Arterial stiffness in patients with severe obstructive sleep apnea

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SCHOOL OF MEDICINE

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Diploma thesis

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1. INTRODUCTION

1.1. Sleep-related breathing disorders.

Sleep apnea is characterized by recurrent episodes of apnea occurring during sleep. An apnea is defined as a cessation of inspiratory airflow lasting 10 seconds or more, while the term hypopnea refers to a decrease in inspiratory airflow (by at least 30%) lasting 10 seconds or more with an associated drop in oxygen saturation or arousal from sleep (1).

The term sleep-disordered breathing (SDB) encompasses a group of disorders such as obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed apnea. OSA refers to airflow cessation despite inspiratory effort because of blockage within the upper airways, while in CSA both airflow and inspiratory efforts are absent. Mixed apnea begins as a central apnea and ends as an obstructive apnea (2).

1.2. Obstructive sleep apnea

1.2.1. Definition

OSA, also referred to as obstructive sleep apnea-hypopnea (OSAH), is a common disorder of repeated pharyngeal collapse and cessation of inspiratory airflow during sleep, which leads to oxygen desaturation and disrupted sleep. Pharyngeal collapse can be divided into complete or partial. Disturbances in gas exchange lead to oxygen desaturation, hypercapnia, and sleep fragmentation, which leads to symptoms of OSA - e.g., cardiovascular, metabolic, and neurocognitive effects (3). OSA is associated with excessive daytime sleepiness (EDS). Furthermore, it is commonly called obstructive sleep apnea syndrome (OSAS).

1.2.2. Risk factors

The obese population and males are at greater risk for OSA development. Obesity potentially increases the probability of airway collapse by directly affecting the anatomy of upper airway as fat is accumulated in surrounding structures (5). Fat is deposited within the tongue, impairing the function of the genioglosses muscle according to magnetic resonance imaging (MRI) studies (6). Obesity may also affect the respiratory control because of the effect on lung volumes.

Male predisposition to OSA is not entirely certain (7). Males have the tendency to gain

more weight centrally than women leading to fat stored in upper respiratory structures and visceral abdominal structures (8). However, differences in pharyngeal airway cross-sectional areas in males suggests that fat deposition may not significantly affect the airway structures. The airway in men tend to be longer than in women regardless of body height increasing the incidence of airway collapse according to several studies (7).

Age is another important risk factor (9). Older populations tend to have a loss of elastic recoil in the lung leading to airway narrowing by lung volumes. Due to poorer quality of sleep, the loss of collagen and lower arousal threshold increases the collapsibility of the airway. Old age causes reduction in function the upper airway dilator muscles (10-12).

Additional risk factors for the development of OSA include genetic factors and ethnic origin, which affect craniofacial anatomy, obesity, and lung volume. Menopause, independent of age and body-mass index, is also a risk factor. Menopause could be related to redistribution of body fat to central regions and loss of lean muscle mass (11-13).

Smoking is also a risk factor due to the inflammation of the airways, nasal stuffiness, reduced airway sensation, and reduced arousal threshold or frequent arousals because of unstable sleep, although the exact mechanism is not understood (13).

1.2.4. Epidemiology

As aging is a risk factor for OSA, the OSA prevalence increases 2-3 times in elderly (>65 years) compared with individuals aged 30-64 years, (14-15), with an estimated rate as high as 65% in a community sample of people older than 65 years (16-19).

According to the Wisconsin cohort study, composed of men and women in the workforce between the ages of 30-60 years, it was indicated that 24% of men and 9% of women had an apnea-hypopnea index (AHI) ≥5. Prevalence estimates for an AHI ≥10 and AHI ≥15 were 15% and 5% in men, and 9% and 4% in women, respectively (17). In population-based studies, the ratio of OSA between men and women is 2-3:1 (20). This could be due to physicians' bias having a higher rate of suspicion for men often with more referrals for OSA testing (21). Women typically have no classic OSA symptoms (loud snoring, witnessed apnea and excessive daytime somnolence) but may complain about feeling lethargic (22). Sex

hormones may also play an important role in the pathogenesis of OSA. OSA is more prevalent in post-menopausal women than pre-menopausal women, and hormone replacement therapy in post-menopausal women may protect against the disorder (23, 24).

The prevalence of OSA in children is inconclusive due to variability of data in several studies, which is based on discrepancies in diagnostic criteria. Studies involving laboratory-based polysomnography and relatively large general pediatric population samples reported OSAS prevalence rates of 1.2–5.7 percent. Adenotonsillar hypertrophy, obesity and craniofacial dimorphism are contributing factors to the development of pediatric OSA. Race and ethnicity also play a role. Individuals of Asian heritage are of greater risk due to lower levels of body mass index, likely to the craniofacial structural components which narrow the nasopharynx. In the United States, African-Americans are at higher risk than other ethnic groups (4, 18, 25, 26).

1.2.5. Pathophysiology

The human upper airway is a complex, multifunctional structure involved in performing functional tasks such as speech, swallowing of food/liquids, and the passage of air for breathing. The upper airway's anatomy and neural control have developed to allow these different tasks. The airway consists of muscles and soft tissues but lack bony or rigid support with a collapsible portion extending from the hard palate to the larynx. The upper airway has the ability to change shape and morphing to produce speech and swallowing during wakefulness, and also to collapse at inconvenient times during sleep (27-29).

From a structural perspective, a narrow airway is more likely to collapse than a larger one. The cross-sectional design of the upper airway measured by computed tomography and magnetic resonance imaging during wakefulness is reduced in patients with OSA compared to patients without OSA (27-29). The surrounding soft tissue structure is changed in OSA patients, which may put the upper airway at danger of collapse (27).

