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Association Between Sleep Apnoea and Cardiovascular Outcomes in Patients with Obesity

Dr Ghanshyam Kumar[1], Dr Sumit Kumar Vishwakarma[2]

[1]PG Diploma in Internal Medicine Scholar, Ramnath Prasad institute of Higher Education Foundation, East Champaran (Bihar).
[2]Assistant professor, General Medicine, Ramnath Prasad institute of Higher Education Foundation, East Champaran (Bihar).

Abstract

Background: Sleep apnoea is a global disease with a rising incidence along with the increasing prevalence of obesity. Repeated episodes of apnoea result in fragmented sleep and daytime sleepiness which can further lead to cardiovascular disorders. Since obesity shares many of its pathogenetic mechanisms with sleep apnoea , it is an active confounder in the link between sleep apnoea and cardiovascular diseases. Obesity significantly increases the risk of CAD and is also associated with a number of other risk factors for atherosclerosis, including hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, reduced HDL cholesterol, and low levels of adiponectin. OSA and obesity share similar pathophysiologic mechanisms potentially leading to cardiovascular disorders.

Aim: The aim of this review is to study the association between Sleep Apnoea and cardiovascular Outcomes in Patients with Obesity. Analysis of pathophysiology of sleep apnoea and CVD can help to better understand the relationship between OSA and CVD. In this review, we discuss the growing epidemic of obesity and OSA, highlighting the common pathogenic hypotheses linking these risk factors to CVD. Alongside, we also try to highlight the therapeutic rationale of OSA as a way to reduce CVD risk.

Data source: Standard texts in medicine like Harrison's principles of internal medicine 21st edition , Current medical diagnosis and treatment 61st edition, Goldman Cecil Medicine 26th edition , were taken as references to have a basic understanding of the concept of sleep apnoea and obesity.Electronic database search was also performed for articles to support our association using the key term obstructive sleep apnoea and obesity .Data was also sourced from published studies and databases published by national and international organizations.

KEYWORDS: Obesity, Sleep apnea, Metabolic syndrome, Cardiovascular disorders, Inflammation, Intermittent hypoxia, Intrathoracic pressure changes, Arousals, Oxidative stress.

Introduction

Sleep apnoea is a common disorder that causes patients to temporarily stop or decrease their breathing repeatedly during sleep. The resulting fragmented, non-restful sleep that can lead to symptoms such as morning headache and daytime sleepiness. This leads to various pathogenetic pathways which set the ground for onset of cardiovascular disorders. Epidemiologic studies and current evidence suggests a role

for sleep apnoea in the development of cardiovascular disorders. However, obesity is an active confounder in this relationship. Obesity has not only increased the rate of CVD but also has ushered sleep apnoea as an additional CVD risk factor.

OSA and obesity share similar pathophysiologic mechanisms potentially leading to cardiovascular disorders.Obesity significantly increases the risk of CAD and is also associated with a number of other risk factors for atherosclerosis, including hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, reduced HDL cholesterol, and low levels of adiponectin. Given its close tie with major cardiovascular risk factors, sleep apnoea is commonly linked to the pathogenesis of a wide array of cardiovascular diseases (CVDs) including hypertension, heart failure, arrhythmias, coronary artery disease, stroke, cerebrovascular disease and pulmonary hypertension (PH). Thus sleep apnoea an under diagnosed but a major contributor to cardiovascular disease in obesity.

OBESITY

Obesity is a disorder of energy imbalance, where there is a surplus of energy consumption compared to its expenditure. Increased caloric intake with modern diet that is high in simple carbohydrates and saturated fatty acids, combined with sedentary lifestyle are the main culprits in the obesity pandemic.

Definition of obesity[1]

a. Adults BMI 30 kg/m2 or higher or, alternatively, 20% higher than suggested ideal body weight.

b. Children and adolescents BMI at the 95th percentile or higher

Prevalence of obesity:

Prevalence of overweight and obesity among adults greater than 18 years age: 43% (43% men, 44% women) i.e.approx 2.5 billion[2][3]

Prevalence of obesity among adults more than 18 years age : 16% approx 890 million[2][3]

Prevalence of obesity among boys : 9.3% in 2022. i.e. approximately 94 million boys[4]

Prevalence of obesity among girls : 6.9% in 2022 i.e. approximately 65 million girls[4]

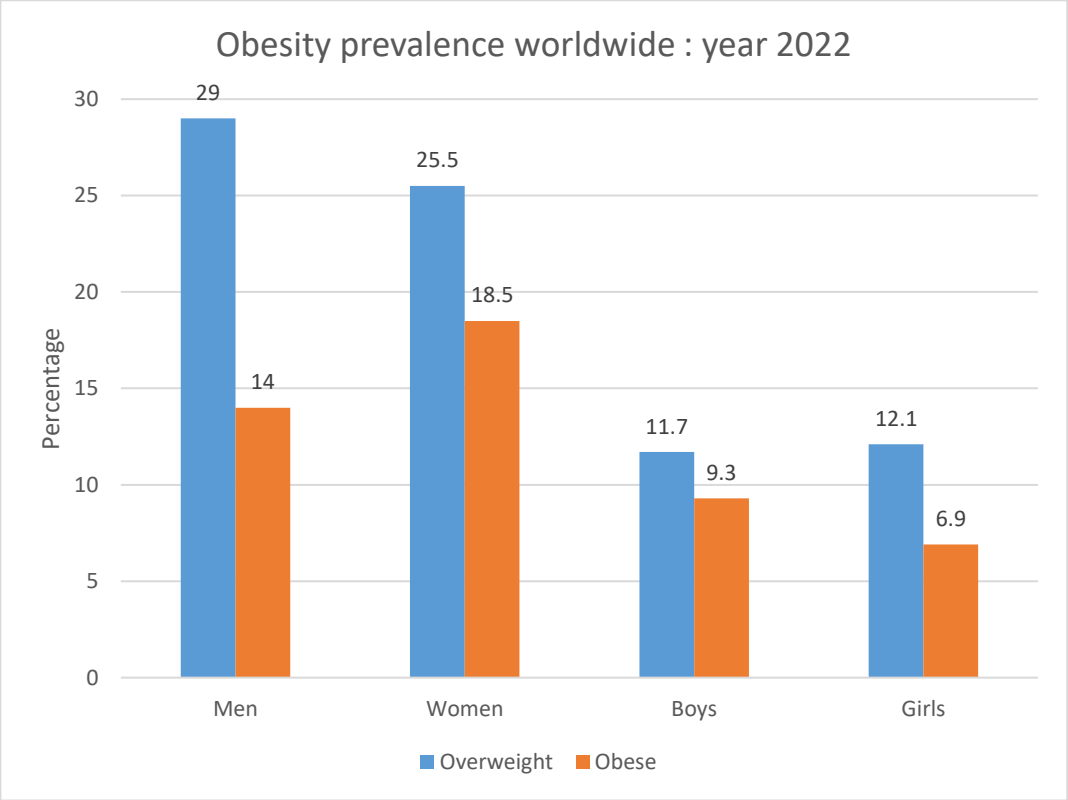


Fig.1 Obesity prevalence worldwide in year 2022

Percentage of indian women in age group 15-49 years with BMI ≥ 30 or obese : 6.4%[5] .
Percentage of indian men in age group 15-49 years with BMI ≥ 30 or obese : 4 % [5]
Prevalence of overweight among men 18.9%[5]
Prevalence of overweight among women 17.6% [5]
Men (age 15-49 Years) Who Are Overweight Or Obese (**BMI ≥25**.0 Kg/m2) (%): 22.9%[5]
Women (age 15-49 Years) Who Are Overweight Or Obese (**BMI ≥25**.0 Kg/m2) (%) : 24%[5]
Percentage of Indian children under 5 years who are **overweight** (weight for height) : **3.4**% [5]
Men (age 15-49 Years) Who Have High Risk Waist-to-hip Ratio (≥0.90) (%): 47.7%[5]
Women (age 15-49 Years) Who Have High Risk Waist-to-hip Ratio (≥0.85) (%): 56.7%[5]

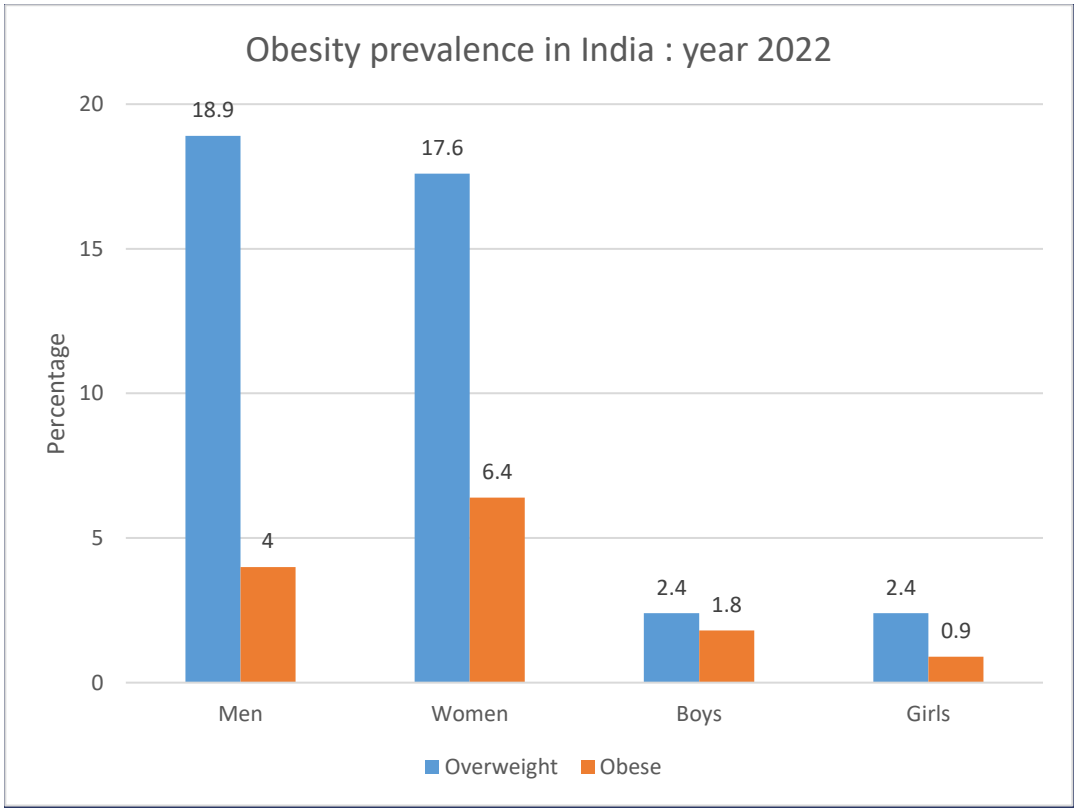


Fig.2 Obesity prevalence in India in year 2022

The preliminary finding on the status of abdominal obesity reveals that 40% of women and 12% of men are abdominally obese in the country. It is found that the **22.1% of men** tend to have BMI above the cut-off range and 11.9% of them have a WC above the cut-off range. For women it is found that **23% of women** have BMI above the cut-off range of 25 and 39.6% of women have WC above the cut-off range of 80 cm. Abdominal obesity is a significant health concern for women in India, as many women with a healthy BMI still have excess abdominal fat, which increases their risk of metabolic diseases and other health complications. The prevalence of abdominal obesity among women in India is quite high, with about 4 in 10 women having a waist circumference higher than the prescribed cut-off mark for abdominal obesity, which puts them at an increased risk of metabolic complications and non-communicable diseases. Several other studies have reported the similar pattern of gender disparity in obesity where findings reveal that women tend to be more abdominally obese than man.

