Cardiology and Sleep Apnea
The Intersection and Collision:
A Deeper Dive

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Sleep Disorders: Classification, Screening, Treatment, and Impact on Cardiometabolic Risk

DR. LEE A. SURKIN: Welcome to the Sleep Medicine Section of the Foundations of Cardiometabolic Health Certification Course. I'm Dr. Lee Surkin, board-certified in sleep medicine, cardiovascular disease, and nuclear cardiology, founder of the American Academy of Cardiovascular Sleep Medicine, president of Empire Sleep Medicine, and chief medical officer of VirtuOx and Nexus Dental Systems.

I have the distinct pleasure of also introducing our other speaker, Dr. Chrisopher Lettieri who is board certified in pulmonary disease and critical care medicine and sleep medicine, as well as professor of medicine at the Uniformed Services University of the Health Sciences and, was previously program director and chief of sleep medicine at the Walter Reed National Medical Center.

We've broken down our talk on sleep medicine into two parts. The first will be a joint effort that will cover an introduction to sleep, in general, followed by a review of more commonly seen sleep disorders. The second section will be handled by me and is a deeper dive into obstructive sleep apnea and cardiovascular disorders.

Sit back and listen closely. There will be a lot of information coming your way. And we'll do our very best to keep you awake and not lull you to sleep. I have no conflict-of-interest disclosures to make.

The outline of part 1's talk today will cover normal sleep physiology which will be handled by me and then Dr. Lettieri will come on and discuss the effect of sleep on common medical disorders, the impact of insufficient sleep, understanding and treating insomnia, obstructive sleep apnea, restless leg syndrome, and then I'll come back to end part 1 with a discussion about narcolepsy.

Part 2 will be cardiology and sleep apnea, the intersection, and collision. A deeper dive into both disorders.

Regarding normal sleep physiology. Sleep is a process of cycling and regulation. It's characterized by sustained immobility and coalescence, reduced responsiveness to external stimuli, and we go through a sequence of stages starting with wake and four different sleep stages that I'll review with you shortly that have all characteristic brainwave patterns.

There are normal physiological changes during sleep that involve temperature, ventilatory hemodynamic changes, and more. Sleep has an effect on common medical disorders such as cardiovascular, the immune system, central nervous system, and hemodynamics. And there is a significant impact on disease processes in individuals with chronic sleep debt.

Sleep is broken down into non-REM sleep which accounts for approximately 75% of our

sleep cycle and REM sleep which accounts for approximately 25% of our sleep cycle. Non-REM sleep is broken down into stages N1, N2, and N3. And REM sleep is nomenclature-wise called stage R.

Sleep stage N1 is where we enter sleep. It accounts for less than 5% of the total sleep and is characterized by light sleep and of course, the transition from wake. Stage N2 which typically accounts for 50% of our sleep cycle is characterized by also light sleep, decreased muscle tone, a slowing of the heart rate and body temperature, and brainwaves becoming slower in frequency. Sleep stage N3 accounting for approximately 20% of sleep is characterized by states of deep sleep which has very slow brainwave activity, no significant eye movement, or significant muscle activity.

And sleep stage R or REM sleep accounting for approximately 25% of sleep is where we dream. We have faster brainwaves that are actually quite similar to the brainwaves during awake and there is physiologic atonia, physiologic loss of muscle tone. We are dependent on breathing with our diaphragms during REM sleep.

The role of sleep involves physiologic restitution and recovery. Breaking it down into slow-wave sleep or sleep stage N3 and REM sleep, sleep stage R. Slow-wave sleep involves growth hormone secretion, protein synthesis, muscle building, and recovery with processed memories during slow-wave sleep. Bones grow, immune function restores, and the glymphatic system clears the glymphatic brain build-up that occurs during the day. REM sleep is where we consolidate memory and of course, dream and there's emotional processing.

Sleep is regulated through a number of different processes. The most common is the circadian rhythm which involves a process that lasts just over 24 hours. In fact, 24.2 hours. We have entraining agents that govern sleep regulation and we also have other extrinsic activities that involve sleep regulation. When light hits the retinal ganglion cells it stimulates the suprachiasmatic nucleus which is the main center of sleep regulation. It is our internal clock. The suprachiasmatic nucleus then sends out signals to the other cortical processes in the brain that stimulate physiology and behavior.

Entraining agents which most importantly is light is the primary entraining agent. It's called the zeitgeber. It stimulates wakefulness and causes a reduction in melatonin production by the pineal gland in the brain. Melatonin production occurs during dim light initially and builds throughout the night before it drops towards the middle to the end of the sleep cycle. And it promotes sleep, promotes sleep consolidation, and allows individuals to fall asleep during a normal amount of time which is roughly 20 minutes or so.

Other sleep regulatory processes are activities. For example, if we are overly active close to bedtime it may result in a difficult time falling asleep. If we eat large meals closer to bedtime the same might happen. If the ambient temperature's too high we may actually get less way of deep sleep.

The sleep-wake circadian cycle is a two-process system. There is the sleep drive at the top and then there's a circadian alerting system. And they work in concert with each

other and in fact, in opposition.

We have a homeostatic sleep drive taken from 9:00 a.m. to 9:00 a.m., so a 24-hour period of time. Where when we first awaken our homeostatic sleep drive is at its lowest and gradually builds during the day as we engage in our activities and metabolic processes. We break down ATP for energy which results in an accumulation of adenosine which is felt to be a primary inducer of sleep drive.

And we have the circadian alerting system which is lowest when we initially wake up but gradually builds during the day. And there's actually a dip in the early afternoon which many of us experience. A degree of lack of alertness in the early part of the afternoon. But then it picks up nicely towards the evening and then it falls rapidly when we go to sleep.

There is an increase in the hemostatic drive to sleep during the day. That builds towards our sleep time. And an increase in the alerting signal that falls off dramatically at bedtime. And then we sleep and then the process resets the next day.

There are respiratory physiology changes during sleep that involve a reduction in minute ventilation, a reduction in title volume, oxygen saturation, and PO2. There's also an increase in mean pulmonary arterial pressure, airway resistance, and PCO2. The mucociliary clearance is diminished, our cough reflex is absent, and pulmonary function decreases along with ventilatory profusion mismatch, as well as hypoventilation.

Pulmonary function decreases during sleep. Our PFTs follow a circadian rhythm. The pulmonary expiratory flow residual and forced expiratory volume are lowest in the morning times. In fact, the lowest flow rates occur between 10:00 p.m. and 8:00 a.m. with a nadir at 4:00 a.m. This contributes to nocturnal asthma, decreased exercise performance in the morning, worsening of COPD in the night and morning, and it is in association with an increased morning risk of myocardial infarction. Dr. Lettieri will go through this in a bit more detail in his section.

Nocturnal hypoventilation occurs despite a decrease in energy expenditure. There is an increase in PCO2 during sleep. As I said before, a diminished hypoxic and hypercapnic respiratory drive, decreased central respiratory drive during sleep, decreased minute ventilation and title volume, functional residual capacity decreases, as well as alveolar ventilation.

At this point, I'm going to turn the first part of our talk over to Dr. Lettieri. Where he will do his section and then I'll come back for a discussion about narcolepsy. Thank you.

Narcolepsy

DR. SURKIN: Welcome back to our section on narcolepsy. Narcolepsy is a very interesting neurologic sleep disorder that according to the International Classification of Sleep Disorders has two different types, type 1 and type 2. Both have characteristic daily

periods of irrepressible need for sleep, excessive sleepiness, daytime lapses into sleep, and the symptoms, by definition, have to be present for at least three months to classify as a disorder.