During inspiration, intraluminal pharyngeal pressure becomes more and more negative, producing a "sucking" force. Because the pharyngeal airway lacks bone or cartilage, the patency of the airway depends on the pharyngeal dilator muscles stabilizing effect. These muscles are in a continuous state of activation during wakefulness, neuromuscular output is reduced during the onset of sleep. Patients with a collapsible airway, the decline in

neuromuscular inputs results in temporary pharyngeal collapse demonstrated as collapse ("apnea") or near collapse ("hypopnea"). Pharyngeal collapse is eliminated when ventilatory reflexes become activated and produce arousal, stimulating an increase in neuromuscular activity, and finally, causing the airway to open. The airway tends to collapse at the soft palate, base of the tongue, lateral pharyngeal walls, or epiglottis. OSA may be most severe in the supine position due to gravitational forces, and REM sleep because of the low neuromuscular output to skeletal muscles (4).

Individuals with a narrow pharyngeal lumen involve comparatively elevated concentrations of neuromuscular innervation to preserve patentability during wake-fullness and are therefore predisposed to excessive airway collapse during sleep. Due to fat deposition, enhanced lymphoid tissue, or genetic variation, the airway lumen may be reduced with the enlargement of soft tissue structures (tongue, palate, and uvula) (4).

A significant contributor to OSA pathogenesis is thought to be the interaction between pharyngeal patency and lung volume. Upper airway mechanics can be modulated by modifications in lung volume during wakefulness and sleep in healthy people (30-34). Hoffstein and colleagues proved that a lung volume depends on the upper airway cross-sectional area measured during wakefulness across the spectrum from residual volume to total lung capacity. Lung volumes affect the caudal traction of the pharynx and subsequently the rigidity of the pharyngeal wall (4). When lung volume is decreased, there is a rearrangement of the diaphragm and thorax toward the head. This motion results in a loss of caudal traction on the upper airway, resulting in a more collapsible airway (35-38).

The activation of the pharyngeal muscle is integrally connected to the ventilatory drive. Factors linked to ventilation control, especially ventilation sensitivity, arousal threshold and neuromuscular reactions to CO2. The buildup of CO2 during sleep activates both the diaphragm and pharyngeal muscles, which makes the upper airway more rigid which can negate inspiratory suction pressure. The maintenance of airway patency depends on the anatomical predisposition to collapse (4). Pharyngeal collapse can occur if the ventilator control system is overly sensitive to CO2, causing broad fluctuations in ventilation and ventilation drive and upper airway instability. Increases in CO2 during sleep lead to an arousal of the CNS, causing the individual to move from a deep state of sleep to a lighter state or to awaken. A low threshold of arousal, an awake state due to a low level of CO2 or ventilation drive, can initiate the CO2 mediated process of pharyngeal muscle compensation and prevent

airway stabilization. Alternatively, a high arousal threshold, may prevent the cessation of apneas, prolonging its duration, and exacerbating oxy-hemoglobin desaturation severity. Any deficiency in the capacity of the muscles to compensate during sleep can lead to pharyngeal collapse (4).

1.2.6. Clinical presentation

A detailed sleep history and clinical examination are critical for the evaluation of patients with OSA. The sleep history should be taken with assistance of members of the household or bed partner. Clinical features alone or abnormal respiratory events during a sleep study alone are insufficient for diagnosis of the disorder. Diagnosis requires matching clinical symptoms and objective findings from a sleep study (39, 40). However, there is no a completely reliable test to diagnose the disorder.

The hallmark night-time symptoms are snoring and witnessed sleep apnea as a result of narrowing of the upper airway or pharyngeal collapse. Patients may also present with choking, snorting, or gasping displaying termination of individual apnea and sudden airway opening. Also frequent awakening or sleep disturbance may be described by patients, which is more prevalent among female and older adults (4).

The most common daytime symptoms are EDS and falling asleep during daytime. However, there is no correlation between the severity of OSA and EDS. The most commonly used questionnaire to evaluate the subjective sleepiness of the patient is the Epworth Sleepiness Scale 24 (41), which asks patients to rate their tendency to fall asleep in eight distinct circumstance; watching television; sitting inactive in a public place, a theatre or a meeting; as a passenger in a car for 1 hour; lying down to rest in the afternoon; sitting and talking to someone; sitting quietly after a lunch without alcohol; and in a car while stopped for a few minutes in traffic. Other symptoms include a dry mouth, nocturnal heartburn, diaphoresis of the chest and neck, nocturia, morning headaches, trouble concentrating, irritability, and mood disturbances (4). Also, cognitive and attentional disorders could be tied to OSA.

Physical findings represent etiologic signs of OSA. On physical examination, patients present with hypertension and regional (central) obesity, indicated by large waste and neck circumference. The oropharynx may reveal a small orifice with crowding due to an enlarged

tongue, a low-lying soft palate with a bulky uvula, large tonsils, a high-arched palate, and/or micro/retrognathia. Nasal cavity should be inspected for polyps, septal deviation, and other signs of obstruction due its predisposition to pharyngeal collapse. A cardiac examination should be done to detect left or right sided heart dysfunction because patients with heart failure increase the risk for OSA. A neurological evaluation is also required to assess the possibility neuromuscular and cerebrovascular diseases which also increases the risk of OSA (4).

1.2.7. Diagnosis

The severity of OSA must be established before initiating treatment in order to determine the risk of developing the complications of sleep apnea. This establishes an appropriate baseline and greater efficiency of the following treatment. Diagnostic criteria for OSA are based on clinical signs and symptoms determined by a comprehensive sleep evaluation, consisting of sleep orientated history and physical examination and findings identified by sleep testing (42). The diagnosis of OSA beings with a comprehensive sleep history obtained in one of three settings; routing health maintenance examination, an evaluation of symptoms of OSA, and a comprehensive evaluation of patients of high risk for OSA. Questions asked during health maintenance include history of snoring and daytime sleepiness and evaluation for the presence of obesity, retrognathia, or hypertension. Positive findings should lead to a more comprehensive examination. An extensive history of sleep in a patient suspected of OSA should include an evaluation of snoring, witnessed apnea, gasping/choking episodes, excessive sleepiness not explained by other variables, including sleepiness severity assessment by the Epworth Sleepiness Scale, total sleep amount, nocturia, morning headaches, sleep fragmentation/sleep maintenance insomnia, and decreased concentration and memory. An evaluation of secondary conditions that may occur as a result of OSA, including hypertension, stroke, myocardial infarction, *cor pulmonale*, decreased daytime alertness, and motor vehicle accidents, should also be obtained (43).