Etiology of obesity:

Obesity is a multifactorial condition. The factors playing a role in eating and weight control include: G*enetic*, C*ultural*, S*ocioeconomic*, B*ehavioural*, and S*ituational*, *Metabolic*, *Physiological* and now even *Viral (adenovirus)*.

Mostly obesity is *primary*, that is, no obvious cause exists other than an imbalance in energy intake and energy expenditure. When energy expenditure is less than energy intake, there will be weight gain. Most patients with obesity have essential obesity (analogous to essential hypertension). There are, however, secondary causes. Less than 1% of patients who are obese have an identifiable secondary cause of obesity.[1]

Other causes of obesity (though not common) include :

Genetic syndromes: Lawrence–Moon-Biedl , Prader-Willi, Alstrom, Carpenter, Cohen, Beckwith Wiedemann.
Endocrine diseases :Cushing's syndrome, hypothyroidism, insulinoma, craniopharyngioma,Turner's syndrome, male hypogonadism and polycystic ovarian syndrome.
Neurological disorders.
Drugs
Psychotropic medications :
Tricyclic antidepressants
Monoamine oxidase inhibitors
Specific SSRIs
Atypical antipsychotics
Lithium
Specific anticonvulsants
β-adrenergic receptor blockers
***Diabetic medications* :** Insulin , Sulphonylureas , Thiazolidinediones
Highly active antiretroviral therapy
Tamoxifen
***Steroid Hormones* :** Glucocorticoids , Progestational steroids

Evaluation or Assessment of obesity:
Three commonly used objective methods of estimating obesity in clinical practice[6]:
1. Body Mass index (BMI),
2. Waist-to-hip ratio (WHR), and waist circumference (WC) and
3. Fat distribution.

Calculation of BMI : **Weight (in kg)/ Height (in meters squared)**
Limitations of BMI: **Does not differentiate between fat and muscle**: A high BMI may indicate high muscle mass rather than fat.
Classification of generalised obesity is done on basis of BMI.

Table 1. Nutrition status and WHO criteria BMI cut off [7]

NUTRITIONAL STATUS	BMI CUTT OFFS
Underweight	<18.5 kg/m^2
Normal Weight	18.5–24.9 kg/m^2
Overweight (preobese)	>25 -29.9 kg/m^2
Obese Class I obesity Class II obesity (Morbid obesity) Class III obesity (extreme obesity) Super morbid obesity BMI	≥30 kg/m^2 30-34.9 kg/m^2 35-39.9 kg/m^2 > 40 kg/m^2 >50 kg/m^2

Table 2. WHO classification of BMI for the asian population.[8][9]

NUTRITIONAL STATUS	CUTT OFF FOR ASIANS
Underweight	<18.5 kg/m^2
Normal Weight	18.5–22.9 kg/m^2
Overweight	>23 -24.9 kg/m^2
Obese	>25 kg/m^2
Class I obesity	**25-29.9 kg/m^2**
Class II obesity	30–34.9 kg/m^2
Class III obesity (extreme obesity / morbid obesity)	≥ 35 kg/m^2
Super morbid obesity BMI	>50 kg/m^2

For children under 5 years of age:

- overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and
- obesity is weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.

Children aged between 5–19 years

Overweight and obesity are defined as follows for children aged between 5–19 years:

- overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; and
- obesity is greater than 2 standard deviations above the WHO Growth Reference median.

Table 3. Indian cut-offs for Indicators of obesity.[9]

PARAMETER	INDIAN CUT-OFF MALE	INDIAN CUT-OFF FEMALE
Waist Circumference (WC	>90,	>80
Waist-Hip Ratio (WHR)	>0.9	>0.85
Wrist circumference	16.5 cm	15.7 cm
Neck circumference (NC)	35.25 cm	34.25 cm
Body Fat Percentage	>25%	>30%
Body Mass Index	>23 kg/m2 – Overweight, >25 kg/m2 – Obesity	

Table 4 . Classification of -Waist-Hip ratio.[9]

Health Risk	Women	Men
Low	0.80 or lower	0.95 or lower
Moderate	0.81–0.85	0.96–1.0
High	0.86 or high	1.0 or high

WHR as a measure of abdominal obesity could be erroneous but some studies have shown it to closely correlate to coronary heart disease.

Measurement of the waist circumference is a surrogate for visceral adipose tissue and should be performed in the horizontal plane above the iliac crest[10].

Table 5. Ethnic specific cutpoint values for waist circumference[11]:

ETHNIC GROUP	WAIST CIRCUMFERENCE
Europeans Male Female	 >94 cm >80 cm
South Asians & Chinese Male Female	 >**90** cm >**80** cm
Japanese Male Female	 >85 cm >90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available.
Sub Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean & Middle eastern (Arab) populations	Use European data until more specific data are available

Body Fat Distribution (Fat Phenotypes)

On the basis of distribution of body fat, obesity may be classified into android obesity and gynoid obesity.

Android obesity (Apple shaped obesity, Abdominal obesity, Central obesity)	*Gynoid* obesity / Gluteo-femoral obesity / Pear shaped obesity
Fat deposited in the abdomen above the waist . greater waist:hip ratio central obesity (as judged by the waist circumference) correlates with increased visceral adiposity and has worse health outcomes due to its association with *coronary heart disease*, *diabetes mellitus*, *hypertension ,dyslipidaemia, insulin resistance and metabolic syndrome.*[12]	Fat deposited on the hips and buttocks or below the waist. Waist:hip ratio of ≤0.8 in females or <0.9 in males[12] Better prognosis in terms of cardiovascular disease.[12] Gynoid obesity makes the person more prone to *mechanical disorders*, such as *varicose veins* and *disorders of the joints.*

Since men typically carry excess weight in the upper body and women in the lower body, men rather than women, should be targeted for weight reduction. Waist circumference correlates well with

abdominal fat content. In men, there is an *increased risk* if the *waist circumference is 85 cm or more* and *substantial risk* if it is *90 cm or more* and for women, the figures are *80 cm or more*, respectively.

Ageing leads to a decline in muscle mass, increase in body fat ("sarcopenic obesity"), and redistribution of body fat thereby increasing truncal fat. These body composition changes may be more marked in Asian Indians who have a high amount of truncal adiposity and low muscle mass[13].

Recent update on obesity : the new two-tier obesity classification system.

New approach considers measurement of obesity through waist circumference or waist to hip ratio in addittion to BMI. As per new guidelines, at least one measurement of body size in addition to BMI or two measurements of body size regardless of BMI should be carried out before categorizing someone as obese.

The assessment can be done through direct body fat measurement (via bone densitometry scan or DEXA) regardless of BMI.

Excess body fat can be pragmatically assumed in those with a very high BMI (>40 kg/m^2).

The term overweight has been replaced with Obesity — grades I and II — instead.

Stage 1 Obesity: increased adiposity (BMI>23 kg/m^2) without discernible effects on organ functions or daily activities. This stage of obesity, currently not causing any pathological problems ("Innocuous obesity"), could progress to Stage 2 obesity, which has association with mechanical and disease related problems.

Stage 2 Obesity : a more advanced state characterized by **heightened adiposity (generalized and abdominal)**, impacting both physical and organ functions, resulting in functional limitations during day-to-day activities, and contributing to co-morbid diseases. The criteria for Stage 2 Obesity include a mandatory **BMI exceeding 23 kg/m^2** , increased abdominal adiposity **excess waist circumference** or **waist-to-height ratio and any** one of the following impacting physical and organ functions: Mechanical conditions (e.g. knee arthritis due to excess weight) OR Presence of diseases associated with obesity (e.g. type 2 diabetes).

Additionally, the presence of one or more symptoms indicative of limitations in daily activities or one or more obesity-related comorbid conditions/diseases are needed to support the stage 2 obesity[14]

Table 6 . Revised measurement criteria for obesity :

	For men	For women
Waist circumference	>90 cm	>80 cm
Waist to hip ratio	>0.90	>0.85
Waist to height ratio	>0.50	>0.50

Complications and outcomes of obesity [1]:

Various outcomes of obesity are :

- Type 2 diabetes mellitus with macrovascular complications
- Hyperlipoproteinemias or Hyperlipidemia ,
- Coronary artery disease
- Myocardial infarction (obese patients are 250% more likely to develop coronary artery disease than are non-obese patients)
- Cerebrovascular disease
- Thromboembolic disease

- Left ventricular hypertrophy and congestive heart failure
- Sleep apnea.
- Restrictive lung disease
- Pickwickian syndrome
- Metabolic syndrome
- Cholelithiasis and cholecystitis
- Infertility
- Endometrial carcinoma , Colon cancer, Postmenopausal breast cancer.
- Gout
- Hernias and esophageal reflux
- Psychosocial disabilities
- Increased risk of obstetric and surgical morbidity
- Osteoarthritis

Metabolic syndrome is characterised by having three of any of the following five criteria:

- Hyperinsulinaemia (elevated fasting plasma glucose)
- **Decreased HDL** (as opposed to LDL levels, which are not required in making the diagnosis)
- Central obesity
- Hypertriglyceridaemia
- Hypertension (>130/85)

Metabolic syndrome confers a threefold increase in the risk of cardioembolic events.

Treatment options in obesity

Prevention and treatment of obesity requires a multidimensional approach.

- Physical activity
- Stress management
- Lifestyle changes
- Dietary modifications

The realistic goals of weight management should be aimed at[15]

- Preventing further weight gain
- Reducing bodyweight
  Short-term goal: 5–10%, or 0.5 to 1 kg per week of weight loss.
  Interim goal: Maintenance of reduced weight
  Long-term goal: Additional weight loss, if desired.
- Maintenance: The achieved lower bodyweight over long term

Available Evidence/Guidelines[13]:

1. *Some observational data indicate that individuals performing at least 45–60 min of activity on most days gain less weight than less active men.*
2. *At least the equivalent of 150 minutes/week of moderate-intensity aerobic physical activity for substantial health benefits and 300 minutes/ week of moderate-intensity physical activity for more extensive health benefits.*
3. *To prevent weight regain after weight loss, 60-90 min of daily moderate-intensity physical activity is recommended.*

Recommendations for Patients with Obesity:
Gradual initiation and increase in duration of physical activity among sedentary individuals is recommended. Aerobic exercise is of the greatest value for individuals who are obese. The ultimate minimum goal should be to achieve 60 min of continuous moderate-intensity aerobic exercise 7 times per week. Once an individual loses weight, a maintenance phase with the same duration, intensity, and frequency of exercise should be continued for an indefinite period.