Narcolepsy type 1 has the presence of one or more of the following. Cataplexy which we'll review shortly is characterized by a weakening of voluntary musculature. The multiple sleep latency tests or MSLT is the most common sleep test utilized to diagnose narcolepsy. It typically follows an overnight polysomnogram and involves a series of anywhere from three to five daytime naps. Where we ask the individual, the patient, to try to go to sleep and we measure the length of time it takes them to fall asleep. And whether or not they go into REM sleep during daytime naps and how many REM sleep periods they have.

The qualifications for a positive MSLT involve mean sleep latency overall naps taken of less than or equal to eight minutes with at least two or more sleep-onset REM periods. This would be characteristic of narcolepsy, but not highly sensitive or specific.

Also, CSF hypocretin levels that measure less than 110 picograms per ML or mean values obtained in normal subjects with the same standardized assay. This is highly specific for narcolepsy type 1. Narcolepsy type 2 has all the characteristic symptoms of narcolepsy type 1 except cataplexy. And hypocretin levels tend to be normal.

Signs and symptoms of narcolepsy typically occur 10 or more years prior to the diagnosis. And it may be associated with misdiagnoses. The economic and medical burden of narcolepsy is very high. And the symptoms include cataplexy in type 1 only, excessive daytime sleepiness, fragmented sleep, sleep paralysis, hallucinations auditory or visual upon falling asleep or awakening, very vivid and frequent dreaming. People often report dreaming in color. And automatic behaviors.

Cataplexy is typically muscle weakness that's triggered by an emotion. And you'll see here on the graph a list of typical emotions that can trigger cataplexy. The most common are more positive emotions such as laughing, joking, anger, stress, or sex in descending order. It can typically involve the legs or knees, followed by the jaw, slurred speech. And the last common is generalized falling to the ground. It affects any voluntary muscle that can be involved and can be as subtle as drooping of the eyelid or head drooping. And that's more commonly seen in children.

The interesting thing about cataplexy which differentiates it from loss of consciousness is that consciousness is typically maintained.

Associated features of narcolepsy, as mentioned, include sleep paralysis which is defined as a sudden inability to move on falling asleep or on awakening. The episodes are generally brief and benign and can last up to a minute or so. And they end spontaneously. It's obviously quite frightening to the individual that experiences this.

Hallucinations, as I mentioned earlier, upon falling asleep which is called hypnagogic or upon awakening which is called hypnopompic. And they may be auditory or visual.

Headaches can occur in associations with depression amongst a whole slew of different

medical disorders that I'll be discussing shortly.

The prevalence is rare. The worldwide estimates are approximately 20 to 55 out of 100,000. The US Healthcare Claims Database from 2008 to 2010 showed an overall prevalence of 79.4 out of 100,000. And there is a regional disposition or prevalence in the north-central United States tends to have the highest incident of prevalence compared to the western part of the United States which is lowest.

The incidence of narcolepsy without cataplexy or type 2 is greater than narcolepsy type 1 with cataplexy. There's a 50% greater incidence in women compared to men. And the prevalence is highest in ages 21 to 30 with a median age of onset at 16 years of age.

Here's a graph showing the typical age of onset, ranging from very young to elderly with a more common age of onset in the 20-to-30-year range.

From a pathophysiology standpoint, narcolepsy type 1 is associated with at least a 90% loss of orexin and hypocretin. You're going to hear me talking about orexin and hypocretin. Those are interchangeable. They are exactly the same. A 90% loss of orexin or hypocretin-producing neurons in narcolepsy with cataplexy.

Here are your CSF hypocretin levels on the Y-axis with different disorders, starting with narcolepsy with cataplexy, having the lowest of CSF hypocretin, followed by narcolepsy without cataplexy type 2. And then idiopathic hypersomnia, sleep apnea, and controls.

There is an HLA or genetic predisposition to narcolepsy. The etiology is felt to have an autoimmune pathology. HLA is linked to many autoimmune diseases and narcolepsy has the strongest known HLA association. The HLA, DRT2, and DQB1-0602 are tightly associated with narcolepsy with cataplexy as is multiple sclerosis. HLA-DQB1-0602 is found in roughly 90% of patients with type 1 narcolepsy. And carrying this gene increases narcolepsy risk by 200-fold.

Therapeutic approaches are basically meant to improve the quality of life. This is a chronic disorder without a cure. It involves pharmacotherapy, behavior interventions, and psychosocial interventions. Pharmacotherapy is aimed at wakefulness-promoting agents, reduction in cataplexy, and improving the individual's sleep continuity which tends to be very fragmented.

Behavioral interventions involve therapeutic napping, optimizing an individual's sleep-wake cycle. Having them go to bed at consistent times and wake up at consistent times with a daytime nap tends to be refreshing. And of course, avoidance of cataplectic trigger which I mentioned earlier.

Narcolepsy and cardiovascular disease are very interesting as well. And I'm going to review with you a fair amount of preclinical data that shows the association between narcolepsy and cardiovascular disorders.

Orexin A and D are associated with orexin receptors 1 and 2 that are present throughout the rat myocardium and centrally. It exerts a central effect on increasing heart rate and blood pressure. Orexin and orexin 1 receptor containing nerve fibers have been identified

in the paraventricular nucleus which is a central site for integration of sympathetic outflow and cardiovascular function. Orexin A activates both orexin 1 and 2 receptors. Orexin B activates orexin 2 receptors only. Only orexin B affects myocardial contractile shortening. It has also been shown to exert a cardioprotective effect after ischemia and reperfusion.

Humans with congestive heart failure demonstrated a negative correlation between orexin B receptors and heart failure severity. The fewer orexin B receptors that are present this is associated with greater severity of heart failure.

Sleep-related changes in blood pressure are blunted in mice lacking orexin. And the heart rate of type 1 narcolepsy tends to be more variable during awake states and normal to high during sleep. In fact, arousals during sleep lead to a blunted heart rate response. When looking at arousal-related increases in heart rate control populations have a much greater response in heart rate compared to type 2 narcolepsy which is much greater than type 1 narcolepsy.

Orexin loss is linked to sleep fragmentation and endothelial dysfunction. Endothelial dysfunction has been shown to be induced by chronic sleep fragmentation.

A very elegant study by McAlpine. Apo E knockout mice were taken and studied. This is a group of mice that are prone to developing atherosclerosis. And these mice were subjected to sleep fragmentation, resulting in a reduction in orexin production. And these mice were found to develop larger atherosclerotic lesions.

Interestingly enough, there's a reversible component. In these mice who were administered orexin, they were shown to have a result in a reduction in sleep fragmentation and a reduction in atherosclerosis severity.

Mice that are deficient in orexin receptor 2 with narcolepsy phenotype of increased cardiac dysfunction and myocardial scarring. We know that sleep fragmentation causes orexin deficiency and we know that narcolepsy type 1 is an orexin deficiency disorder, suggesting a bidirectional relationship when it comes to endothelial dysfunction and cardiovascular disorders.

Regarding extracardiac implications. Sleep fragmentation decreases in orexin are also discovered in the bone marrow. This is another study by McAlpine's group. And it was shown to be associated with an increase in pre-neutrophils which results in an increase in colony-stimulating factor 1 which promotes inflammation, white blood cell production, and leads to atherosclerosis. Colony-stimulating factor 1 also has a direct effect on the arterial wall.

And we also know that orexin deficiencies are associated with reduced leptin signaling in mice with sleep fragmentation which is also associated with increased production of white blood cells, inflammation, suggesting a metabolic contribution.

Narcolepsy is also associated with blunted blood pressure dipping or non-dipping. First, blood pressure dipping is a normal physiologic response defined as a 10 to 15% reduction in blood pressure during sleep. This has been shown to be a protective or normal

physiologic response. The absence of dipping or non-dipping defined as a less than 10% decrease in blood pressure during sleep has been independently associated with an increased risk of cardiovascular mortality and morbidity, independent of blood pressure and other cardiovascular risk factors, as well as congestive heart failure.