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic systems (44). Special attention should be given to factors such as obesity, upper airway narrowing, and disorders that can contribute to OSA. Features to be evaluated that may suggest the presence of OSA include increased neck circumference (> 17 inches in men, > 16 inches in women), body mass index (BMI) > 30 kg/m^2, a modified

Mallampati score of 3 or 4, (45) the presence of retrognathia, lateral peritonsillar narrowing, macroglossia, tonsillar hypertrophy, elongated/enlarged uvula, high arched/narrow hard palate, nasal abnormalities (polyps, deviation, valve abnormalities, turbinate hypertrophy) and/or overjet.

Sleep study is the most important investigation in the process of making diagnosis of OSA. There are three major types of sleep studies: full polysomnography, respiratory polygraphy and overnight oximetry. Polysomnography is the diagnostic gold standard and includes the assessment of oximetry, snoring, body, and leg movements, oronasal airflow, excursion of the chest and abdomen, as well as an electrocardiogram, electroencephalogram, and electro-oculogram, and electromyogram, to identify sleep stages. Respiratory polygraphy usually includes all these assessments but without an electroencephalogram, electro-oculogram and electromyogram. Respiratory polygraphy and oximetry equipment is appropriate for home sleep studies that allow patients to sleep in their own setting and possibly better represent ordinary ambient circumstances than a sleep laboratory. In comparison, polysomnography usually needs a sleep laboratory and a qualified technician to set up and monitor the sleep study throughout the night and is therefore resource-intensive (4, 45).

Oximetry alone can recognize OSA in most patients with a high clinical probability, while false-positive oximetry could happen with Cheyne–Stokes breathing (46) and low baseline oxygen saturation. False-negative findings may happen in non-obese patients and those with mainly hypopnea; therefore, in milder instances of OSA, oximetry is of limited value.

Imaging studies, including cephalometric radiography, MRI, CT, and fiberoptic endoscopy, can be used to identify anatomic risk factors of OSA. Cardiac testing may provide evidence of impaired systolic or diastolic ventricular function or abnormal cardiac structure. Overnight surveillance of blood pressure often shows a "non-dipping" pattern (absence of a typical 10 mmHg drop in blood pressure during sleep relative to wakefulness). Measurements of arterial blood gas during wakefulness are generally normal. Waking hypoxemia or hypercarbia suggests the coexistence of cardiopulmonary disease or syndromes of hypoventilation. Patients with serious nocturnal hypoxemia may have high haemoglobin values. A multiple sleep latency test or a wakefulness test can be helpful in quantifying sleepiness and helping to differentiate OSA from narcolepsy (4).

1.2.8. Treatment

A complete approach to the treatment of OSA are need to reduce the risk factors and effects of the disease. The clinician should try to define and resolve lifestyle and behavioral variables, as well as comorbidities that may exacerbate OSA. Treatment optimization is to promote weight loss, optimize sleep duration (7-9 h); regulate sleep schedules; encourage patient to avoid sleeping the supine position; treat nasal allergies; increase physical activity; eliminate alcohol ingestion (which effects pharyngeal muscle activity) within 3 h of bedtime; decrease sedating medications (4).

Nasal continuous positive airway pressure is the treatment of choice for adults with OSA (47). The first recording of being an effective means of preventing pharyngeal airway collapse was 1981 (48). The mechanism of continuous positive airway pressure (CPAP) is disputed, but it likely includes maintaining a positive pharyngeal transmural pressure so that the intraluminal stress exceeds the surrounding pressure (49). CPAP increases end-expiratory lung volume, which stabilizes the upper airway (50). The decision the start the treatment should include discussion with the patient, with the possible alleviation of symptoms, and potential cardiovascular protection (47, 51, 52). CPAP has substantial advantages for some patients and adherence are approximately 60–70%, much the same as adherence to inhalers in patients with asthma, anti-convulsant medications in patients with epilepsy, and maintenance of excellent glycaemic control in diabetes (47).

Patients who are most likely to have a long-term use of CPAP include those who snore heavily, have severe sleep apnea, and excessive daytime sleepiness (53, 54). Short term use and early benefits are the best predictors of long-term use of CPAP. Efforts to get the most benefit of CPAP are done before, or shortly after, starting treatment.

Some points should be considered when managing patients who are struggling to adhere to CPAP. First, intensive support can be advantageous to some studies. Education and support can enhance adherence: patients who recognize the advantages of therapy and are helped with troubleshooting problems are likely to react favorably. Second, some patients have nasal complications that restrict their capacity to tolerate continuous positive airway pressure nasal pressure. Nasal decongestants and heated humidification can be useful for these patients. In rare cases, nasal surgery can improve adherence. Third, although randomized trials have not

shown one type of mask to be better than another, some patients prefer a full face mask to a nasal mask, while others prefer a nasal pillow device. Fourth, some patients react well to hypnotherapy if they develop insomnia or commonly wake up when using continuous positive airway pressure. Some data support the use of eszopiclone in patients who are beginning continuous positive airway pressure. Clinical experience indicates that consolidating sleep (stabilizing or preventing fragmented sleep) can allow adherence so that hypnotherapy is no longer required once the patient has become accustomed to the new machinery. Sedatives should be used with caution in patients with OSA (55, 56).