Table 7. - Guidelines for Physical activity for Overweight and Obesity[13]

Intensity	Duration	Frequency
Moderate-intensity aerobic exercise	60 min	Daily
Vigorous-intensity exercise	60 min	3 or more days per week

The average weight loss expected with diet, physical activity and behavioral therapy is around 5%–10%[15]
A structured program is essential for successful long-term weight loss. Most successful weight loss programs are multidisciplinary, concentrating on hypocaloric diets, behavior modification to change eating behaviors, aerobic and strengthening exercise, and social support. Also, concomitant depressive disorders, a frequent comorbidity, require attention for successful weight loss and maintenance.
The weight loss program must contain three essential components:
(1) a nutritionally balanced diet,
(2) aerobic and strengthening exercise, and
(3) a reduction in the percentage of calories derived from fat.
Current recommendations suggest that the energy intake should be approximately 500 calories less than energy output in a weight loss program.
Low-carbohydrate diets, although effective in rapid short term weight loss, have not been proved to be more effective long term than a balanced calorie-restricted diet. In
addition, the long-term effects of carbohydrate-restricted diets are not known.
The importance in strength training is receiving new attention. Research has shown that larger muscle mass burns fat and calories more efficiently. Many weight loss programs now emphasize a balance between aerobic activity and muscle strength training. There is good evidence that other benefits (e.g., improved proprioception and balance in the elderly) may derive from strength training.

Medications
Pharmacologic therapy should be reserved for adults with a BMI ≥30 kg/m^2 or a BMI ≥27 and at least one weight related comorbidity, such as hypertension, dyslipidemia,
cardiovascular disease, obstructive sleep apnoea, or type 2 diabetes, who have not achieved ≥5% weight loss with lifestyle modification. All weight-loss drugs have been
associated with weight regain when the drug is stopped.[7][16][17].
FDA approved drugs for obesity : Orlistat, Liraglutide, Lorcaserin , Phentermine-Topiramate , Bupropion - Naltrexone , Semaglutide , Setmelanotide , Tirzepatide

Bariatric surgical intervention can effectively treat obesity. Three procedures are available and include laparoscopic sleeve gastrectomy, Roux-en-Y gastric bypass, and laparoscopic adjustable banding. Surgery is limited to those with a BMI of 40 or greater or a BMI of 35 if significant comorbidities exist. Weight loss is estimated at 60% to 70% of excess body weight after 1 year and 50% after 10 years. The procedures are associated with 60% to 80% remission of T2DM and beneficial health effects in many other chronic illnesses. Family physicians do need to follow these patients over time for maintenance of continued nutritional balance. Overall these procedures have a mortality risk of less than 0.5% (mostly from pulmonary emboli, respiratory failure, and anastomotic failures). Short-term complications include stomal stenosis, infection, and constipation. Long-term complications can include dumping syndrome, cholelithiasis, and nutritional deficiencies[1].

Sleep apnea:

Sleep related breathing disorders (SBDs) are associated with impaired ventilation during sleep and disruption of sleep.

Sleep related breathing disorders is a general term which includes both *obstructive sleep apnoea (OSA)* and *central sleep apnoea (CSA).*

Obstructive sleep apnoea is characterised by periodic episodes of complete or incomplete upper airway obstruction[18].

CSA usually results from reduction in overall respiratory drive[18].

Classification of Sleep-related breathing disorders[19][20] :

A. Obstructive sleep apnea/hypopnea syndrome (OSAHS): more common
B. Central sleep apnea (CSA). : including Cheyne-stokes breathing.
C. *Sleep related hypoventilation disorders*

1. Obesity-hypoventilation,
2. Congenital and Idiopathic central alveolar hypoventilation,
3. Hypoventilation due to medical disorders and respiratory suppressants.

These categories and clinical disorders can overlap, but each has distinctive features.

Apnoea means *cessation of airflow for at least 10 seconds.*

Apnoea can be *obstructive* (respiratory effort without airflow), *central* (absence of both airflow and respiratory effort) or mixed.

Hypopnoea is a reduction in airflow of 30% from a baseline for longer than 10 seconds and is associated with an oxygen desaturation ≥ 4%. The apnoea-hypopnoea index (AHI), is the total number of apnoeas and hypopnoeas per hour of sleep. An apnoea-hyponoea index of more than 5 is indicative of OSA[18].

Patients with brainstem dysfunction may have central apnoeas, whereas patients with obesity , chest wall , neuromuscular , and central nervous system disorders with hypoventilation will often manifest sleep-related hypoventilation and hypoxemia in association with central or obstructive apnoeas[21].OSA is a form of *sleep disordered breathing* characterized by recurrent episodes of partial or complete upper airway closure during sleep, resulting in frequent arousals and sleep fragmentation, apnoeas (complete obstruction) and hypopnoeas (partial obstruction), intermittent hypoxaemia and autonomic fluctuation.These periodical episodes of respiratory disruption cause both acute and chronic pathophysiological stress, en route to onset of cardiovascular disease (CVD) including systemic hypertension, congestive heart failure (HF), arrhythmias, atherosclerosis, stroke and pulmonary hypertension (PH)[22][23][24][25][26]

Central Sleep Apnoea Central sleep apnoea is prevalent in patients who use opiates (Chapter 31), during which cluster breathing with central apnoeas is characteristic, and in patients with congenital and acquired central nervous system and/or cervical spine disorders, in which Biot-type breathing is characteristic .

Cheyne-Stokes breathing, the most common form of central sleep apnoea, is manifested as a crescendo-decrescendo breathing pattern with central apnoea or hypopnoea as the nadir of the breathing effort cycle ; central sleep apnoea with Cheyne-Stokes breathing is prevalent in patients with heart failure, in which it is an independent predictor of increased mortality. Patients with heart failure and Cheyne-Stokes breathing tend to have lower awake arterial carbon dioxide tensions ($PaCo_2$) than other patients who have heart failure. The increased mortality in this setting has been correlated with the severity of the associated nocturnal hypoxemic burden[21].

CSA is less common and may occur in combination with obstructive sleep apnoea, as a primary condition, or secondary to a medical condition (such as heart failure) or medication. Patients with CSA often report frequent awakenings and daytime fatigue and are at increased risk for heart failure and atrial fibrillation[19]

Sleep-Related Hypoventilation

Patients with sleep-related hypoventilation may note daytime sleepiness, fatigue,
morning headache, or unrefreshing sleep. Sleep-related hypoventilation is common in individuals with central obesity (often in association with obesity hypoventilation syndrome), neuromuscular and chest wall disease, central hypoventilation disorders (with disordered respiratory control), COPD, and narcotic use[21].

Epidemiology of OSA

The exact prevalence of OSA is unknown.

Western data estimates the prevalence of *OSA* between **0.3% to 4 %**, affecting **2%** to **4 %** of **males** and **1%** to **2%** of **females**, with a large number of individuals still undiagnosed[18][27].

Much higher prevalence has been estimated in certain subgroups (i.e., 20% to 90% of persons referred for sleep studies)[28][29].

Community based epidemiological studies from India have shown that the prevalence of OSAS is 2.4% to 5 % in males and 1 to 2% in females. There is no considerable variation in the prevalence of OSAS compared to rest of the world where it is 4% in males and 2% in females[27][18]

Approximately 34% and 17% of middle aged men and women, respectively, meet the diagnostic criteria for OSA[30].

The prevalence of OSA is two to three fold higher among men than among women. Factors that predispose men to OSA include android pattern of obesity (resulting in upper-airway and abdominal fat deposition) and relatively greater pharyngeal length, which increases collapsibility. Premenopausal women are relatively protected from OSA by the influence of sex hormones on ventilatory drive. The decline in sex difference in older age reflects an increased OSA prevalence in women after menopause[31]

Higher level of progesterone leads to lower prevalence of OSA in premenopausal women compared with older women, as progesterone stimulates ventilation in upper tract muscles[32]

OSA is particularly uncommon in nonobese, premenopausal women; however, the rates of OSA in postmenopausal women not taking hormone therapy approach the rates of OSA in men of a similar age and body mass index[33][34][35].

Race:

Individuals of East Asian ancestry appear to be at increased risk of OSA at relatively low levels of body mass index, reflecting the greater influence of craniofacial risk factors. In the United States, African Americans, especially children and young adults, are at higher risk for OSA than their white counterparts[36].

Age :

An aging population contributes to increasing risk of OSA.The prevalence of OSA increases with age, especially in persons older than 60 years. OSA occurs most often in overweight, middle-aged men.OSA prevalence varies with age, from 5 to 15% among middle-aged adults to >20% among elderly individuals, although in a majority of affected adults, the disorder is undiagnosed. There is a peak due to lymphoid hypertrophy among children between the ages of 3 and 8 years; *with airway growth and lymphoid tissue regression during later childhood, prevalence declines*. Then, as obesity prevalence increases in adolescence and adulthood, OSA prevalence again increases[33][36][37][38][39][40].

Obesity :

OSA occurs most often in overweight, middle-aged men. Obesity is increasing in developed countries and so the incidence of OSA is also predicted to rise.

Factors that predispose men to OSA include android pattern of obesity (resulting in upper-airway and abdominal fat deposition)

Then, as obesity prevalence increases in adolescence and adulthood, OSA prevalence again increases.

OSA is also more prevalent among persons who are obese. Both an aging population and a growing rate of obesity contribute to the increasing rate of OSA.[33][36][37][38][39][40]

Medical conditions:

The prevalence of OSA is especially high among patients with certain medical conditions, including diabetes mellitus, hypertension, and atrial fibrillation[36].

OSA prevalence is as high as 40% to 80% in patients with hypertension, heart failure, coronary artery disease, pulmonary hypertension, atrial fibrillation, and stroke. Despite its high prevalence in patients with heart disease and the vulnerability of cardiac patients to OSA-related stressors and adverse cardiovascular outcomes, OSA is often underrecognized and undertreated in cardiovascular practice[30].

Prevalence of OSA increases with

- *Aging*
- *Menopause*
- *Obesity*
- *Endocrine conditions : Acromegaly, Hypothyroidism,diabetes mellitus*
- *Hypertension*
- *Atrial fibrillation*
- *Children with Enlarged tonsils* obstructive sleep apnoea
- *Children with Trisomy 21*

Etiology and risk factors of Sleep apnoea

Table 8. Factors that predispose to Sleep apnoea.