It's more common in narcolepsy than controls, 31% versus 3% in a study by Dauvilleirs. It's consistent when controlling for sympathetic activity in non-REM sleep and it is associated with increased risk of sleep fragmentation, arousals, periodic limb movements of sleep, and periodic limb movements of sleep with associated arousals.

Moving on to the BOND study which was a retrospective study, looking at five years of US claims from 2006 to 2010. Where almost 56,000 adults were identified as greater than 18 years of age, 9300 of which had either type 1 or type 2 narcolepsy. And they were compared to matched controls. And this graph here shows a very profound association between narcolepsy and many different comorbid disorders such as respiratory diseases. In the yellow, they are more common in narcolepsy compared to the control population. Musculoskeletal system disorders, connective tissue disorders, neurologic disorders. The list goes on and on.

And when honing in on cardiovascular disorders, the results showed a significantly increased odds ratio for stroke, myocardial infarction, cardiac arrest, and coronary revascularization in this narcolepsy population.

Taking a closer look at the BOND study data. In yellow, again, are the narcolepsy patients compared to gray which is the control. It's much more common than the control in narcolepsy patients who have hypertension, coronary disease, congestive heart failure, as well as sleep apnea, restless leg syndrome, and periodic limb movement disorder. Along with headaches, mood disorders, diabetes, and anxiety disorder. This feels like and it is a cardiometabolic disorder which is quite important and I believe underdiagnosed.

Here are the cardiometabolic comorbidities in narcolepsy. Arterial hypertension, ischemic heart disease, dyslipidemia, diabetes type 2, and arrhythmias.

Obesity is very closely associated with narcolepsy. It's common in adults and children and it is a significant risk factor, obviously, for cardiovascular disorders. Obesity predisposes to cardiometabolic disorders and of course, obstructive sleep apnea. And it's most obvious in children and occurs at the time of onset of narcolepsy.

Providers should pay close attention to children with precocious puberty because this is more commonly associated with the narcolepsy patient population and should be screened for in this patient with precocious puberty.

Therapeutic interventions, as mentioned earlier, are medications that are focused on wakefulness promotion, stimulants, and deep sleep promotion to reduce the degree of sleep fragmentation, as well as medications that have been shown to reduce cataplexy. I'm not going to go through all of these other than here is your list of more commonly used medications that I'll describe in a couple of slides. What their specific benefits are. Here's the slide.

Modafinil, pitolisant, sodium oxybate, and solriamfetol have strong recommendations in the treatment of narcolepsy. All effectively treat excessive daytime sleepiness. Sodium oxybate and pitolisant as of this time are the two drugs that are approved in the treatment of cataplexy. And armodafinil, dextroamphetamine, and methylphenidate are wakefulness-promoting and/or stimulant medications as well. There are many agents under investigation that we hope to add to our arsenal of treatments in the near future.

And at this point, this will complete our discussion of narcolepsy and part 1 of our discussion today in the Sleep Medicine section of our course. Thank you very much for your attention. And please do stay tuned for part 2 which is the discussion on obstructive sleep apnea and cardiovascular disease, a deep dive. Thank you very much.

Cardiology and Sleep Apnea - The Intersection and Collison: A Deeper Dive

Welcome back for part 2 of our discussion in the Sleep Medicine section of our program. This part will be a deeper dive into the correlation between obstructive sleep apnea and cardiovascular disorders which I like to call the intersection and collision.

The outline will involve a clinical vignette, demographics, cardiovascular effects of sleep disorder breathing, and then we'll take a deep dive into different cardiovascular disorders of hypertension, arrhythmias, congestive heart failure, coronary artery disease, cerebrovascular accident, and then talk about some treatment options.

NM is a 57-year-old male with a BMI of 42 with a history of hypertension, hypercholesterolemia, type 2 diabetes, and tobacco abuse. He is sedentary is excessive daytime sleepiness. He has shake-the-wall snoring. His wife has to sleep in a separate room. He's on antihypertensive medications including an ACE inhibitor, a beta-blocker, statin therapy, aspirin, an oral type 2 diabetes agent, and omega-3 fish oil. Needless to say, this is a very common patient that we all see in our clinical practices.

Obstructive sleep apnea affects 4% of men and 2% of women when symptoms and the syndrome are present. When considering specifically all comers with an abnormal sleep study, it involves 24% of men and 9% of women. In the United States, it's estimated that somewhere between 20 and 40 million people have obstructive sleep apnea and only roughly 15 to 20% have been diagnosed. We have an awful lot of work to do as clinicians.

We know that the incidence of obstructive sleep apnea increases with age, the incidence of cardiovascular disease increases with age, and the risk factors between the two cluster together.

Obesity has been perhaps the single biggest risk factor for the OSA explosion in the United States. Looking at decades from '85 to '95 to '05 to 2014 you see that our map gets progressively browner and rust-colored. Which corresponds to the prevalence of obesity in the United States. It's mostly brown to rust in 2014 and even greater at this point.

This brings to mind a patient that I saw roughly 15 to 20 years ago. His name is David. I won't share his last name for HIPPA reasons. But David is originally from Italy and he is a male model. And he came to see me about 15 years or so ago with debilitating symptoms of palpitations. I worked him up from a cardiac standpoint and it turned out his palpitations were seemingly very closely associated with his job as a male model. He would get very stressed and anxious and develop significant palpitations.

I reassured him. We spoke about different treatment modalities that he could endorse to mitigate his symptoms. And then he was lost to follow up until recently when it turns out that he decided to give up his male modeling job. He moved down south in the United States and adopted the western lifestyle of sedentary activities and the southern diet.

And the reason he came back to me recently was that he had a recurrence of palpitations. But this time, it was associated with snoring, excessive daytime sleepiness, unrefreshing sleep, and low and behold sleep apnea symptoms.

This was David when he first came to see me about 15 years ago and this is David when he recently saw me. Needless to say, David now has obstructive sleep apnea, hypertension, and he is on treatment for both.

Sleep apnea, as I said earlier, is more than 80% undiagnosed and is highly prevalent in other chronic conditions. For every four individuals that know they have obstructive sleep apnea, 22 don't know that they have it. And the comorbidities are dramatically linked to cardiovascular disorders. Stroke, type 2 diabetes, obesity, arrhythmias, heart failure, and drug-resistant hypertension.

A few words about cardiovascular disease. We know that it's been the number one killer since 1990. In 1999, 33% of deaths from cardiovascular disease occurred in the elderly population which means that 67% occurred in the younger population. We know we need new treatment paradigms and we've come a long way over the last several decades at reducing the risk of death from myocardial infarction with better treatment modalities. But it still remains the number one killer.

We know that death from myocardial infarction occurs from 6:00 a.m. to noon and death from obstructive sleep apnea tends to occur from midnight to 6:00 a.m. I'll share with you that specific data shortly.

When considering independent predictors of myocardial infarction, look at overweight, hypertension, smoking, and obstructive sleep apnea. There's a very pronounced increase in the odds ratio that shows that obstructive sleep apnea is a very significant independent predictor of myocardial infarction.

When looking at normal sleep physiology which we covered in part 1. But I'll re-review it for those of you in part 2. Non-REM sleep accounts for 75 to 80% of our sleep which is characterized by decreased sympathetic nerve activity, nocturnal dipping which is that 10 to 15% decrease in blood pressure, following the circadian rhythm pattern, decreased cerebral blood flow, regular breathing pattern, decreased minute ventilation, and decreased muscle tone. Whereas REM sleep accounts for 20 to 25% of our sleep. It has sympathetic nerve activity, heart rate, and blood pressure similar to that of the awake

state. There is increased cerebral blood flow and irregular breathing patterns. Respiration is dependent on our diaphragm due to physiologic muscle atonia.