There are several alternative options to patients whom are unable to use CPAP. Bi-level positive pressure can be used (preferred in some patients with expiratory pressure discomfort), although randomized trials (57) showed no significant advantage relative to continuous positive airway pressure. Second, expiratory pressure relief strategies - eg, C-Flex (Philips Respironics; Murraysville, PA, USA) or expiratory pressure relief (EPR) (Resmed; San Diego, CA, USA) - potentially improves discomfort during expiration in certain patients. Most data (58) propose that such intervention does not produce any significant advantage compared to standard continuous positive airway pressure. Third, auto-titration positive airway pressure has been used to modify pressure on an *ad-hoc* basis to support secure ventilation. Some patients who need to manage varying pressures (e.g. dependent on body posture or sleep stage) can benefit from variable pressure devices that can reduce the pressure applied when appropriate. However, most randomized trials (59) showed no progress in adherence to auto-titration contrary to the standard continuous positive airway pressure. Some data (60) propose that auto-titration positive airway pressure worsens results, presumably because variations in intrathoracic pressure lead to arousal from sleep and hemodynamic instability. Therefore, the data supporting emerging technologies to enhance adherence is not substantial (61), but occasional benefits can be seen in clinical practice.

For patients with unsuccessful use of CPAP, other options are available. They include oral devices, upper airway surgery, positional therapy, and other conservative measures. Different oral devices work in different ways but generally they apply pressure to the jaw to prevent retroglossal collapse. Oral devices are preferable to continuous positive airway pressure in some patients, especially those with mild-to-moderate disease (62, 63). The effectiveness of oral devices varies and little data on outcomes have been recorded (64-67).

Simple surgical procedures can also be done on the soft palate, such as somnoplasty,

laser-assisted uvulopalatopharyngoplasty, but with minor improvements of symptoms. Less than 50% of patients have any significant changes, therefore doctors rule against this procedure. However, surgical procedures can alleviate the use of CPAP, so some researchers advocate for surgical treatments (68-71). Aggressive surgical approaches, for example, maxilla-mandibular advancement are an effective means of treating OSA, but are avoided because patients do not desire to undergo major surgery. Research is still ongoing to determine which procedure is most efficient (72). Experimental procedures are not available (73-75), therefore, further study is needed to determine the most optimal treatment for OSA.

Conservative options can also benefit patients suffering of OSA. Avoidance of alcohol use is beneficial because it can exacerbate symptoms. Sleeping for 7-8 h per night can help alleviate sleepiness. Avoiding sleeping in the supine posture can help patients whose apnea is caused by sleeping position, although these patients prefer CPAP for this treatment (76). Weight loss in general can reduce apnea severity or even lead to the resolution in some patients (77). However, if body weight increases with CPAP it is necessary that physicians instruct patients on proper diet and exercise (78).

Symptoms related to sleepiness continues in some patients despite use of CPAP (79, 80). The cause is undetermined, but related to the irreversible consequences of OSA. These particular patients require symptomatic relief to improve sleep duration and adherence. The use of stimulants can provide treatment for sleepiness but OSA itself. Randomized controlled trials using the stimulant, modafinil, to treat residual sleepiness in patients who use CPAP. However, studies (81) have shown that use of CPAP is compromised. Continued use of CPAP is required in these patients.

Sedatives or hypnotics may be useful in patients of low arousal threshold, while oxygen or acetazolamide may improve OSA in patients with unstable ventilator control (82). Patients with anatomical abnormalities at the level of the velopharynx, palate surgery may be beneficial (83). Patients of upper airway muscle dysfunction, treatments such as hypoglossal nerve stimulation (73), muscle training exercises (84), or different approaches to increase hypoglossal nerve output may be beneficial. Patients with multifactorial disease, combination treatment may be required. New future treatment strategies (85) will primarily be focused on the mechanisms of disease. Drugs in the future will either block the apnea, or increase the severity of the symptoms.

1.3. Arterial stiffness

1.3.1. Arterial stiffness

Arterial stiffness, also known as the loss of arterial elasticity, represents the mechanical property of artery resistant to deformation (86). It is caused by structural changes in the vascular wall, including fibrosis, medial smooth muscle cell necrosis, breaks in elastin fibers, calcifications and diffusion of macromolecules into the arterial wall (87-89). Arterial stiffness can be calculated by applying a stress to the artery and measuring the resultant strain. The ratio of stress to strain (Young's modulus) gives the stiffness of the material.

Physiological elements of arterial stiffness are various. Firstly, dealing with pressure. The arterial wall has a curvilinear stress/strain relationship because it is stress dependent, therefore the wall stiffness increases with the increasing tending pressure (90). Heart rate effect on arterial stiffness has also been explored with its reliance on arterial pressure (91). Measureable differences in carotid-femoral pulse wave velocity up to 12% between heart rates of 60 and 100 bpm independent in changes in arterial pressure according to pacing studies (92).

Passive wall pressure causes arterial wall stiffness through mechanical properties of the cell wall. The extensibility is due to variability of distending pressure, determined by load bearing components, mainly elastin and collagen and wall matrix components such as calcium (93). Over longer periods of time, the artery starts to change and goes through a process of structural arrangement and differences in quantities in collagen and elastin. This alters stiffness and thickness of the artery, and luminal diameter (94).

Remodeling is due to the chronically applied forces, such as pulse pressure and endothelial shear stress. Remodeling can also be caused by genetic predisposition in collagen and elastin networks, and by environmental factors. Endothelial derived factors in the smooth component of the vascular smooth muscle media causes changes in the distribution of the transluminal pressure load on elastin and collagen structural components (98). These mediators may be vascular endothelium dependent (nitric oxide, endothelin, prostacyclin) or circulating (noradrenalin, angiotensin) (95-97).

Nitric oxide (NO), is especially important because its role in regulation of small and large artery stiffness (99, 100), through its cyclic guanosine monophosphate (cGMP) dependent mechanism, and its potency (101). Endothelial dysfunction normally occurs with aging and inflammation, with decrease NO availability, which impairs vascular reactivity and structural components of the cell wall (102).