Major risk factors[30]	Additional risk factors[18][27][31][36][41][42][43][44][45] :
Obesity or BMI ≥ 25 kg/m^2 Male sex Age > 35 years	Anatomical abnormalities or Craniofacial factors: Mandibular retrognathia Micrognathia Maxillary retropositioning Inferiorly positioned hyoid bone or Caudal displacement of hyoid bone, Intra-nasal obstruction Macroglossia Enlarged or low placed soft palate Enlarged lymphoid tissue around the upper airways. A positive family history of OSA Sedentary lifestyle Genetic syndromes that reduce upper airway patency (e.g., Pierre-Robinson syndrome (mid face hypoplasia), Down syndrome, Treacher-Collins syndrome),Pfeiffer syndromes (craniofacial synostosis), Crouzon syndromes and Apert syndromes Adenotonsillar hypertrophy (especially in children) *Nasal obstruction* – Deviated nasal septum, rhinitis, polyps, adenoids. Menopause (in women) Endocrine syndromes (e.g., acromegaly, hypothyroidism) PCOD Alcohol and sedatives Higher Epworth sleepiness scale (ESS); mean apnoea duration; oxygen desaturation index (ODI); and nocturnal oxygen desaturation (NOD). Benzodiazepines Testosterone therapy Muscle relaxants

Pathophysiology of OSA

The pathophysiological mechanisms underlying OSAS are complex and multifactorial, and furthermore, the underlying causes of OSAS vary substantially between afflicted individuals[46]. OSA results from the interplay between unfavorable upper airway anatomy and sleep-related alterations in airway function[47].There are *anatomical factors* and *functional (non-anatomical) factors* involved in the mechanism of upper airway collapse. For a better explanation of mechanisms, a model of 'PALM' pathogenesis was proposed[46], which can be summarized as *pharyngeal critical closing pressure (Pcrit,*

P), decreased respiratory arousal threshold (arousal threshold, A), increased loop gain (loop gain, L), and *upper airway dilator muscle activity (muscle responsiveness, M).*

Normal sleep-related physiological phenomena influence respiratory mechanics. These include, but are not limited to, reduced pharyngeal diameter , decreased muscle activity, heightened upper airway resistance, impaired respiratory load compensation, and a slight (5 mmHg) increase in arterial carbon dioxide. Other physiologic endophenotypic factors include variations in arousal threshold, loop gain (a measure of ventilatory instability), and critical closing pressure of the airway.

Anatomical and Morphological abnormalities are the most common factors contributing to upper airway obstruction.

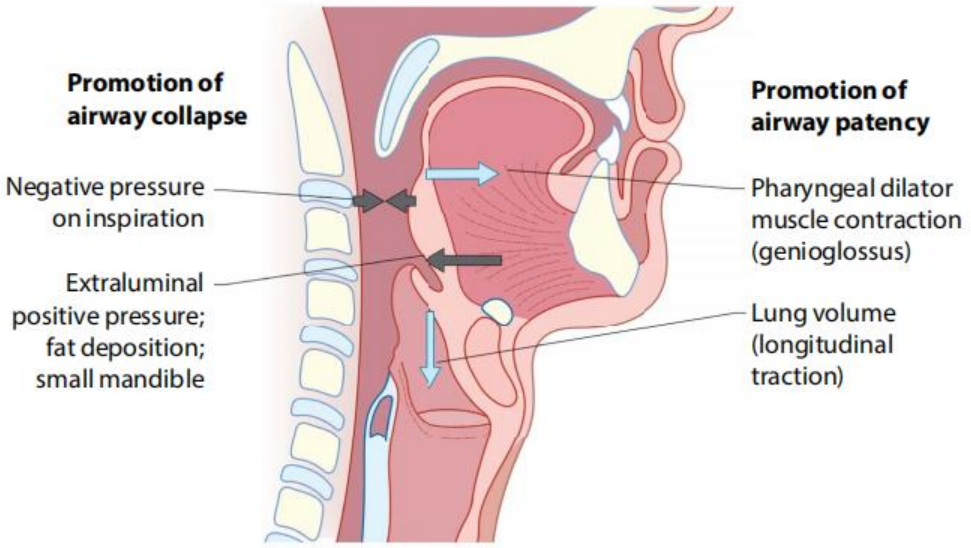


FIG.3 Airway anatomy affects both dilation and collapse of the airway. The sum of these factors affects the critical pressure.

Upper airway collapse

Upper airway anatomical abnormalities are a key factor in the pathogenesis of OSAS. Almost all patients have upper airway anatomical abnormalities to varying degrees, that is, upper airway stenosis and collapse caused by abnormal bone structure and soft-tissue hyperplasia.

Upper airway anatomical abnormalities include[48]

1.relative stenosis due to fat deposition in the upper airway caused by obesity and

2.absolute stenosis due to morphological abnormalities in the maxillofacial structure.

Nocturnal rostral fluid shift: Patients with leg edema due to cardiac and renal failure or venous insufficiency may experience a shift in leg fluid volume from the leg to the neck during the night (nocturnal rostral fluid shift), which may lead to upper airway collapse[49].

The degree of airway collapse can be measured by calculating the Pcrit.

*Passive airway collapsibility. I*ndividual airway collapsibility is also a key factor in upper airway obstruction[50][51][52].

The importance of abnormal pharyngeal susceptibility to collapse in the pathogenesis of obstructive apnoea was demonstrated by studying the Pcrit in patients with OSAS and in control subjects[53].

A highly collapsed upper airway is the leading cause of OSAS pathogenesis, and the passive Pcrit technique is considered the gold standard for measuring the degree of pharyngeal airway collapse[54].
The Pcrit is the critical pressure at which the airway fails to remain open and collapses[51][55]
In normal individuals, Pcrit is negative,implying that the upper respiratory airway tends to remain open. In patients with OSAS, the critical pressure is less negative, which means that the upper respiratory airway is more likely to collapse and become occluded during sleep[56][57].
Pcrit is higher in patients with greater upper airway collapsibility. The critical closing pressure of the airway was higher in patients with OSAS than in those without the disorder[58][59].
Pcrit is a vital part of categorizing subjects with OSAS into various endotype groups, which could provide help for the treatment and response prediction of OSAS patients.

Decreased respiratory arousal threshold

At least one-third of OSAS patients have a decreased respiratory arousal threshold[60].
Arousal plays a dual role in the mechanism of OSAS. On the one hand, arousal from sleep at the end of a respiratory event is an important protective mechanism for restoring pharyngeal patency[61], and patients will resume normal breathing and relieve airway obstruction through neuromuscular and respiratory compensation mechanisms during arousal[62].
Thus, respiratory arousal is considered a potentially lifesaving event that could avert asphyxia during sleep. On the other hand, a decreased respiratory arousal threshold is the cause of recurrent microarousal in OSAS patients which might lead to the interruption of sleep continuity, prevent deeper and more stable sleep, reduce the ability to recruit upper airway dilator muscles, and may contribute to further obstructive respiratory events[61][62][63][64].
Individuals with a more intense arousal tendency to airway stenosis elicit a greater ventilatory response and are, therefore, more likely to experience instability in ventilatory control[65].
Theoretically, hyperventilation during arousal would also reduce pharyngeal muscle activity[61][62],
and in many cases, arousal might promote the cyclical breathing pattern of OSAS[64].The respiratory arousal threshold is measured by the lowest pressure in the esophagus produced during a respiratory event or perturbation of a breath taken before awakening. Evidence suggests that the magnitude of the intrapleural pressure generated by breathing is a major stimulus for the initiation of arousal from sleep[66][67][68].
Although arousal thresholds vary widely between individuals, patients with OSAS tend to have diminished arousal responses to airway obstruction compared with controls, which may exacerbate upper airway dilator hypotonia, leading to an inability to recruit dilator muscles to open the airway before arousal occurs[65][69].

Increased loop gain

Loop gain refers to the overall sensitivity of the respiratory control system.
Loop gain is a key pathophysiological feature that contributes to OSAS. In ventilatory control, loop gain is a measure of respiratory instability, which refers to unstable ventilatory chemoreflex control[70][71][72].
High loop gain indicates exaggerated response to airway obstruction ; it is often associated with increased chemoreflex sensitivity, leading to unstable breathing patterns during sleep. Eckert's study has shown that approximately 36% of OSAS patients have high loop gain[46].
Components of loop gain: The loop gain consists of the control gain, plant gain, and cycle time[73].

Control gain refers to the response degree of the brain's respiratory centre to changes in PaCO2, *Plant gain refers to hoe the respiratory system* responds to the reduction in CO2 by ventilation, and together they determine the overall loop gain. Cycle time refers to the feedback time from the change in PaCO2 and PaO2 in blood being received by the sensor to the ventilatory response of the body[74].

High control gain represents a *strong* chemoreceptor response to a small change in PaCO2, and high plant gain indicates that a *mild* ventilatory response can cause a significant change in PaCO2[75].

For example, upper airway muscles are innervated by neuronal fibers from the respiratory center, high ventilation caused by high loop gain can expel more CO2, and low serum CO2 levels reduce the central ventilatory drive in the dilator muscles of the upper airway, thereby reducing pharyngeal muscle activity[76].

Thus, the higher the loop gain is, the less stable the ventilatory chemoreflex control. Unstable ventilatory chemoreflex control could promote airway collapse in OSAS due to hypocapnic (produced by hyperventilation after obstructive apnoea) hypotonia of the upper airways. Obstructive apnoea is followed by hyperventilation, producing hypocapnia and respiratory depression, which contribute to the instability of ventilatory chemoreflex control and high loop gain[69][70][77][78]and increased CO2 from hypoventilation leads to the development of rapid and large negative inspiratory pressure, also leading to a collapse of the upper airway.

Decreased upper airway dilator muscle activity during sleep and impaired sympathetic neural activity

When the person is awake, patency of pharynx and upper airway is maintained by the neuronal activation of dilator muscles of the upper airway (the genioglossus major upper airway dilator and palatoglossus)which contract actively during inspiration to preserve airway patency and prevent airway narrowing and collapse. Sleep onset is accompanied by a decline in neuromuscular output and thus during sleep, the upper airway dilator muscles become hypotonic impairing the ability of these muscles to maintain pharyngeal patency. During normal sleep, activity of the pharyngeal and respiratory muscles is reduced, especially during rapid eye movement (REM) sleep when the diaphragm is virtually the only active muscle [36][40][43][77]

During inspiration, intraluminal pharyngeal pressure becomes increasingly negative, creating a "suctioning" force. Apnoeas occur when the airway at the back of the throat is sucked closed when breathing in during sleep [40].