Cardiovascular effects of apnea. We'll start with the definition of apnea is which is a cessation of breathing for a minimum of 10 seconds. That is a 90% or greater reduction in breathing for 10 seconds. This results in a drop in the blood oxygen level and an increase in the PCO2. We know that hypoxia is independently associated with cardiovascular disease. Our central nervous system responds by increasing heart rate and blood pressure and constricting blood vessels in the periphery.

We then engage in the Muller maneuver which as a result of airway closure there is a reflex intense contraction of the thoracic in opposition to the abdominal musculature until the airway ultimately opens. And this results in a dramatic increase in the negative intrathoracic pressure, resulting in increased cardiac pressures. And ultimately, over time, an alteration in heart rate variability and blood pressure variability.

It's very important to understand this concept of transmyocardial pressure. As I said before, when the airway is obstructed there is a dramatic increase in the negative intrathoracic pressure. With every inspiration, we take there is a decrease in pleural or paracardial pressure which increases with positive airway pressure.

Transmural pressure quite simply equals intracardiac pressure. Let's say, for example, systolic pressure of 120 minus the extracardiac pressure which tends to be in the 5 to 10 range. Now, the transmyocardial pressure determines wall stress and afterload. Each inspiration, as I said, increases transmyocardial pressure. Positive airway pressure decreases preload and afterload.

Let's consider the example of the systolic pressure of 120 millimeters of mercury in the left ventricle. The airway obstructs. There is a dramatic increase in negative intrathoracic pressure. The transmural pressure of the heart is the intracardiac pressure. Let's say 120 millimeters of mercury minus the extracardiac pressure which in the setting of an obstructive airway can be up to -150 to -300 millimeters of mercury. When you take 120 minus a -150 you now have a dramatic increase in the transmural pressure of the heart. This is the wear and tear that the heart experiences with every airway obstruction.

We know that obstructive sleep apnea is an inflammatory disease. A study published in Circulation in 2002 showed a linear correlation between increasing levels of C-reactive protein on the Y-axis with increasing severities of obstructive sleep apnea based on the apnea-hypopnea index.

This slide summarizes the pathophysiologic abnormalities in sleep disorder breathing very well. It's recently published and I want to take you through it gradually. Starting with sleep reduction and fragmentation. We have reduced sleep efficiency, reduced REM sleep which we spoke of earlier. It's associated with an increase in the inflammatory response.

We've just spoken about transmural pressure, afterload, venous return, oxygen demand, and all these negative effects that airway obstruction imparts on the heart.

Going across to the upper right, we have cyclical hypoxemia and reoxygenation,

contributing to increased inflammatory responses. Sympathetic nervous system activation also results in increased inflammatory cytokines, an increase in muscular sympathetic activity which both promote insulin resistance, and the new has an increased likelihood and increased predisposition to thrombosis or clotting through an increase in fibrinogen platelet activation which increases the risk of paradoxical embolism and endothelial dysfunction develops due to systemic inflammation, oxidative stress, and sympathetic activation.

The cardiovascular manifestations of obstructive sleep apnea involve vascular inflammation, an increased risk of clotting tendency, oxidative stress, hypertension, pulmonary hypertension, diastolic dysfunction, endothelial dysfunction, obesity, arrhythmias, heart failure, diabetes, and metabolic syndrome which I will call cardiometabolic syndrome.

OSA & Hypertension

Moving on to our deeper dive into cardiovascular disorders. We'll first discuss hypertension. We know that 50% of obstructive sleep apnea patients have hypertension, 30% of hypertensive patients have obstructive sleep apnea. Hypertension becomes more difficult to control as obstructive sleep apnea worsens in severity. Obstructive sleep apnea is present in 65 to 80% of patients with drug-resistant hypertension. Three or more antihypertensives are required as a definition of resistant hypertension.

The JNC-7, years ago, concluded that obstructive sleep apnea is indeed an independent cause of hypertension, and treating obstructive sleep apnea can lead to degrees of improvement in blood pressure control.

When looking at the odd's ratio of incident hypertension at a four-year follow-up. This data was all adjusted for baseline hypertension, age, gender, BMI, waist circumference, and alcohol and tobacco use. You can see here that as obstructive sleep apnea worsens this category is mild and this category AHI of greater than 15 is designated as moderate or severe. There is a steady increase in the risk of incident hypertension.

When considering resistant hypertension, obstructive sleep apnea in this study was very closely associated with an increased risk of an association with resistant hypertension even more so than primary hypertension, aldosteronism, renal artery stenosis, and others. When you have a patient requiring three or more antihypertensive medications think obstructive sleep apnea.

Here is the JNC-7 report, identifying obstructive sleep apnea as an identifiable cause of hypertension.

Moving on to obstructive sleep apnea and cardiac arrhythmias. We know that there's an increased risk of arrhythmias as obstructive sleep apnea worsens. It occurs in 50% of obstructive sleep apnea patients and most commonly includes premature ventricular

contractions, non-sustained ventricular tachycardia, sinus arrest, bradycardia, and atrial fibrillation.

We know that treating obstructive sleep apnea tends to improve arrhythmias. We also know that atrial fibrillation is more difficult to convert to sinus rhythm in the setting of sleep apnea that is untreated. I'll share data with you on that. And we also know that ablation procedures to cure atrial fibrillation have a high failure rate in patients who have untreated obstructive sleep apnea.

Regarding atrial fibrillation specifically. Obesity and hypoxemia are independent predictors of atrial fibrillation in patients younger than 65. There is an 82% recurrence of atrial fibrillation if obstructive sleep apnea is untreated after cardioversion. Fifty percent of patients presenting for cardioversion have obstructive sleep apnea. And the mechanisms tend to involve left atrial enlargement. It's more common in obstructive sleep apnea. Recurrent hypoxemia, catecholamine swings, and repetitive arousals during sleep.

In a study by Gami published in 2007, looking at the cumulative frequency of atrial fibrillation over time. Comparing patients without obstructive sleep apnea to those with. You can see that the incidence steadily increases over time in the obstructive sleep apnea patient population with only a very gradual increase over time. But much more significant in the obstructive sleep apnea population.

Looking at adjusted odd's ratio and 95% confidence interval for the association between atrial fibrillation and OSA. Considering body mass index along with neck circumference, hypertension, diabetes, and atrial fibrillation. You can see that there's a very strong increased odds ratio in the association between atrial fibrillation and obstructive sleep apnea, along with body mass index and hypertension.

When considering the impact of weight combined with obstructive sleep apnea severity and the incidence of atrial fibrillation. As we go from blue to red to green the BMI increases and as we go along the X-axis the severity of obstructive sleep apnea worsens. When looking at the percent of atrial fibrillation on the Y-axis you can appreciate that as individuals get heavier and heavier with worsening obstructive sleep apnea there's a much greater incidence of atrial fibrillation. The risk factors of elevated body mass index need to be considered along with obstructive sleep apnea as far as the risk of atrial fibrillation is concerned.

This study is the seminal study that was published in Circulation in 2003, compared the 12-month recurrence of atrial fibrillation to a control group, a treated obstructive sleep apnea group, and an untreated group. When comparing the control group to the treated obstructive sleep apnea group there's no significant difference in the 12-month recurrence of atrial fibrillation. But when comparing the control group with the untreated group, as well as the treated group with the untreated group, there is a statistically significant increased risk of recurrence of atrial fibrillation at 12 months.

