study, with 373 subjects enrolled. There were 186 subjects in the lab arm of the study, with standard clinical evaluation followed by in-lab PSG. If they were positive for OSA, they either completed a split night study with both the diagnostic and introduction to PAP done the same night, or, if they did not meet the criteria for a split night, they returned for a second night of study. There were 187 subjects enrolled in the home arm of the study, which included a PM test and a trial of APAP. Subjects were at least 18 years of age and with a high probability of AHI > 15 events/h, based on a clinical algorithm and an Epworth Sleepiness Scale score > 12 . The AASM clinical guidelines state that PMs or home sleep testing should be used only in patients with a high probability of a positive sleep test. A PM is not designed to be a screening exam, and the AASM clinical guidelines state that if a home sleep study is negative in a patient suspected of having sleep apnea, the patient should return for an in-lab PSG study. The clinical algorithm used in the HomePAP study was primarily based on an adjusted neck circumference in centimeters. After measuring the neck circumference, additional centimeters were added for other clinical signs, including snoring, hypertension, witnessed apneas, or gasping. The portable monitoring test was followed by an APAP titration in the home and based on the results of downloads from the APAP machines, and the subject was then prescribed a fixed CPAP machine to use at home. Follow-up occurred at 1 month and 3 months, to look at various outcomes. An important finding from this study is that PAP usage was significantly higher at 3 month follow-up in the home arm versus the lab arm. This study showed that the home arm had an increase in usage in CPAP both in minutes per day and in percentage of nights used. Initial acceptance of CPAP therapy was the same, with 94% of lab subjects and 93% of home subjects accepting and willing to use the therapy at least initially. Most importantly, and the reason why CMS advocated for the use of PM, the home arm cost of providing both the diagnostic and therapeutic options for these subjects was 25% less than the in-lab arm, based on reimbursable costs through CMS. A key finding in this study was that the majority of the subjects in both the home and the in-lab arms did not meet CMS criteria for compliance at 1 month, though the home arm improved significantly at 3 month follow-up.

At the time of the CMS decision, many of the studies evaluating the efficacy of PMs had been conducted on select groups of participants in which the senior popula-

tion was not well represented. There was some concern that the studies showing PMs had comparable results with PSG might not generalize to all age groups. The final study in this review relates to the use of PMs to diagnose sleep apnea in the elderly. Morales et al evaluated the feasibility of a 2-stage screening process for OSA in older adults.⁵¹ A total of 461 participants were enrolled in the study, with 452 completing all required testing and follow-up. Thirty percent of the subjects were male, the average age was 71, 61% were African American, the average neck circumference was 38 cm, and the BMI was 29.9 kg/m². A key finding in this study was that the best predictor of OSA in older adults was the neck circumference, and not BMI, which is in contrast with middle-age adults. This again helps us to recognize that different markers and different predictors apply to different populations. Only 30% of subjects with moderate to severe sleep apnea had an Epworth Sleepiness Scale score > 10. Therefore, the Epworth Sleepiness Scale, which is a validated tool for use to determine excessive daytime sleepiness in the middle-age population, may not be the best tool to use to determine sleepiness in the elderly. Based on the results of this study, PM can be useful in the evaluation of senior patients when utilized in a 2-stage process combining at least 3 clinical signs of apnea, neck circumference, age, and sex, followed by the PM recording.

Summary

In this paper the important recent literature on asthma and SDB is reviewed. It is our hope that this will help to familiarize the reader with the important literature in these subject areas.

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