Partial narrowing or incomplete obstruction of airway results turbulent airflow which causes *snoring*.(44% of men and 28% of women aged 30–60 snore)[43].

Critical narrowing of airway or near collapse of airway causes *hypopnoeas & c*omplete occlusion of airway causes *apnoea[40]*.

The airway may collapse at different sites, such as the soft palate (most common site of occlusion of pharynx during sleep in sleep apnoea), tongue base, lateral pharyngeal walls, and/or epiglottis[19].

In addition, lung volumes influence the caudal traction on the pharynx and consequently the stiffness of the pharyngeal wall. Accordingly, low lung volume in the recumbent position, which is particularly pronounced in the obese, contributes to collapse (less caudal traction on the pharynx and thus less stiffness of pharyngeal wall)[19].

OSA may be most severe during rapid eye movement (REM) sleep, when neuromuscular output to the skeletal muscles is particularly low and diaphragm is virtually the only active muscle, and in the supine

position due to gravitational forces.

Recurrent episodes of complete or partial upper airway obstruction, result in hypoxe-mia and hypercapnia, which in turn stimulate the peripheral chemoreceptors, triggering acute autonomic and cardiorespiratory responses. The stimulation of the CB chemoreceptorsincreases respiratory muscle activity, producing inspiratory efforts, negative intrathoracic pressure, micro-arousals, and restoration of airflow[79][80].

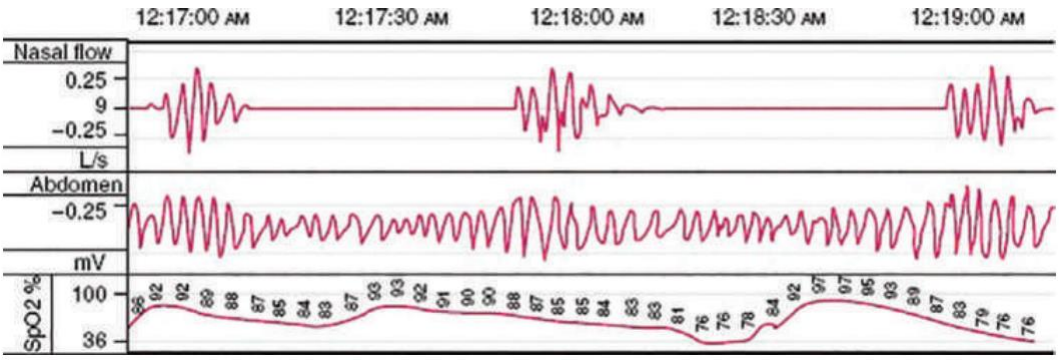


Fig. 4. Polysomnographic tracing of a patient with obstructive sleep apnoea during 2 minutes of non–rapid eye movement sleep. Displayed are airflow in the upper airway ("nasal flow"), recorded with a nasal pressure transducer; respiratory effort ("abdomen"), recorded by inductance plethysmography; and oxygen saturation of hemoglobin (SpO2), recorded with pulse oximetry[21].

Central sleep apnoea in patients with heart failure is characteristically of the Cheyne-Stokes breathing type, mediated by interacting physiologic variables, including lung volume changes, circulatory timing, and a higher than normal gradient between inspired and arterial carbon dioxide tensions (PCo_2). The ventilatory response to a change in blood gases is augmented. The net effect is oscillation of ventilation between central apnoea and hyperpnea, as sleep and awake states oscillate.

Central apneas in other circumstances may be linked to dysfunctional neural chemosensitivity responses resulting in subsequent apnoea, as is seen in the idiopathic, medication-related, and central alveolar hypoventilation syndromes.

Sleep-related hypoventilation without central or obstructive apnoea is pathogenetically linked to neural inhibition of postural respiratory muscles and perturbed respiratory mechanics[21].

Clinical presentation of OSA

A history of daytime hypersomnolence, loud snoring, restless sleep, or morning headaches is suggestive of obstructive sleep apnoea[81].

The cardinal manifestations of obstructive sleep apnoea include loud, chronic snoring; excessive daytime somnolence; and witnessed sleep-related choking or gasping[21].

Symptoms (%) of obstructive sleep apnoea[40] :

Loud snoring *95 %*

Daytime sleepiness *90 %*

Unrefreshed sleep *40 %*

Restless sleep *40 %*

Morning headache *30%*
Nocturnal choking *30 %*
Reduced libido *20 %*
Morning 'drunkenness' *5%*
Ankle swelling *5%*
Insomnia, which is common in the general population, may coexist with OSA.
Although difficulty falling sleep is rarely caused by OSA, awakening at apnoea termination may cause difficulty maintaining sleep, a symptom more likely to be reported by women than by men, and often responds to treatment of OSA[19].

Screening & Evaluation of sleep apnoea:
OSA is widely underdiagnosed; 86% to 95% of individuals found in population surveys with clinically significant OSA report no prior OSA diagnosis.
History
This helps to identify the signs and symptoms of SDB as well as to ascertain the differential diagnosis and to request for appropriate tests for diagnosis. When possible, a sleep history should be obtained with assistance from a bed partner or household member. The patient's routine sleep-wake schedule can also be ascertained.
Sleep schedule
The patient's sleep patterns, onset of sleep, awakening including weekdays and weekends is elicited. This data is compared with that of polysomnography.
Sleep problems
There are number of sleep disorders with overlapping symptoms. A thorough sleep history is essential and questions detailing the signs and symptoms of sleep disorders must be asked.
Family and medical history
Risk factors for SRBD include male gender, obesity, middle age or older individuals, crowded airways and anatomic abnormalities like retrognathia or micrognathia, large tongue and low set palate.
Medications
Details of medications being used by the patient, especially stimulants, wake promoting substances, sedatives-hypnotics and other sleep promoting substances must be elicited.
Questionnaires *[18]*[85]
Sleep questionnaire : Sleep Disorder's Questionnaire and the Pittsburgh Sleep Questionnaire.
Sleepiness questionnaire : Epworth Sleepiness Scale (widely used), the Karolinsky Questionnaire, Stanford Sleepiness Scale, the Profile of Mood States, the Pictorial Sleepiness Questionnaire, the Berlin Questionnaire, and a number of other visual analogue scales.
Depression questionnaire : Zung Depression Inventory and the Beck Depression Inventory.
Commonly used screening questionnaires include the **Berlin Questionnaire**, the **STOP-BANG** (Snoring, Tiredness, Observed Apnea, Blood Pressure, Body Mass Index, Age, Neck Circumference, and Gender), and the **STOP**, which include symptoms of snoring, sleepiness, and other features associated with increased OSA risk such as obesity, increased neck girth, and hypertension. These questionnaires have reported sensitivity between 77% and 89% but lower specificity (32%–34%)[86].
The Epworth Sleepiness Scale, which focuses on the single problem of propensity for dozing, has higher specificity (67%) but low sensitivity (42%)[87] and is therefore a poor screening tool. Screening

instruments may underperform in certain groups, including women, who more commonly report fatigue and insomnia symptoms than sleepiness, and in patients with underlying CVD, HF, or AF and those after stroke.

EPWORTH SLEEPINESS SCALE[43][40]

How likely are you to dose off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0= would never doze

1. slight chance of dosing
2. moderate chance of dozing
3. high chance of dosing

Situation

- Sitting and reading
- Watching TV
- Sitting and inactive in a public place (theatre or meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after lunch (without alcohol)
- In a car, while stopped for a few minutes in the traffic.

Normal <9

Excessive daytime somnolence >9 - causes include obstructive sleep apnea.Other conditions causing excessive daytime somnolence include narcolepsy, restless leg syndrome and periodic limb movement disorder.

The STOP BANG tool[43][40] is also a useful screening tool and should flag appropriate patients to refer for further investigation. It may help discriminate OSA from simple snoring.

Questions

Snoring: Do you snore?

Tiredness: Do you often feel tired, fatigues or sleepy?

Observed apneas

Pressure : Do you have high BP or are you on treatment for it?

BMI>35

Age >50 years

Neck circumference male ≥ 43 cm , Female ≥41 cm

Gender : Male

Low risk for OSA if answer is 'yes' to 0-2 questions

Intermediate risk for OSA if answer is 'yes' to 3-4 questions

High risk for OSA if answer is 'yes' to 5-8 questions

Screening is not indicated in asymptomatic patients, but a high degree of clinical suspicion in symptomatic patients should prompt the physician to obtain polysomnography [21].

Examination findings:

Obesity

Increased neck circumference

Craniofacial abnormalities

Mallampati score ≥ 3

Laboratory Assessment :

Since symptoms and signs do not accurately predict the severity of sleep-related breathing disturbances, specific diagnosis and categorization of OSA severity requires objective measurement of breathing during sleep. The current gold standard technique of diagnosing SRBD is overnight polysomnography (PSG).

Sleep is characterised by three states: wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.

Non-rapid eye movement sleep consists of 1, 2, 3, and 4 while REM sleep consists of a single stage that is divided into phasic REM and tonic REM sleep. These sleep stages are defined by recordings taken by electroencephalographic (EEG) activity recorded from central and occipital derivations, electrooculographic (EOG) activity from left and right eye and from submental electromyographic (EMG) recordings. Using measurement of electroencephalography (EEG), electrocardiographic (ECG), and electromyographic (EMG) activities, nasal airflow and thoracoabdominal movement, PSG would allow identification of SDB subtype and severity. Sleep stages are recorded in 30 second epochs. The total length of recording is called the total recording time (TRT). The addition of all the epochs scored in one of the five sleep stages, after sleep onset, is called the total sleep time[18].

In addition, apnea-hypopnea index (AHI; the number of apneic and hypopneic events per hour of sleep) is the most widely employed parameter for OSA quantification or severity.

A*pnoea–hypopnea index (AHI)*[40][82]:

- AHI <5: normal
- AHI 5–15: mild OSA
- AHI 15–30: moderate OSA
- AHI >30: severe OSA.

Nevertheless, AHI is only a modest predictor for the consequences of OSA, highlighting the requirement for more sensitive indicators of disease severity and metrics of OSA complications [83].

A negative in-laboratory PSG usually rules out OSA. However, false-negative studies can result from night-to-night variation in OSA severity, particularly if there was insufficient REM sleep or less supine sleep during testing than is typical for the patient[19].

HSAT uses a portable detecting device and is becoming available as an alternative OSA testing strategy. Compared with PSG, HSAT is cost-effective and less resource-intensive despite limited sensitivity and possible outcomes of false-negative results[84].If there is a high prior probability of OSA, a negative home study should be followed by PSG[19].