Now, we're going to break for a bit for a case study. This is an actual patient that I saw that will demonstrate a very interesting arrhythmia associated with obstructive sleep

apnea. This is a 70-year-old male who was referred to me for a syncopal episode, loss of consciousness. While moving furniture he bent over to pick up a chair, became dizzy, and passed out. He had no associated chest pain, palpation, shortness of breath, incontinence, or seizure activity. He regained consciousness and felt back to baseline and went back to his work.

He was referred to me by his primary care provider. Sleep history indicated that when he awakens in the morning he felt refreshed. He was not aware of snoring. He did experience intermittent excessive daytime sleepiness, denied morning headaches. There were no witnessed apneas. And he denied awakening choking or gasping for air from sleep. And his Epworth Sleepiness Scale was negative. Anything greater than 11 out of 24 is consistent with pathologic sleepiness based on the Epworth Sleepiness Scale.

His past medical history was significant for hypertension, hyperlipidemia, gout, and morbid obesity. His physical exam revealed a blood pressure of 154/87. Heart rate was 72. Respirations were 18. Weight of 274. BMI of 41.7. And his exam was fairly unremarkable. He had a soft murmur and trace pitting edema.

I performed a cardiac evaluation which revealed a normal nuclear stress test with a normal ejection fraction. Both on that and on echocardiography. There was no significant valvular disease and he did have evidence of grade 1 diastolic dysfunction. His carotid ultrasound revealed mild diffuse noncritical plaquing.

I placed an ambulatory cardiac telemetry monitoring. That very first evening at 2:00 in the morning I got a call from the monitoring company that this had occurred. They had contacted the patient. He was in sinus rhythm on strip number 62, number 63 sinus rhythm, and then he developed a 2 to 1 AV block. And then strip number 64 this happens. Which shows some atrial activity and is likely consistent with a complete heart block without a ventricular escape rhythm.

The patient was called in response to this, awakened from sleep. He was angry with the monitoring company and refused to take any action.

About three hours later at 5:00 in the morning, this happened. A similar event. And this time, I called the patient and demanded that he allow us to contact 911 to which he agreed. And his emergency department evaluation was completely unremarkable. Labs, telemetry monitoring, et cetera.

He was discharged from the emergency department and I brought him in that evening for an in-lab polysomnogram which revealed severe obstructive sleep apnea with an apnea-hypopnea index of 64. It was very severe in REM sleep with an AHI of 118. He developed episodes of marked bradyarrhythmia with a complete heart block associated with respiratory events mostly in REM sleep. With desaturations to a low of 68%.

Here is a screenshot of a one-minute epoch in the sleep lab. And what I want you to do focus on are the following signals which would be his heart rate channel. Here he goes from sinus rhythm into an episode of pause of asystole here. And in purple or blue is his airflow. And you can see here that he's breathing normally and then during this highlighted area he develops an obstructive event. The R here means he's in REM

sleep. He subsequently has a marked desaturation and then arousal which results in resumption of sinus rhythm with a brief episode of sinus tachycardia before settling down into sinus rhythm.

This is a closer view of the event where you can appreciate much better the cardiac arrhythmia with the obstructive event, the significant desaturation, arousal, and then restoration of sinus rhythm PVC here. Each time this gentleman had episodes of REM sleep he had a cardiac arrhythmia manifestation.

His management involved bringing him back in the next night for a CPAP titration study which is where CPAP actually bilevel optimized his obstructive sleep apnea and he had no further episodes of cardiac arrhythmia during any stage of sleep during that study. He was advised 100% strict adherence to his PAP therapy which he endorsed and has continued to endorse. And follow-up cardiac monitoring did not reveal any further evidence of cardiac arrhythmias.

OSA & Congestive Heart Failure

This section of our talk will involve sharing data about obstructive sleep apnea, central sleep apnea, and congestive heart failure.

Congestive heart failure is defined as heart failure with reduced ejection fraction. Typically, an ejection fraction of less than 40 to 50% and heart failure with preserved ejection fraction and an ejection fraction of 50% or greater.

Fifty to seventy-five percent of congestive heart filature patients have obstructive sleep apnea according to a study by Oldenburg published in 2007. We know that untreated moderate or severe obstructive sleep apnea, an AHI of greater than 15 along with congestive heart failure is associated with an increased risk of mortality.

Cross-sectional data from the Sleep Heart Health Study showed that the presence of obstructive sleep apnea is associated with a 2.38 relative increased risk of the likelihood of having heart failure independent of confounding factors.

And we know that central sleep apnea increases as heart failure with reduced ejection fraction worsens and is associated with an increased risk of mortality.

A discussion about heart failure central sleep apnea would not be complete without at least a brief review of Hunter-Cheyne-Stokes Breathing. And I've been repeatedly reminded that this is Hunter-Cheyne-Stokes Breathing by my colleague and friend, Dr. Javaheri who discovered that Dr. Hunter apparently first defined or described Hunter-Cheyne-Stokes Breathing. I will forever call this Hunter-Cheyne-Stokes Breathing.

Anyway, focusing on the red and the blue signals here. And this is a five-minute screenshot of an in-lab polysomnogram. You can appreciate here that in the red which is the flow there is no flow here or here. And in the effort signals are obtained by elastic

belts placed around the chest and the abdomen. The effort signal shows no effort. This is defined as a central apnea event. No flow no effort. The airway is open.

What then happens as there is a trigger for respirations there is a gradual increase or a crescendo in airflow which then peaks and then follows a decrescendo pattern before resulting in another episode of central sleep apnea.

As a cardiologist, I've always looked at this as the crescendo and decrescendo pattern of a significant aortic stenosis murmur. But that's another discussion.

This is Hunter-Cheyne-Stokes Breathing and it is closely associated with heart failure.

Looking at congestive heart failure survival in a population of normal or mild untreated obstructive sleep apnea versus untreated obstructive sleep apnea. The study was published in 2007 showed that in the untreated obstructive sleep apnea group there is a significantly increased risk of mortality compared to the group that is normal or only has mild untreated obstructive sleep apnea. As obstructive sleep apnea worsens, there is an increased risk of mortality in the heart failure patient population.

The CANPAP trial was the Canadian continuous positive airway pressure trial for central sleep apnea and heart failure. The hypothesis of this study was that CPAP improved survival without cardiac transplantation in patients with central sleep apnea and heart failure.

All patients had their medical therapy optimized. Two hundred and fifty-eight patients were enrolled in the study with heart failure and central sleep apnea. They were randomly assigned to CPAP or no CPAP and followed for a couple of years.

The results showed that in the CPAP group the apnea-hypopnea Index, norepinephrine levels decreased. The mean SPO2 left ventricular ejection fraction and six-minute walk distance increased. There was no difference in the number of hospitalizations, quality of life, ANP or BNP levels. There was an early divergence in survival without transplant seen in the control group with divergence in 18 months favoring CPAP. However, the overall event rates, death, and cardiac transplantation did not differ. This was a neutral study.

However, the data was looked at post hoc in CPAP responders versus CPAP non-responders. In the CPAP responders group, which had an average AHI of 6.5 which is still not optimal compared to the control group or the CPAP non-responders there was a significant survival benefit favoring the use of CPAP. But this is a post hoc analysis of the CANPAP data.

Now, a device called adaptive servo-ventilation which is a very sophisticated positive airway pressure device has been developed, specifically targeting effective treatment of Hunter-Cheyne-Stokes Breathing. And the way it works. It uses pressure support. And as you have a continually increasing flow that we spoke of earlier of Hunter-Cheyne-Stokes Breathing the pressure support will gradually decrease. And as there is a gradual decrease in flow, the pressure support will gradually increase and will be at its peak during the central apnea event where there is no flow. What comes out at the end is a normalized airflow pattern with the use of adaptive servo-ventilation.

When I first heard about this amongst most sleep physicians in the country we were very excited in the thought that this was potentially going to become the Holy Grail of treating the central apnea patient who had heart failure.