Inflammation contributes to arterial stiffness by degrading elastin through serum elastin and matrix metalloproteinase (MMP-2 and MMP-9) (103, 104). Increased pulse wave velocity (PWV) has been found to be linked with increased levels of these enzymes, in addition to elevated C-reactive protein (CRP), a well-established marker of inflammation (105). Stiffness of the arteries due to the autonomic nervous system is determined by load bearing components of elastin and collagen, and smooth muscle cell tone (106). Signals of smooth muscle tone regulate arterial stiffness and hemodynamic of the vessels. Antihypertensive medication that lower blood pressure improves endothelial function, but influence arterial stiffness though passive decrease in applied distending stress.

1.3.2. Arterial stiffness in OSA patients

Several mechanisms contribute to arterial stiffness in patients with OSA. Altered inflammation, oxidative stress and sympathetic activity affect endothelial function are observed in OSA (107, 108). Intermittent hypoxia increases production of reactive oxygen species, inducing oxidative stress on the vessel (109, 110). Cellular function is affected through excessive oxidative stress, progressing endothelial dysfunction, increasing inflammation, thus increasing metabolic and cardiovascular complications of OSA such as atherosclerosis (109). Oxidative stress also decreases the function of nitric oxide synthase further contributing to arterial stiffness (111).

Numerous studies discovered that C-reactive protein, tumor necrosis factor-a (TNF-alpha), interleukin-6 (IL-6), interleukin-8 (IL-8), and cell adhesion molecules increased in circulation of independent of obesity in OSA patients (108, 112, 113). Increased inflammation increases arterial stiffness through atherosclerosis. CPAP is the gold standard treatment for maintaining upper airway patency during sleep. Improvements have been shown in endothelial function and sympathovagal tone (114, 115). Thus, arterial stiffness parameters in OSA patients improve during use of CPAP therapy.

2. OBJECTIVES

The aim of the present study was to compare arterial stiffness parameters and laboratory parameters between OSA patients and healthy control subjects.

Hypothesis:

1. Parameters of arterial stiffness will be increased in OSA patients in comparison with the control subjects.
2. There will be correlation between parameters of arterial stiffness and polysomnographic indices in OSA patients.

3. SUBJECTS AND METHODS

3.1. Subjects

Our study included 35 male patients with newly diagnosed severe OSA, from the Split Sleep Medicine Centre (University Hospital of Split, University of Split School of Medicine). The control group was adjusted for gender, age and body mass index (BMI) and it enrolled 35 healthy volunteers. All the participants from the control group were previously examined to exclude existence of any OSA symptoms and fulfilled screening tool for OSA risk assessment questionnaire (STOP-BANG). Subjects with STOP-BANG score ≥3 were excluded from control group. Inclusion criteria was: newly diagnosed severe OSA (AHI >30 event/hour), age above 18 years, male gender. Exclusion criteria was: diabetes mellitus, significant cardiovascular disease, patients previously treated for OSA, patients taking lipid-lowering drugs, female gender.

Approval of the present study was obtained by Ethics Committee of the University of Split School of Medicine. Procedures were undertaken in accordance with the Declaration of Helsinki and informed consent was obtained from all the participants.

3.2. Anthropometric characteristics of study participants

Calibrated scale (Seca, Birmingham, UK) was used to assess body height and weight of the study participants. Tape measure was used to measure waist and neck circumference.

3.3. Sleep assessment

All OSA patients underwent full-night polysomnography at the Split Sleep Medicine Centre during which following measurements were recorded: electrooculography, electroencephalography, mental and tibial electromyography, thoracic and abdominal movements, electrocardiography, nasal airflow, pulse oximetry, and snoring intensity (Alice 5LE, Philips Respironics, Eindhoven, Netherlands). Apnea was defined as a complete cessation of airflow for at least 10 seconds, while for the hypopnea airflow is decreased by more than 50% for at least 10 seconds, in combination with a reduction in oxygen saturation of at least 3%.

3.4. Biochemical analysis

Venous blood samples were obtained from each participant after a fasting time of 12 hours. High sensitivity C-reactive protein (hsCRP) was determined by the immunoturbidimetric method on Architect c16200 system (Abbott, Chicago, IL, USA).

Haemoglobin A1c (HbA1c) levels were measured by using high-performance liquid chromatography (HPLC) (Tosoh G8, Tosoh Bioscience, Tokyo, Japan). Total cholesterol, HDL, LDL and triglyceride levels were analysed by using standard laboratory methods (ARCHITECT ci16200, Abbott, Chicago, IL, USA).

3.5. Arterial stiffness measurements

Applanation tonometry readings were obtained using SphygmoCor (Version 8.1; AtCor Medical, Inc., Sydney, Australia). During measurement a tonometric transducer is placed on the subject's radial artery. Device calibration was made based on an average of two consecutive blood pressure measurements. A trained physician performed measurements for all the included participants. Readings of pulse wave velocity (PWV), peripheral and central augmentation index (pAIx, cAIx), central systolic blood pressure were obtained.

3.6. Statistical analysis

Statistical program IBM® SPSS Statistics for Windows® (version 25.0, IBM, Armonk, NY, USA) was used to perform all the analysis. Categorical variables were shown as whole numbers (N) with percentages (%). Continuous variables were shown as mean ± standard deviation. T-test for independent samples was used to assess differences between continuous variables. Chi-squared test was used for categorical variables. Correlations between arterial stiffness parameters with polysomnographic, anthropometric and laboratory parameters were tested with Pearson's correlation test. Statistical significance was set at $P<0.05$.

4. RESULTS

Baseline anthropometric characteristics are presented in Table 1. The OSA group and control group did not differ in age, height or weight. However, the differences were observed in neck circumference (41.8 ± 4.1 vs. 38.1 ± 2.7 cm, P <0.001) and ESS (9.9 ± 4.1 vs. 4.6 ± 3.2, P <0.001) values between OSA and control group.