INDICATIONS FOR POLYSOMNOGRAPHY[21]

POLYSOMNOGRAPHY IS ROUTINELY INDICATED FOR:

- Diagnosis of sleep-related breathing disorders (SRBDs), including suspected obstructive sleep apnoea (OSA) in patients with heart, brain, neuromuscular, or lung disease

- Patients with sleep-related symptoms and heart, brain (stroke), neuromuscular, lung, or other major organ disease
- Positive airway pressure (PAP) titration in patients with sleep-related breathing disorders
- A preoperative clinical evaluation to evaluate for the presence of OSA before upper airway surgery or oral appliance therapy for OSA
- Patients suspected of nocturnal movement disorders
- Patients suspected of narcolepsy or unexplained excessive daytime sleepiness may require polysomnography and multiple sleep latency test on the ensuing day

Follow-up Polysomnography:

- After titration of oral appliance treatment or final fitting in patients with OSA
- Following surgical treatment of patients with moderate to severe OSA
- After surgical or dental treatment of patients with SRBDs whose symptoms return
- Substantial weight gain or loss in patients on PAP for SRBD
- Insufficient clinical response to PAP therapy
- Evaluation of patients with sleep behaviors that are potentially injurious or suggestive of unusual or atypical parasomnias or in which specific motor patterns are in question

POLYSOMNOGRAPHY IS *NOT* ROUTINELY INDICATED FOR:

- Patients whose symptoms resolve with continuous positive airway pressure (CPAP) treatment
- Diagnosis of chronic lung disease
- Diagnosis of typical, uncomplicated, and noninjurious parasomnias when the diagnosis is clearly delineated
- Patients with a seizure disorder who have no specific complaints consistent with a sleep disorder
- Diagnosis or treatment of restless legs syndrome, except where diagnostic uncertainty exists
- Establishing the diagnosis of depression
- Diagnosis of circadian rhythm sleep disorders

Advancements in PSG recordings have made it possible to collect data other than EEG, EOG, EMG, electrocardiogram (ECG), oxygen saturation and snoring intensity like Oesophageal pH,accessory EMG and nasal pressure. These data are useful in diagnosing conditions like nocturnal acid reflux . After a diagnosis of sleep apnoea is established, a continuous positive airway presure (CPAP) titration is done and the ‘split-sleep ‘ study does away with the conventional two-night sleep study. Infant and pediatric sleep studies are possible with the help of specialised personnel using paediatric specific equipment[18].

Consequences of OSA and associated conditions[27][21][38][39] :

Adult OSA

- More frequent and longer hospitalizations.
- Motor vehicle accidents & Work related injuries.
- Increased morbidity and mortality rates.
- Decreased quality of life scores.
- Psychiatric disorders like depression, bipolar disorder, delirium, anxiety
- Impaired neurocognitive function e.g. potentiation of Alzheimer’s disease
- Impaired quality of life
- Erectile dysfunction

- Cardiovascular: Congestive heart failure , Systemic and pulmonary hypertension , Coronary artery disease , Hypertension , Arrhythmias including atrial fibrillation.
- Insulin resistance and diabetes mellitus
- Cerebrovascular : Stroke, Transient ischemic attack.
- Metabolic syndrome
- Pulmonary: COPD , Asthma , Interstitial lung disease.

Pediatric OSA : poor school performance, enuresis, failure to thrive, learning disability,obesity,Attention deficit hyperactivity disorder.

Treatment of sleep apnoea

LIFESTYLE CHANGES AND WEIGHT REDUCTION

MEDICAL WEIGHT LOSS

POSITIVE AIRWAY PRESSURE : Positive pressure is delivered by a mask or similar device.

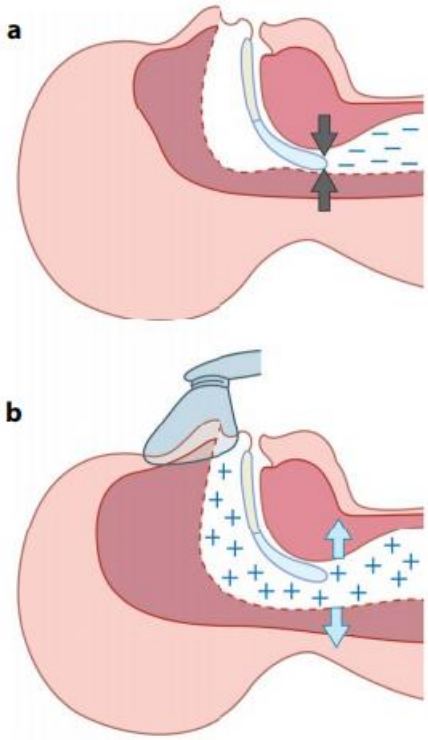


FIG.5 Positive airway pressure. (a) Demonstrates the anatomy of airway collapse. Note negative pressure in airway and extrinsic forces on airway causing collapse. (b) Effect of positive airway pressure opening the airway and restoring patency

Positive pressure may provide a mechanical stent to the upper airway in OSA patients and prevent apnoea in all sleep stages, preferably in supine and
lateral positions. As higher pressure can be uncomfortable for sleep, the minimal pressure that reasonably eliminates most respiratory disturbances like snoring and arousal together with elimination of oxygen desaturation is recommended. The American Academy of Sleep Medicine guidelines for **CPAP** recommend its use in patients who have **apnoea-hypopnoea index (AHI) greater than 20** and for **symptomatic patients who have an AHI or respiratory arousal index greater than 10**[88].

CPAP: provides a constant inspiratory and expiratory pressure to stent the airway. autotitrating PAP machine. This automatically adjusts pressure within a range of pressures set by the physician, as needed throughout the night.

Bilevel positive airway pressure (BiPAP): BiPAP delivers increased inspiratory pressure and a decreased expiratory pressure. The goal of decreased expiratory pressure is to preserve the stenting effect while making expiration easier, and allowing therapy to be better tolerated, especially at high inspiratory pressures. This mode may also provide better ventilation for patients with neuromuscular conditions that cause difficulty

with expiration against a continuous pressure.

Adaptive servo-ventilation (ASV): a non-invasive treatment for SDB that involves monitring breathing patterns and adjusts the air pressure to help stabilise breathing. It is used to treat CSA and co-existing OSA.

ORAL APPLIANCE THERAPY[89] : mandibular advancement to enlarge the airway space and decrease upper airway collapsibility.

UPPER AIRWAY STIMULATION[90]: hypoglossal nerve stimulation of protrusor muscles of the tongue, which leads to increased airflow and decreased pharyngeal collapse.

POSITIONAL THERAPY : sleep apnoea is frequently worse in the supine position. There are positional devices to help with side sleeping.

SURGERY : upper airway surgery, upper airway neurostimulation, and bariatric

surgery.

Interactions between Sleep apnoea and obesity

There is a bidirectional correlation between obesity and OSA.

In severe obesity, the prevalence of sleep apnoea was estimated to vary between 40% and 90%[91].By the way, it should be noted that the prevalence of OSAS varies significantly based on the population being studied and how OSAS is defined (eg, apnoea -hypopnea index threshold, scoring criteria used and testing methodology).

Over 70% of patients with OSA are overweight or obese[92].Obesity, is found in about 70% cases of OSA because parapharyngeal fat deposits tend to narrow the pharynx[93][94].

According to several reports, OSAS and obesity are important risk factors for metabolic disorder and also can act synergistically[95][96].Both obesity and OSAS are associated with similar adverse cardiovascular, metabolic and neurocognitive outcomes. Current evidence suggests that the association of OSAS and obesity promotes weight gain, obesity and, type 2 diabetes in a variety of ways creating multiple complex vicious cycles[97][98].Many reports have concluded that sleep deprivation, OSAS and obesity may be interrelated, and both conditions increase the severity and effects of the other.

Various conditions closely related to obesity, such as oxidative stress, systemic inflammation, visceral fat accumulation, dyslipidemia and insulin resistance (IR) may also occur as OSAS-associated manifestations.

Obstructive sleep apnoea (OSA) has been studied closely as one of the major associated illness in obese patients.Obesity is one of the most important independent risk factor in the pathogenesis of OSA.Obstructive sleep apnoea is a common sleep disorder, effecting 17% of the total population and 40-70% of the obese population[99][100].

There are many potential mechanistic factors, including *increased sympathetic nerve activity, vascular endothelial dysfunction, intermittent hypoxia, inflammation, oxidative stress* and *metabolic dysregulation* in linking obesity with OSAS as well as the upper airway dysfunction and respiratory control instability. Interaction between pharyngeal structural properties and neuromuscular regulation determines pharyngeal airway collapsibility. Obesity impacts on this balance by reducing lung volume and narrowing the pharyngeal airway, with neural compensation for these abnormalities being lost during sleep[101].Obesity increases fat deposit in tongue, upper airway lumen and muscles which decreases luminal diameter of upper respiratory tract and makes it more prone to collapse during sleep , thus leading to susceptibility to OSAS[97].

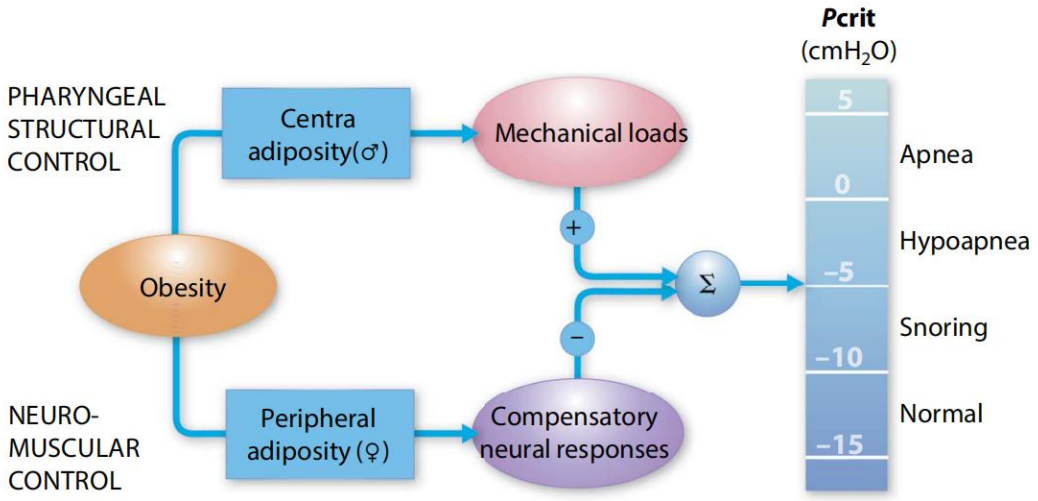


Fig. 6. Illustration relating obesity, body fat distribution, upper airway collapsibility critical pressure (Pcrit), and sleep apnoea pathogenesis. Mechanical loads and neuromuscular responses sum (Σ) to increase (+) and decrease (−) Pcrit, respectively. Mechanical and humoral effects of regional adipose depots can affect these components, which can mediate differences in sleep apnoea susceptibility between men and women[101].