That brought upon the SERVE-HF trial which enrolled 1300 patients with chronic heart failure all with a left ventricular ejection fraction of less than or equal to 45%. They all had New York Heart Association Class 3 or 4 heart failure or Class 2 with at least greater than or equal to one hospitalization in the previous 24 months. These were pretty significantly ill heart failure patients.

The subjects had predominant central sleep apnea, central sleep disorder breathing defined as an AHI of greater than or equal to 15 of which at least 50% of the events were central. And they were randomized to adaptive servo-ventilation or usual care.

I remember I was giving a talk at a sleep conference in, I believe, May 2015 when this quite unfortunate data was released. And that was that the SERVE-HF trial surprisingly did not show any statistically significant difference in the primary outcome of all-cause time to all-cause mortality or unplanned hospitalization for worsening heart failure. In fact, it also showed a 2.5% absolute increase in the risk of annualized cardiovascular mortality. The study was halted prematurely and there was a black box warning issued not to use adaptive servo-ventilation therapy in patients who had a left ventricular ejection fraction of less than or equal to 45% with central sleep apnea and heart failure.

Well, I can tell you, at this point, quite a few of my patients were already being treated with adaptive servo-ventilation. And needless to say, I contacted all of them with this warning to discontinue therapy. And most of them agreed to go back on CPAP. However, there were several of them that despite this warning took it upon themselves to make the decision independently to continue adaptive servo-ventilation therapy because of how well they were feeling and how well or well how much improved their heart failure had become. Interesting.

Well, I'll mention later that there is an ongoing study called the ADVENT-HF trial which has enrolled both patients with obstructive sleep apnea and central sleep apnea with the use of an adaptive servo-ventilation from a different company. This study is still ongoing and has not been stopped prematurely. We are all looking forward to the results of this study.

Thinking about different types of treatment options for central sleep apnea. What if we were to stimulate the diaphragm via the phrenic nerve to promote respiration?

A company came out with a device that can sense central sleep apnea events and deliver a stimulatory effect to the phrenic nerve, promoting respiration, promoting breathing. And the early data approximately five to six years ago resulted or showed a reduction in arousals by 14 per hour with this therapy, a reduction in the AHI by 22 events per hour, and a 95% reduction in the central apnea index. Subjective improvement in both sleepiness and quality of life measures improved desaturation index, and long-term outcomes were announced in October 2020, confirming a sustained benefit through five years. This is a therapeutic option for this patient population.

Acetazolamide has been studied in both obstructive and central sleep apnea. And here is a meta-analysis of 28 studies including 524 treatment subjects and 553 control subjects that were treated with acetazolamide from 1 to 90 days. This is a short-term meta-analysis compared with controls. Acetazolamide reduced the apnea-hypopnea index by almost 40%. Felt to possibly be secondary to acetazolamide's respiratory stimulatory effects. The reduction was similar in both obstructive and central sleep apnea patients. The improvements were significantly greater with higher doses, so it was dose-dependent. And the acetazolamide improved the SPO2 nadir by 4.4% along with sleep quality measures. Long-term efficacy has not been established, but a randomized trial is underway.

Ongoing congestive heart failure trials. As I mentioned, the ADVENT-HF trial and the LOFT-HF trial which is investigating the impact of low flow oxygen therapy on hospital admissions and mortality in patients with heart failure and central sleep apnea.

OSA & Coronary Artery Disease

Moving on to our discussion about obstructive sleep apnea and coronary artery disease. Obstructive sleep apnea is associated with an increased risk of myocardial infarction and stroke independent of other variables. It is linked to the vulnerable plaque on CT scanning.

What is vulnerable plaque? Well, as coronary artery disease develops there's typically a lipid-filled plaque with a thin cap to it that over time will mature and become more calcified as it enlarges. We've known for decades that the most likely plaque that results in myocardial infarction is the less stenotic or the less severely blocked plaque that tends to be more lipid-filled with a thinner cap, making it more likely to ulcerate, rupture, and then go on to an infarction. These smaller more lipid-filled thinner capped plaques tend to also have a greater degree of inflammation involved and those are classified as vulnerable plaques. We'll discuss a study about that shortly.

Obstructive sleep apnea also tends to worsen other cardiovascular risk factors. When you have obstructive sleep apnea you get heavier diabetic control, which tends to be more challenging, et cetera. And yet obstructive sleep apnea is not, at this point, considered an established cause of coronary artery disease. We know we need more studies. And the possible mechanism of this involves recurrent hypoxia, decreased coronary blood flow, repetitive arousals from sleep, increased transmyocardial pressure that we spoke of earlier, snoring, mechanical forces, and systemic inflammation.

There's also, believe it or not, an impact that daylight saving time has. And I want to share with you briefly a study which was a meta-analysis looking at daylight saving's time and acute myocardial infarction. Where seven studies were reviewed with greater than 115,000 subjects. And the data revealed that there was a significantly greater risk of myocardial infarction occurring during the first two weeks following the springtime transition to daylight saving's time.

The American Academy of Sleep Medicine has come out with a position statement that has been endorsed by a number of other sleep-related academies. That daylight saving time results in circadian misalignment. It is associated with an increased cardiovascular disease risk as well as metabolic syndrome and other health risks. Shifting to daylight saving time is associated with an increased risk of cardiovascular morbidity and associated with an increased risk of myocardial infarction, stroke, and hospital admission for acute atrial fibrillation.

A seminal study published in 2008 in the Journal of American College of Cardiology looked at the occurrences of myocardial infarction based on six-hour epochs of time. And what you see here in white or clear are the individuals experiencing myocardial infarction who do not have obstructive sleep apnea and in green are those who do.

And as you can appreciate here as I stated earlier, most myocardial infarctions, again, in the non-obstructive group occur between 6:00 a.m. and noon. But when considering the obstructive sleep apnea patient population most of the myocardial infarctions occur between midnight and 6:00 a.m. Obviously, while they are asleep.

This makes me think about Justice Scalia who died in his sleep and I believe was thought to have obstructive sleep apnea that may not have been treated or may not have been consistently treated. But I'm not 100% sure about that.

Regarding obstructive sleep apnea and the vulnerable plaque which I spoke of a couple of slides ago. This was a retrospective study at the Medical University of South Carolina presented in 2010. Where the investigators measured coronary calcium or hard plaque and the degrees of noncalcified stenotic lesions are vulnerable or soft plaquing.

Ninety-five patients were studied, 49 had obstructive sleep apnea. And yay, 23 were women. Women were present in this study. Almost 50%. The mean age is 51. They were mostly obese. And 46 patients did not have obstructive sleep apnea, half were women. Similar characteristics. There was no difference in hard plaques between the two groups. However, the total number of vessels with vulnerable plaques strongly correlated with the obstructive sleep apnea group and the most stenotic lesions.

Interesting data, an interesting study about the potential impact or at least the association between obstructive sleep apnea and the vulnerable plaque which we know is the more likely one to go on to an acute myocardial infarction.

Regarding the benefits of obstructive sleep apnea treatment and coronary disease. A study by Milleron and published in 2004 looked at 54 patients with coronary disease with significantly severe stenosis and at least moderate obstructive sleep apnea.

Twenty-five patients were treated with PAP therapy or ENT surgery. And the control group was the 29 who refused treatment. There were followed anywhere from four to ten years for major adverse cardiac events defined as death, acute coronary syndrome, heart failure, hospitalization, and the need for revascularization. They were all on similar coronary disease treatments.

The treatment group had an event rate of 6 out of 25 or 24%. The untreated group had an

event rate of 58% and this difference was statistically significant. At least this study showed that treating a group of patients with heart disease and at least moderate to severe obstructive sleep apnea with PAP therapy or ENT surgery may be beneficial, although granted the numbers are quite small.