Table 1. Baseline anthropometric characteristics of study population

Parameter	**OSA group (N=35)**	**Control group (N=35)**	**P***
Age, years	51.4 ± 9.2	52.1 ± 9.3	0.752
Body height, cm	184.1 ± 8.2	183.1 ± 6.3	0.569
Body weight, kg	103.1 ± 13.0	100.6 ± 12.1	0.407
BMI, kg/m^2	30.4 ± 4.1	30.0 ± 3.6	0.665
Neck circumference, cm	41.8 ± 4.1	38.1 ± 2.7	<0.001
Waist circumference, cm	105.3 ± 11.6	102.9 ± 12.8	0.414
Smoking, N (%)	7 (20)	11 (31.4)	0.274
ESS	9.9 ± 4.1	4.6 ± 3.2	<0.001

Data are presented as mean ± standard deviation or as stated otherwise.
BMI - body mass index; ESS - Epworth Sleepiness Scale
* t-test for independent samples or chi-squared test

OSA patients included in the study are classified as severe OSA patients, according to their polysomnographic parameters presented in Table 2. AHI value was 49.1 ± 11.4 events per hour, and ODI value was 46.6 ± 15.3 events per hour.

Table 2. Polysomnographic parameters in severe OSA patients (N=35)

Parameter	**Value**
AHI, events/h	49.1 ± 11.4
ODI, events/h	46.6 ± 15.3
Mean SpO_2, %	91.4 ± 3.0
Minimum SpO_2, %	68.5 ± 10.1
Total sleep time, min	418 ± 85

Data are presented as mean ± standard deviation
AHI - apnea-hypopnea index; ODI - oxygen desaturation index; SpO_2 - arterial oxygen saturation

OSA group had elevated values of hsCRP (2.6 ± 1.2 vs. 1.1 ± 0.8 mg/L, P <0.001) and HbA1c (5.6 ± 0.4 vs. 5.4 ± 0.2 %, P=0.006), when compared to control group. Furthermore, HDL concentration was lower in OSA patients when compared to healthy controls, 1.1 ± 0.2 vs. 1.3.±.0.3 mmol/L, P<0.001. All laboratory parameters are presented in Table 3.

Table 3. Laboratory parameters of study population

Parameter	OSA group (N=35)	Control group (N=35)	P*
Triglycerides, mmol/L	1.8 ± 1.0	1.5 ± 0.8	0.170
Total cholesterol, mmol/L	5.7 ± 1.3	5.6 ± 1.2	0.739
HDL, mmol/L	1.1 ± 0.2	1.3.±.0.3	<0.001
LDL, mmol/L	3.7 ± 1.2	3.7 ± 1.3	0.998
hsCRP, mg/L	2.6 ± 1.2	1.1 ± 0.8	<0.001
HbA1c, %	5.6 ± 0.4	5.4 ± 0.2	0.006

Data are presented as mean ± standard deviation.
hsCRP – high sensitivity C-reactive protein; HDL - high-density lipoprotein, LDL - low-density lipoprotein
* t-test for independent samples

Table 4 shows parameters of arterial stiffness in study participants. Statistically significant higher values of cAIx (26.3 ± 8.8 vs. 18.8 ± 9.0 %, P <0.001) and PWV (9.8 ± 3.1 vs. 7.4 ± 2.2 %, P <0.001) parameters were observed in OSA patients when compared to control group.

Table 4. Parameters of arterial stiffness in study population

Parameter	OSA group (N=35)	Control group (N=35)	P*
SBP, mmHg	131.1 ± 13.4	125.5 ± 10.8	0.058
DBP, mmHg	79.3 ± 7.5	77.8 ± 5.1	0.331
cSBP, mmHg	125.8 ± 11.2	122.9 ± 8.6	0.228
HR, beats/min	71 ± 14	73 ± 16	0.579
pAIx, %	-21.3 ± 11.4	-19.3 ± 9.6	0.430
cAIx, %	26.3 ± 8.8	18.8 ± 9.0	<0.001
PWV, m/s	9.8 ± 3.1	7.4 ± 2.2	<0.001

Data are presented as mean ± standard deviation.
SBP - systolic blood pressure; DBP - diastolic blood pressure; cSBP - central systolic blood pressure; HR – heart rate; pAIx - peripheral augmentation index; cAIx - central augmentation index; PWV - pulse wave velocity
* t-test for independent samples

Correlation of stiffness parameters PWV and cAIx with polysomnographic parameters are presented in Table 5. PWV parameter showed positive correlation with AHI (r=0.476, P=0.003) and negative with minimum SpO_2 (r=-0.369, P=0.029).

Table 5. Correlation between selected arterial stiffness parameters with polysomnographic parameters in severe OSA patients

Parameter	**PWV, m/s** **r (P*)**	**cAIx, %** **r (P*)**
AHI, events/h	0.476 (0.003)	0.212 (0.221)
ODI, events/h	0.313 (0.067)	0.112 (0.521)
Mean SpO_2, %	-0.094 (0.591)	-0.065 (0.710)
Minimum SpO_2, %	-0.369 (0.029)	-0.102 (0.559)
Total sleep time, min	0.012 (0.945)	0.087 (0.619)

AHI - apnea-hypopnea index; ODI - oxygen desaturation index; SpO_2 - arterial oxygen saturation; cAIx - central augmentation index; PWV - pulse wave velocity
* Pearson's correlation test

Table 6 shows correlation between PWV and cAIx with anthropometric and laboratory parameters. PWV parameter showed positive correlation with neck circumference (r=0.406, P <0.001) and hsCRP (r=0.398, P <0.001). cAIx showed positive correlation with neck circumference (r=0.307, P=0.009).