OSA can occur in obesity because the *chest wall movement is restricted*, which results in

1. *mechanical and reflex upper airway narrowing*,
2. *Increased upper airway resistance*,
3. *ventilatory instability*,
4. an *impaired ability to compensate for increased upper airway resistance*.

All these abnormalities may contribute to the *obstruction of the upper airway during sleep*, as well as *NREM sleep-wake cycling* and *respiratory periodicity*.

During REM sleep, *erratic neural drive* and *descending neural inhibition of accessory ventilatory and upper airway muscles* may lead to *severe alveolar hypoventilation and/or obstructive apnoea*[21].

Many cross sectional and longitudinal studies suggest that obesity may impact upper airway neural control. There is an overall decrease in compensatory neuromuscular control mechanisms in obesity (particularly visceral obesity). Defects in upper airway neuromuscular control can increase sleep apnoea susceptibility and severity . These effects may be related to increased circulating levels of inflammatory

cytokines . These cytokines include TNF-α, TNF-α receptor I, IL-6, and IL-1β, which have somnogenic central nervous system activity[102] .

Experimental studies using animal models of a low leptin state such as leptin deficiency have shown that leptin regulates sleep architecture, upper airway patency, ventilatory function, and hypercapnic ventilatory response. However, findings from human studies do not consistently support the data from the animal models[103]

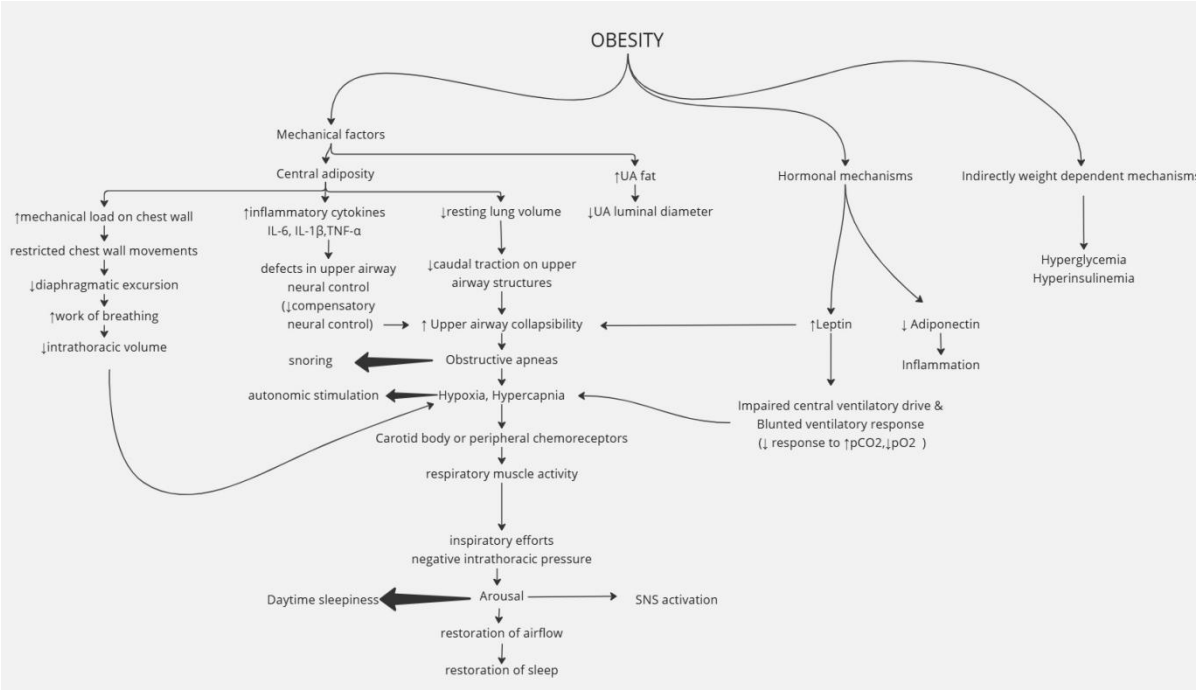
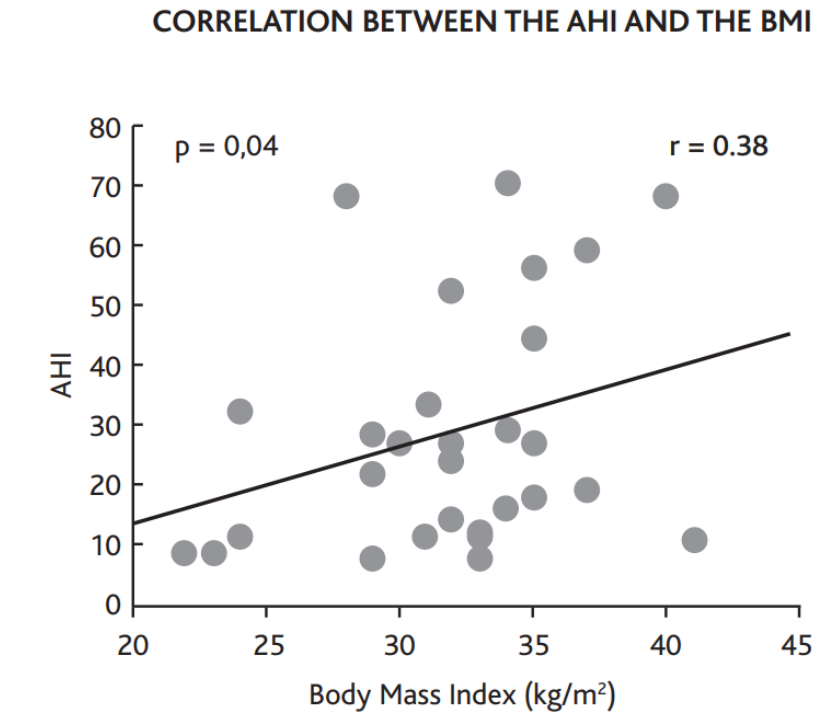


Fig. 7. Pathogenetic pathway of genesis of sleep apnoea from obesity.

Factors that decrease circulating levels of inflammatory cytokines, including continuous positive airway pressure and etanercept , may help improve sleep apnoea by decreasing upper airway collapsibility during sleep . It is therefore possible that humoral effects of obesity and visceral adiposity play a role in the pathogenesis and progression of sleep apnoea by blunting compensatory upper airway neuromuscular responses[102].

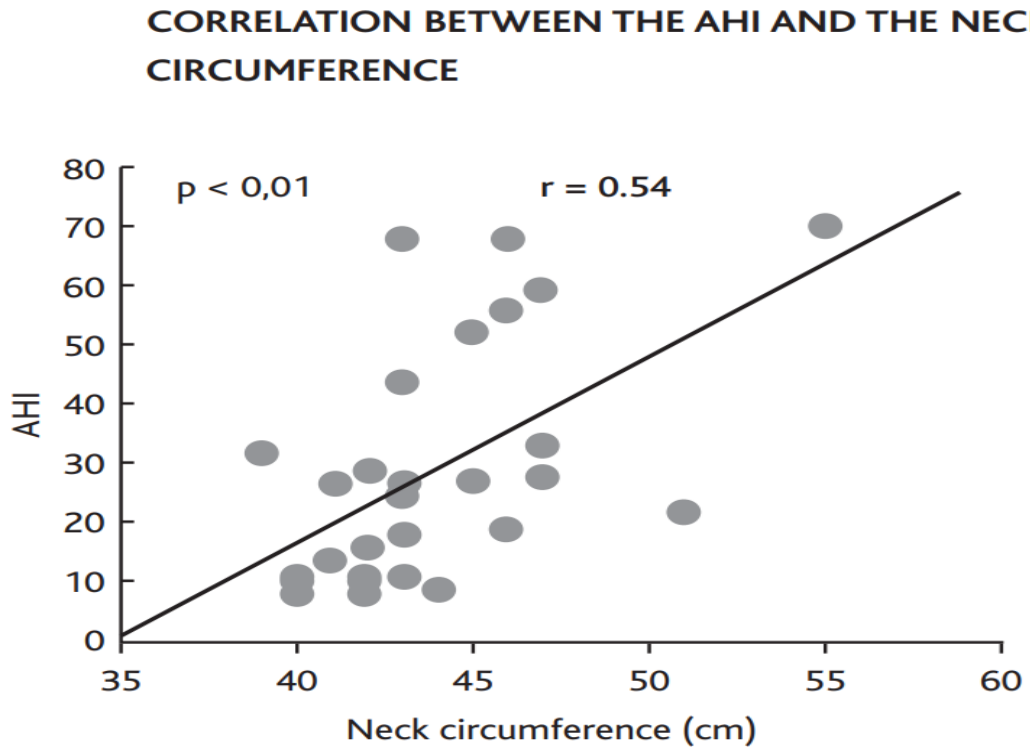
A 10% increase in body weight is linked to a 32% rise in apnoea hypopnea index (AHI), while modest weight control is effective in reducing the incidence of SDB[44].

As a rule of thumb : For every 7-pound drop in weight, expect a 7% drop in AHI[104].



Definition of abbreviations: AHI, apnea-hypopnea index; BMI, body mass index.

Fig.8. Correlation between AHI and BMI [105].



Definition of abbreviation: AHI, apnea-hypopnea index.

Fig.9. Correlation between AHI and neck circumference[105]