Now, that gave rise to four randomized control trials between the years 2012 and 2019. They were really very meaningful trials so far as determining the efficacy of CPAP in the setting of coronary disease.

And what I want you to pay attention to. I'm going to share a fair amount of data from each of these trials with you. First and foremost, would be, I'll call it, the dose of CPAP. How long were these patients on average using CPAP? And what I want everyone listening to understand is that in the four stages of sleep that were reviewed earlier in this talk and in part 1. Non-REM sleep and REM sleep. Thinking about REM sleep which is the deepest stage of sleep. We breathe with our diaphragms. We have physiologic muscle atonia, more obstructive events tend to occur in a deeper sleep.

While REM sleep is we typically have anywhere from three to five REM cycles per night of sleep and they are more weighted in the second half of the night compared to the first half of the night. If you sleep for eight hours you're going to have much more REM sleep in the second four hours than you are in the first four hours. Remember that point for me.

The other points that caught my eye are the percentage of the male population in these studies. Pay attention to those points. And the other factor would be the phenotype that was studied in the obstructive sleep apnea patients. The patients were selected as being non-sleepy and there were researched ethical reasons why. That patient population was studied because of the control group that was not treated.

Starting off with the Barbe study. The effect of CPAP on the incidence of hypertension and cardiovascular events in patients with obstructive sleep apnea. Seven hundred and twenty-three consecutive patients without known cardiovascular disease were studied. Fifty percent had hypertension. All had moderate or severe obstructive sleep apnea. None were sleepy. Epworth Sleeping Scale of less than 10. Three hundred and fifty were treated with CPAP. Three hundred and sixty-six were treated with usual care. Eighty-five percent were male.

The AHI median was 42. The O2 saturation was less than 90% in 8% of the population studied. The primary outcome looked at the effective CPAP treatment on the incidence of hypertension or cardiovascular events. The secondary outcome investigated the association between the incidence of hypertension or cardiovascular events and the severity of obstructive sleep apnea and O2 saturation. They were followed for a median period of time of four years.

Here's the data. The graph on the left shows the cumulative incidence over time, comparing control groups. The CPAP group showed no statistically significant difference between the two groups. However, in a post hoc analysis looking at the similar X and Y axes, parsing out those that weren't defined as non-adherent to CPAP using CPAP less

than four hours per night. To those individuals, subjects using CPAP greater than four hours per night. There was a benefit in treatment. Post hoc analysis.

The study suggested that in patients with obstructive sleep apnea without daytime sleepiness. CPAP compared to usual care did not result in a statistically significant reduction in hypertension or cardiovascular events. The post hoc analysis suggested that the adherent use of CPAP greater than four hours per night may reduce the incidence of hypertension or cardiovascular events.

Moving on to the RICCADSA trial which is the randomized intervention with continuous positive airway pressure in coronary artery disease patients with obstructive sleep apnea. Two hundred and forty-four patients were studied, 85% men, 70% had hypertension, 53 had acute myocardial infarction, 27% coronary artery bypass grafting, 22% had undergone percutaneous intervention, and 28% were diabetic.

They all had very significant obstructive sleep apnea based on polysomnography. And the primary endpoint investigated was the first event of revascularization, myocardial infarction, stroke, or cardiovascular mortality. This was an open-label blinded trial.

The results are looking at probability over time where blue is the CPAP treated group and red is the control. Here, again, no statistically significant difference that would favor treatment in the entire patient population studied. Granted, another small study. And it's even smaller because when parsing out the patients who ended up not completing the study. A fairly significant percentage of patients returned their CPAP devices within one year. Fifty-seven patients.

The conclusion indicated that the routine prescription of CPAP to coronary disease patients with, again, non-sleepy obstructive sleep apnea did not significantly reduce long-term adverse cardiovascular outcomes in the intention to treat population.

Now, the RICCADSA data also reviewed patients based on CPAP adherence, meaning CPAP usage of greater than or equal to four hours. And it showed that there was indeed a significant difference in outcomes based on adherence. Six events occurred in the CPAP users, 43 events occurred in the CPAP non-users, and the incidence of composite endpoints was also less than the CPAP users. And the conclusion based on this data analysis was that there was indeed a significant reduction in endpoints after adjustment for baseline comorbidities and adherence with treatment, adherence with CPAP use greater than four hours.

Moving on to the SAVE trial which is the sleep apnea cardiovascular endpoints. This is a much larger trial looking at 2687 patients with non-sleepy obstructive sleep apnea and established coronary disease or cerebrovascular disease. Eighty-one percent men. All had significant obstructive sleep apnea diagnosed by home sleep apnea tests. This was not in-lab testing. It was a randomized control trial open-label comparing CPAP to usual care. The primary endpoint was the composite of death from any cardiovascular cause, myocardial infarction, stroke, hospitalization for heart failure, or acute coronary syndrome.

The patients were initially started on APAP which is auto-CPAP. Which is initially set to

auto mode for one week and then they were set to a specific CPAP pressure on the machine based on the 90th percentile pressure, demonstrated by the APAP machine.

And interesting data here to share with you. In the first month of usage, the average usage was 4.4 hours per night plus or minus 2.2 hours. And it steadily fell off. It steadily declined over the course of this trial to where at 12 months it was down to 3.5 hours. And then subsequent to that, it remained relatively stable with an overall mean of 3.3 hours. This means you put the CPAP machine on at bedtime and if you sleep eight hours you're maybe capturing one or two episodes of REM sleep, the CPAP comes off, and you spend the rest of the time sleeping without therapy. This study's data was based on an average of 3.3 hours of CPAP usage.

The primary outcome of death, MI, hospitalization, unstable angina, et cetera showed no significant difference between the treatment arm and the control group. Cardiovascular death is 1.9 versus 1.5. Myocardial infarction 3.1 versus 2.9.

The overview concluded was that CPAP as an addition to usual care is not superior to usual care alone for secondary prevention of cardiovascular events in patients with coronary disease and cardiovascular disorders, cerebrovascular disorders, and moderate to severe sleep apnea. CPAP did, however, even at the dosage used, improved daytime sleepiness and health-related quality of life parameters.

On adjusted propensity analysis it appeared that there may be a benefit in patients using CPAP at least four hours every night on average.

And combining the three trials together. The intention-to-treat analysis in gray and the red parses out the patients who are adherence. To the left of the reference line would favor treatment and to the right would not. You can see that some of these trials tend to favor treatment, but the conclusions are that there's no significant benefit based on the specifics of the trial.

Our four randomized control trial is the ISAACC trial which is the impact of sleep apnea syndrome in the evolution of acute coronary syndrome. This was a Spanish multicenter randomized control trial of patients with acute coronary syndrome. Over 2500 patients with acute coronary syndrome underwent sleep testing. Almost 50% had obstructive sleep apnea. They were randomly assigned to CPAP or usual care and followed for a median of 3.3 years.

Cardiovascular events. The results graphed on the right show in red the usual care, in blue the CPAP group, and in dotted is the reference group. Cardiovascular events are similar between the two groups, 16% versus 17%. The mean CPAP use in this patient population is 2.78 hours per night.

The conclusion. CPAP was not associated with an increase in cardiovascular events and treatment with CPAP did not significantly reduce events at 2.8 hours per night.

Dr. Javaheri evaluated five different trials and published a meta-analysis looking at CPAP adherence for the prevention of major adverse cerebrovascular and cardiovascular events in obstructive sleep apnea. The primary outcome was a stroke, acute myocardial

infarction, cerebrovascular or cardiovascular or cardiac death. All patients had CPAP in use of at least four hours per night compared to no CPAP.

And the results revealed an improvement in the primary composite outcome which was statistically significant. CPAP improved cerebrovascular outcomes which were statistically significant, however, there was no statistical significance in the cardiac composite outcome.