Table 6. Correlation between selected arterial stiffness parameters with anthropometric and laboratory parameters in study population

Parameter	**PWV, m/s** **r (P*)**	**cAIx, %** **r (P*)**
Age, years	0.212 (0.078)	0.212 (0.221)
BMI, kg/m^2	0.168 (0.164)	0.112 (0.521)
Neck circumference, cm	0.406 (<0.001)	0.307 (0.009)
Waist circumference, cm	0.209 (0.082)	0.201 (0.107)
Triglycerides, mmol/L	0.068 (0.575)	0.112 (0.355)
HDL, mmol/L	-0.124 (0.306)	-0.136 (0.261)
hsCRP, mg/L	0.398 (<0.001)	0.206 (0.087)
HbA1c, %	0.021 (0.863)	0.098 (0.419)

BMI - body mass index; HDL - high-density lipoprotein; hsCRP – high sensitivity C-reactive protein; cAIx - central augmentation index; PWV - pulse wave velocity
* Pearson's correlation test

5. DISCUSSION

The results of our study showed that OSA patients had increased arterial stiffness, in comparison with the control population. The relationship between OSA and arterial stiffness has been studied extensively.

A community based cross-sectional observational study conducted by Chami *et al.,* which included 381 patients of both genders, assed the carotid-femoral PWV, as it is the gold-standard measure of aortic stiffness. The results of this study have showed that sleep-disordered breathing was associated with increased carotid-femoral PWV. Moreover, the authors concluded that PWV was a strong predictor of cardiovascular risk. It should be acknowledged that the same observation of increased PWV in OSA patients, when compared to healthy controls, was reported in our study. However, our study did not show a correlation between increased PWV and any of metabolic parameters which are considered as cardiovascular risk factors, e.g. triglycerides, HDL or HbA1c values. Moreover, the association of PWV with BMI has also not been observed (116).

A prospective cohort study by Kim *et al*. found that patients with moderate-to-severe OSA (AHI $\geq$ 15) in the group without hypertension had a 2.60 fold increased risk for elevated PWV, compared to population without OSA (AHI < 5). More importantly, this elevated risk was even higher after 6 years, which was the follow up period. The authors concluded that moderate-to-severe OSA was a predictor of future burden of stiffness progression, independent of other factors as obesity, and suggested that OSA without other comorbidities may contribute to the increased risk of cardiovascular disease (117).

Çörtük *et al.* demonstrated that patients with higher AHI had increased aortic stiffness PWV values. It should be acknowledged that stiffness is associated with both the presence and severity of OSA in this study. The same results were observed in our study, as the statistically significant correlation of AHI and PWV were reported. However, our study included only severe OSA patients, which could have influenced our findings (118).

Furthermore, Phillips *et al.* study results have also shown that systemic arterial stiffness was significantly correlated with the degree of OSA severity. Moreover, as the common acute manifestations of OSA are nocturnal and early morning blood pressure elevation, the same authors have also examined the effect of OSA on blood pressure. The Augmentation index of study participants increased from evening to morning ($P < 0.001$) and it was accompanied by an increase in systolic blood pressure and a decrease in pulse pressure amplification. Furthermore, these changes were not accompanied by changes in peripheral blood pressure (119). In our research we have not found a difference between OSA and control group in blood

pressure parameters. Therefore, there is a possibility that our findings could have been influenced by the part of the day in which the blood pressure measurements were performed.

A study published in 2019, which included 362 participants, found an association between the AHI, ODI, sleep time and SpO_2 with arterial stiffness. In our study we have also demonstrated the association between AHI and minimum SpO_2 with arterial stiffness, but not with ODI and total sleep time. However, the same study included both male and female participants, hence it could have an influence on the differences observed between the results from that study and the results from our study (120).

Furthermore, we have observed that hsCRP values were elevated in OSA patients, when compared to control group. Moreover, the hsCRP value was positively correlated with PWV in our study. The association between arterial stiffness and inflammation has been recognized previously, and anti-inflammatory strategies have been proposed in order to reduce arterial stiffness and thus cardiovascular risk (105).

Other than the difference in hsCRP values, our study has also demonstrated that OSA patients have higher values of HbA1c, and lower values of HDL cholesterol, which adds to OSA patients' cardiovascular risks. A study by Divya *et al.*, published in 2019, which explored the association between metabolic syndrome and OSA reported similar findings. In their study the increasing severity of OSA was associated with poorer glycemic control. Furthermore, the mean HDL levels for patients with OSA were lower than in individuals without OSA (121).

Contrary to our results, and to the results of the aforementioned study, a meta-analysis published in 2016, which included 2053 OSA patients, did not found the relationship between HDL values and OSA. Moreover, the same meta-analysis reported that patients with OSA had higher systolic blood pressure, when compared to healthy controls. This relationship has also not been observed in our study, and future studies should be proposed in order to assess the exact relationships between all metabolic syndrome parameters and OSA (122).

The main limitations of our study were that the study included small sample size, and that it was conducted at single center, University Hospital of Split. Another limitation is that this was a cross sectional study which did not include the follow up of the patients. Moreover, this study design could not allow evaluation of causality between OSA and arterial stiffness. However, even with the aforementioned limitations, the results of our study are in accordance with previous similar studies.

6. CONCLUSION

1. The higher values of cAIx and PWV parameters were observed in OSA patients, in comparison to control group.
2. The positive correlation was observed between AHI and PWV and negative correlation was observed between minimum SpO_2 and PWW.
3. The positive correlation was observed between hsCRP and PWV.
4. The positive correlation was observed between neck circumference and cAIx and PWV.
5. OSA patients had higher hsCRP and HbA1c values, when compared to control group.
6. OSA patients had lower values of HDL, when compared to control group.

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8. SUMMARY

Objectives: Obstructive sleep apnea (OSA) could have detrimental effects on overall patients' health. Moreover, OSA without other comorbidities may contribute to the increased risk of cardiovascular disease. The aim of the present study was to compare arterial stiffness parameters and laboratory parameters between severe OSA patients and healthy control subjects.

Patients and methods: This study included 70 participants in total, 35 OSA patients and 35 healthy controls. All OSA patients underwent full-night polysomnography at the Split Sleep Medicine Centre. Venous blood samples were obtained from each participant after a fasting time of 12 hours. High sensitivity C-reactive protein (hsCRP) was determined by the immunoturbidimetric method on Architect c16200 system (Abbott, Chicago, IL, USA). Haemoglobin A1c (HbA1c) levels were measured by using high-performance liquid chromatography (HPLC) (Tosoh G8, Tosoh Bioscience, Tokyo, Japan). Total cholesterol, HDL, LDL and triglyceride levels were analysed by using standard laboratory methods (ARCHITECT ci16200, Abbott, Chicago, IL, USA). Tonometric measurements of arterial stiffness was performed by a trained physician using SphygmoCor (Version 8.1; AtCor Medical, Inc., Sydney, Australia). Readings of pulse wave velocity (PWV), peripheral and central augmentation index (pAIx, cAIx), central systolic blood pressure were obtained.

Results: OSA group had elevated values of hsCRP (2.6 ± 1.2 vs. 1.1 ± 0.8 mg/L, P <0.001) and HbA1c (5.6 ± 0.4 vs. 5.4 ± 0.2 %, P=0.006), when compared to control group. Furthermore, HDL concentration was lower in OSA patients when compared to healthy controls, 1.1 ± 0.2 vs. 1.3.±.0.3 mmol/L, P<0.001. Statistically significant higher values of cAIx (26.3 ± 8.8 vs. 18.8 ± 9.0, P <0.001) and PWV (9.8 ± 3.1 vs. 7.4 ± 2.2, P <0.001) parameters were observed in OSA patients when compared to control group. PWV parameter showed positive correlation with AHI (r=0.476, P=0.003) and negative with minimum SpO2 (r=-0.369, P=0.029). PWV parameter showed positive correlation with neck circumference (r=0.406, P <0.001) and hsCRP (r=0.398, P <0.001). cAIx showed positive correlation with neck circumference (r=0.307, P=0.009).

Conclusion: The higher values of cAIx and PWV parameters were observed in OSA patients, in comparison to control group. However, future studies are needed to elucidate connection between sleep apnea and impairment of arterial stifness.

9. CROATIAN SUMMARY

Naslov: Arterijska elastičnost u pacijenata s teškom opstrukcijskom apnejom tijekom spavanja

Cilj: Opstrukcijska apneja tijekom spavanja (OSA) može imati negativne učinke na zdravlje pacijenata. Nadalje, OSA bez drugih komorbiditete može doprinijeti povećanom riziku od kardiovaskularnih bolesti. Cilj ovog istraživanja je usporediti parametre arterijske elastičnosti i laboratorijske nalaze u pacijenata s teškom OSA-om i zdravih ispitanika.

Ispitanici i metode: U istraživanje je uključeno 70 ispitanika, 35 OSA pacijenata i 35 zdravih kontrolnih ispitanika. Svi OSA pacijenti bili su podvrgnuti cjelonoćnoj polisomnografiji u Centru za medicinu spavanja Split. Svim ispitanicima su izuzeti venski uzorci krvi nakon 12-satnog posta. Visoko osjetljivi C-reaktivni protein (hsCRP) je određen imunoturbidimetrijskom metodom na Architect c16200 sustavu (Abbott, Chicago, IL, USA). Hemoglobin A1c (HbA1c) je mjeren korištenjem visoko učinkovite tekućinske kromatografije (Tosoh G8, Tosoh Bioscience, Tokyo, Japan). Ukupni kolesterol, HDL, LDL i trigliceridi su analizirane koristeći standardne laboratorijske metode (ARCHITECT ci16200, Abbott, Chicago, IL, USA). Tonometrijska mjerenja arterijske elastičnosti proveo je obučeni liječnik koristeći SphygmoCor (Version 8.1; AtCor Medical, Inc., Sydney, Australia). Provedena su mjerenja brzine pulsnog vala (PWV), perifernog i centralnog augmentacijskog indeksa (pAIx, cAIx) te centralnog sistoličkog tlaka.

Rezultati: OSA pacijenti imali su povišene vrijednosti hsCRP (2,6 ± 1,2 naprema 1,1 ± 0.8 mg/L, P <0,001) i HbA1c (5,6 ± 0,4 naprema 5,4 ± 0,2 %, P=0,006), u usporedbi s kontrolnom skupinom. Nadalje, koncentracija HDL-a bila je niža u OSA pacijenata u usporedbi sa zdravim kontrolama, 1,1 ± 0,2 naprema 1,3 ± 0,3 mmol/L, P<0,001. Statistički značajno više vrijednosti cAIx (26,3 ± 8,8 naprema 18,8 ± 9,0, P <0,001) i PWV (9,8 ± 3,1 naprema 7,4 ± 2,2, P <0,001) su opažene u OSA pacijenata, u usporedbi s kontrolnom skupinom. PWV je pozitivno korelirao s AHI (r=0,476, P=0,003), a negativno s minimalnim SpO2 (r=-0,369, P=0,029). PWV je pokazao pozitivnu korelaciju s opsegom vrata (r=0,406, P <0,001) i hsCRP (r=0,398, P <0,001). cAIx je pokazao pozitivnu korelaciju s opsegom vrata (r=0,307, P=0,009).

Zaključak: Više vrijednosti cAIx i PWV parametara su uočene u OSA pacijenata, u usporedbi s kontrolnom skupinom. Međutim, potrebna su daljnja istraživanja kako bi se rasvijetlila povezanost apneje tijekom spavanja s poremećajem arterijske elastičnosti.

10. CURRICULUM VITAE

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