The conclusion was that adequate use of CPAP greater than four hours per night is associated with significant improvement in major adverse cardiac and cerebrovascular events. But primarily a benefit involving the stroke patients.

Dr. Javaheri goes on to opine. This I really want to share with you because it summarizes things nicely. Insufficient sleep duration and obstructive sleep apnea are clearly shown to increase cardiovascular disease, major adverse cerebrovascular and cardiovascular events, and mortality. Intuitively, adequate treatment of obstructive sleep apnea should improve cardiovascular outcomes. Multiple studies have demonstrated beneficial effects of PAP therapy largely limited to modest improvements in blood pressure and atrial fibrillation control.

The randomized control trials from 2012 to 2016 failed to show that CPAP reduces major adverse cardiac and cerebrovascular events. But they're all limited by poor PAP adherence.

OSA & Cerebrovascular Accident

In this section, we'll discuss obstructive sleep apnea and cerebrovascular accident. There are 750,000 strokes annually and 72% of patients with stroke have obstructive sleep apnea in population studies. We know that obstructive sleep apnea tends to proceed the onset of stroke and results from similar cardiovascular causes of hypertension, inflammation, oxidation, et cetera. Snoring is associated with carotid artery disease and I'll share some data with you shortly. And we know that obstructive sleep apnea treatment is very difficult to assess secondary to adherence issues, particularly in the stroke patient that has a motor deficit.

Stroke is most commonly associated with obstructive sleep apnea in 36 to 90% of patients. It's also associated with central sleep apnea in 12 to 40% of patients. Central sleep apnea tends to have a better outcome than obstructive sleep apnea in the stroke patient unless central sleep apnea persists for greater than two weeks in the setting of a large stroke and cardiac dysfunction. Central sleep apnea tends to improve about 50% of the time in the recovery phase of the stroke.

Stroke mechanisms involve endothelial dysfunction, coagulation issues, inflammation, oxidation, metabolic diabetes, hypertension, hypoxia, and hypercapnia.

Looking at the cumulative risk of stroke during a 10-year period of time in the obstructive

sleep apnea patient. A study published in Circulation in 2008 shows that individuals with obstructive sleep apnea have a steadily increased risk of stroke compared to the control population over a lengthy period of time who do not have obstructive sleep apnea.

What about sleep duration? Does that really matter with regard to the risk of stroke? It turns out that it does. A prospective observational study out of Sweden of almost 80,000 subjects was followed for incident stroke or death for a mean period of around 15 years. And the study showed that individuals who both are long sleepers defined in this study as greater than nine hours per night and short sleepers defined in this study as sleeping less than seven hours per night have an increased risk of stroke events. The long sleepers have an increased risk of ischemic stroke and the short sleepers tend to have an increased risk of intracerebral hemorrhage.

Another study looked at sleep duration from the NHANES data from 2005 to 2016. It studied 32,000 patients who completed surveying and identified patients with heart failure, coronary disease, hypertension, dyslipidemia, diabetes, and stroke. The data was adjusted for multiple confounding variables and again showed that both short and long sleep duration was associated with poor cardiovascular health. Specifically, the short sleepers had an increased risk of higher prevalence of stroke and heart failure along with the long sleepers defined as greater than nine hours of sleep.

The sweet spot from a sleep duration standpoint is somewhere between seven and eight hours per night. Certainly, it's not less than six and not greater than nine. Six or seven or greater than nine.

Self-reported snoring patterns predict stroke events. This is a post hoc analysis of the previously discussed SAVE trial which explored major cardiovascular events in those patients who reported snoring prior to positive airway pressure use versus those who denied snoring. And the study showed that snorers with obstructive sleep apnea had a greater risk of stroke, but not necessarily cardiac events. It was independent of CPAP treatment and severity of obstructive sleep apnea but was dose-dependent. Meaning as the snoring progressed from never to as loud as breathing to very loud so too did the hazard ratio increase for cerebral events.

Snoring is not necessarily benign. We know that snoring can induce intimal damage within the carotid arteries which can then obviously develop plaguing and increase the risk of stroke.

Moving on to treatment options. We know that treatment options, CPAP and others, improve quality of life. CPAP is associated with better blood pressure control, a decrease in sympathetic nerve activity, decreased recurrent atrial fibrillation, improvement in cardiac function, decreases in early signs of atherosclerosis, but a very uncertain impact on long-term coronary artery disease. It is clear from the studies that I presented that adherence is key.

Could it involve the patients' phenotype of obstructive sleep apnea in a sleepy versus non-sleepy population? It's certainly possible and studies are ongoing to look at that. Is there a male versus female predisposition? It's certainly possible. The trials had an abundantly

high percentage of male patients that were presented. And there are also uncertain benefits in congestive heart failure patients.

The standard of care, as mentioned earlier, is CPAP. We do not use adaptive servo-ventilation at this point in that select group of patients who have a lower ejection fraction with central sleep apnea. But ongoing data will hopefully be forthcoming soon.

Discuss a few alternative treatment options to CPAP. I'm going to start at the upper right with the scale which would indicate that weight loss is a very good long-term treatment option for obstructive sleep apnea. That would include medical weight loss and inappropriate patients bariatric surgery. A mandibular advancement splint, mandibular advancement device, or oral appliance therapy basically splints the airway open by fixing the teeth in position to now allow the jaw to retrude back into the airway causing an obstruction. This is an excellent first-line treatment option for mild to moderate sleep apnea and can also be used in severe obstructive sleep apnea patients in those who have been introduced to CPAP and don't tolerate it, refuse it, or for whatever reason fail therapy. This should be the next in therapeutic options. The dental appliance.

There are devices that create a one-way valve that allows breathing to enter the nostrils. But when you exhale there is a resistance device that results in expiratory positive airway pressure which then transmits back to the airway to split the airway open. Those can be effective.

Ear, nose, and throat surgery is also effective. Uvulopalatopharyngoplasty can be effective in select patient populations. In addition, ear, nose, and throat surgery paying focus on nasal breathing is critically important. It's critically important to ensure that your patient can breathe adequately in and out of their nose. Because if they can't that can actually predispose to airway obstruction.

And there's an implanted device that stimulates the hypoglossal nerve which is the primary stimulatory nerve for the tongue. Such that every time the patient takes a breath in there's a stimulus to the hypoglossal nerve which actually moves the tongue forward thereby maintaining airway patency.

There's a device out on the market that is a vacuum device that actually allows the tongue to remain in a more forward position.

And I just very recently within the last day or two read a pilot study on a device called variable extrinsic pressure. Variable external pressure is a device that would go around the neck and basically pull the neck forward thereby enlarging the airway. And I'm very much looking forward to larger trials on that device.

In summary, I would claim that obstructive sleep apnea is indeed a validated cardiovascular risk factor. It is independently associated with hypertension, arrhythmias, heart failure, stroke, myocardial infarction, cardiovascular death, and all-cause mortality.

The high prevalence of obstructive sleep apnea contributes to increased cardiovascular risk in the population.

CPAP may result in decreased cardiovascular risk with adherence to therapy. And clearly, we need longer-term and additional trials many of which are underway.

Remember, from the very beginning of our talk, I presented Mr. NM, our vignette patient. Well, here he is sitting comfortably on his chair, drinking a sweetened cola, watching Sunday afternoon football, and making sure that his dog gets adequate exercise. His Sheltie dog gets adequate exercise. Incidentally, NM has become quite friendly with David and they are both on therapy and doing much better at this point in time.

I want to thank you all for your attention to our sleep medicine presentation as part of the Foundations of Cardiometabolic Health Certification course. And I wish you all Godspeed, stay well, and be safe. Thank you very much.