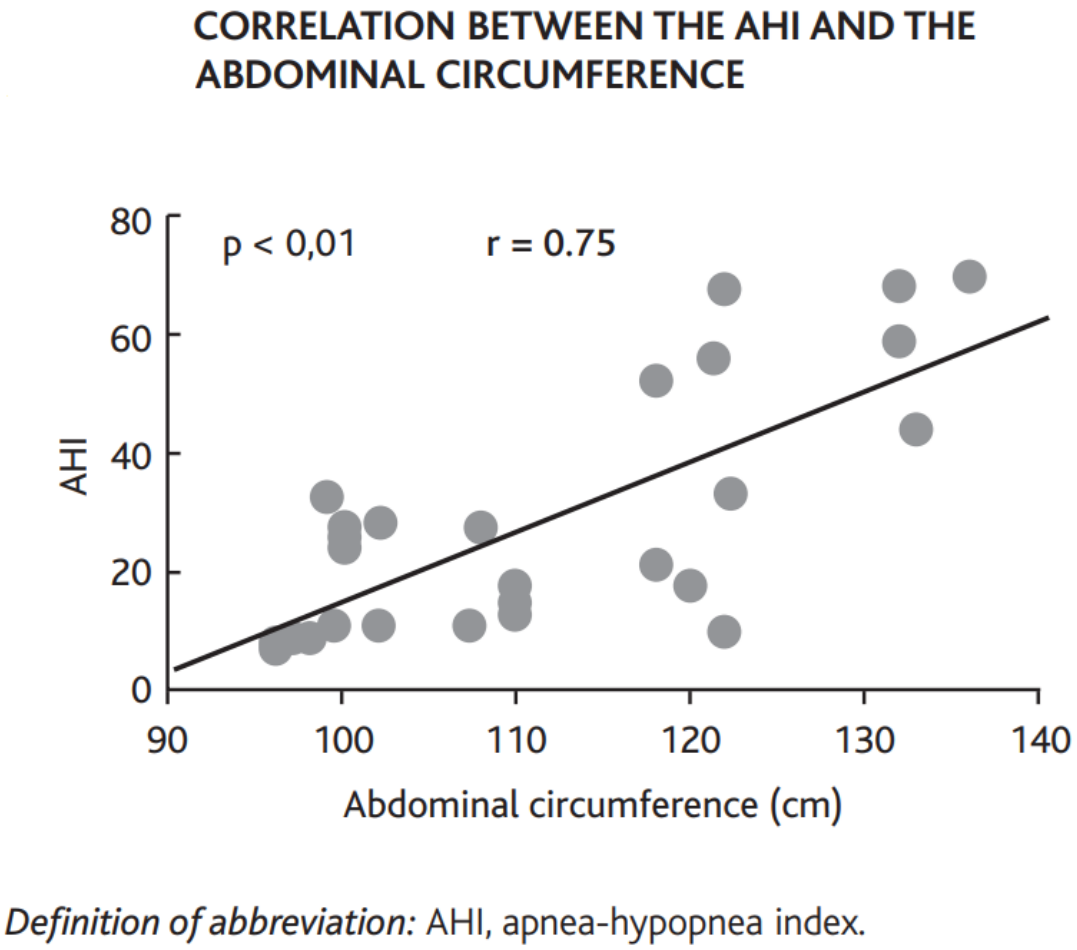


Fig. 10. Correlation between AHI and abdominal circumference[105]

Multiple studies have identified OSA as a critical risk factor for the development of obesity, diabetes, and cardiovascular diseases[106][107] Obesity, is found in about 70% cases of OSA[93].

Pathogenetic mechanism of obesity from sleep apnoea:

Although not all individuals with OSAS are overweight, the vast majority of patients with OSAS are obese[97][108].Although obesity is the main risk factor for the development of OSAS, some authors have suggested that OSAS can cause weight gain and therefore, obesity. There are different causal factors including reduced physical activity, IR and increased ghrelin levels in this process[109].

Sleep is regulated by neuronal and humoral mechanisms that are interdependent.

IL-1 and TNF-α meadiate a large number of neurohumoral factors and appear to be central to sleep activation pathway and pathogenesis of sleep apnoea. Other cytokines that induce sleep include IL-10, IL-6, Interferon, IL-2, IL -4, GM-CSF, FGF. TNF -α is elevated in OSA and may play a role in daytime sleepiness in OSA . TNF - α gene polymorphisms may play a role in polymorphisms may play a role in genesis of hypertension as well as obesity[110].

Both the appetite diminishing hormone Leptin and appetite enhancing hormone Ghrelin are elevated in normal sleep. Recurrent chronic sleep disruption may be associated with *decreased plasma levels of Leptin* and *increased plasma levels of Ghrelin.*Thus chronic sleep apnoea represents a risk factor for weight gain or obesity[111].

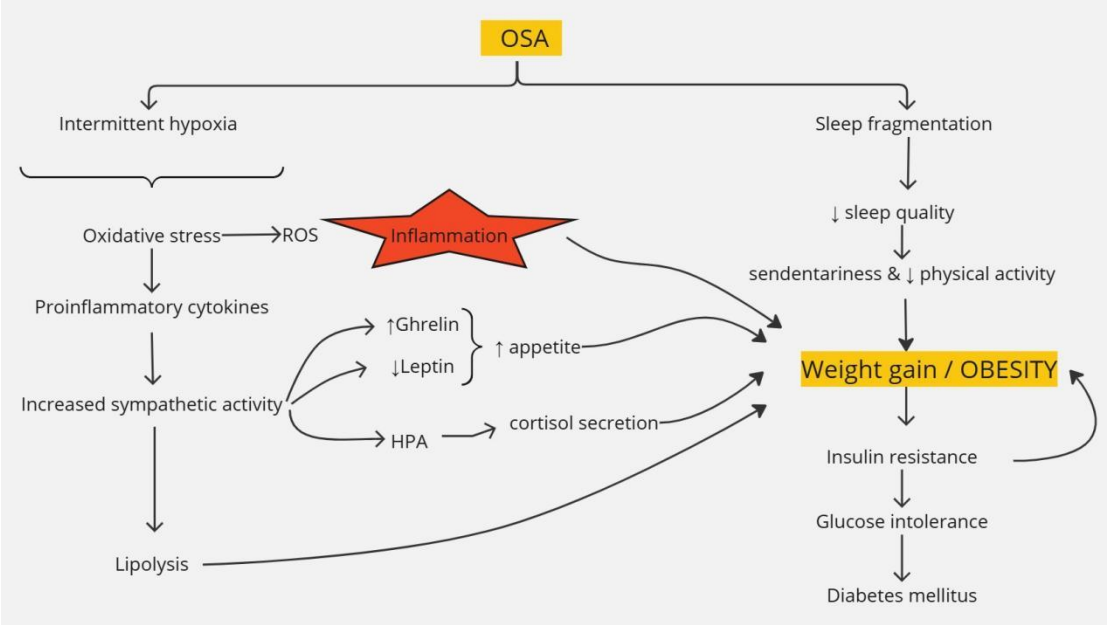


Fig. 11. Pathogenesis of obesity from Sleep apnoea

Carotid bodies (CBs), located bilaterally at the bifurcation of each common carotid artery, are peripheral chemoreceptors that classically sense changes in arterial blood O2, CO2, and pH levels. In response to hypoxia (O2 deprivation), hypercapnia (CO2 retention), and acidosis (pH drop), type I cells, the CB chemosensory unit, release neurotransmitters that act on the nerve terminals of the CB sensitive nerve, the carotid sinus nerve (CSN), to generate action potentials or to inhibit its activity[112]. CSN activity is integrated in the brainstem to induce a set of respiratory reflexes aimed, primarily, at normalizing the altered blood gases via hyperventilation[112] and regulating blood pressure and cardiac performance via sympathetic nervous system activation[113]. Besides its role as an oxygen sensor, in the last few years, the CB has also been proposed to be a metabolic sensor implicated in the control of carbohydrate and lipid metabolism[114][115][116] and in the regulation of peripheral insulin sensitivity and glucose homeostasis.

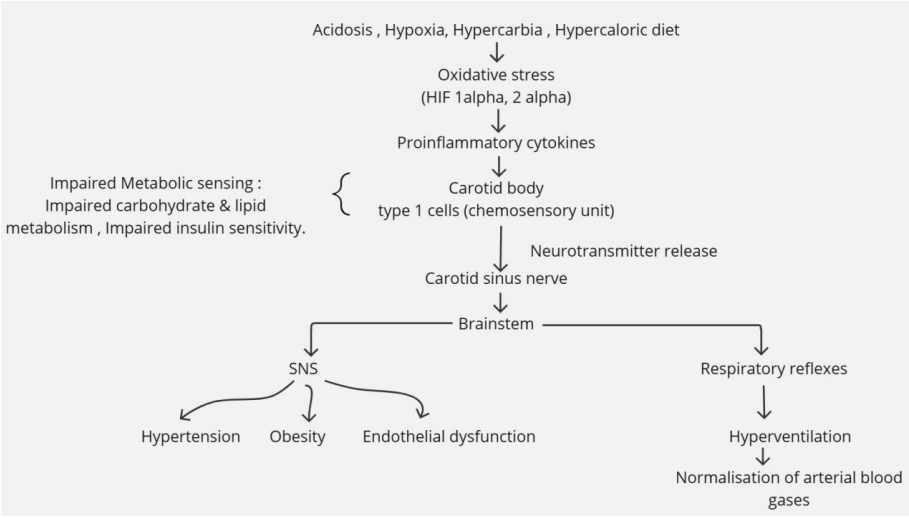


Fig.12. Schematic representation of the carotid body (CB) involvement in the development of obesity, insulin resistance, and glucose intolerance through an increase in sympathetic nervous system activity. Hypercaloric diets and intermittent hypoxia promote an increase in CB activity that

contributes to the augmentation of sympathetic nervous system activity, leading to metabolic dysfunction[117].

Contribution of the carotid body to the pathological effects mediated by sympathetic hyperactivation in human diseases. Diagram show-ing the pivotal role played by the carotid body in the pathological effects mediated by sympathetic hyperactivation in heart failure, obstructive sleepapnea, hypertension, and cardiometabolic diseases. Oxidative stress and inflammation are associated with carotid body chemosensory potentiation,leading to an increase in sympathetic nervous system activity, which promotes autonomic dysfunction, ventilatory instability, baroreflex alterations, hypertension, fibrosis, and insulin resistance. ET-1, endothelin 1; NO, nitric oxide; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus; RVLM,rostral ventrolateral medulla [118].

Interactions between Obesity and Cardiovascular diseases

Elevated body mass index (BMI) is an independent risk factor for the development of type 2 diabetes mellitus, dyslipidemia,chronic kidney disease, ischemic heart disease, stroke, dementia, several malignancies, nonalcoholic fatty liver disease, and obstructive sleep apnoea[119].

Modifiable risk factors, such as being overweight and obese account for more than 70% of the risk for CVD and mortality caused by CVD[120].

Approximately 70–80% of people with CAD have overweight/obesity[121].

Obesity is characterized by a chronic low-grade inflammatory state, and assessing the inflammatory burden becomes pivotal in understanding cardiovascular risk. Elevated levels of inflammatory markers, such as C-reactive protein, may serve as indicators of heightened cardiovascular risk in obese patients [122].

Cardiovascular diseases, such as heart failure and coronary heart diseases, are often among obese people.A standard correlation can be seen between obesity and reasons for CVD. When compared to normal BMI individuals, overweight and obese candidates can experience heart disease earlier by approximately 10 years. The results of study[123] mentioned that the risk of cardiac arrest can be increased by 5% for men and 7% for women, with a BMI increase of 1 kg/m2 . Similarly, 32–49% of obese people and 31–40% of overweight individuals have a high number of heart failures. The span of morbid obesity is firmly connected to the advancement of a cardiovascular breakdown following 20 years of obesity; 70% are at the risk for CVD after 20 years and 90% are at risk for CVD after 30 years[124].

The importance of *obesity* is shown by the Framingham Heart Study that highlighted the pathogenic role of obesity and heart failure onset in 11% of men and 14% of women[123].

It is proven that obese people have a double risk for heart failure when compared with people of a normal BMI[125].

Patients with progressive obesity can suffer from heart failure without having a proper diagnosis for left ventricular brokenness, and are analyzed as having weight-related cardiomyopathy.

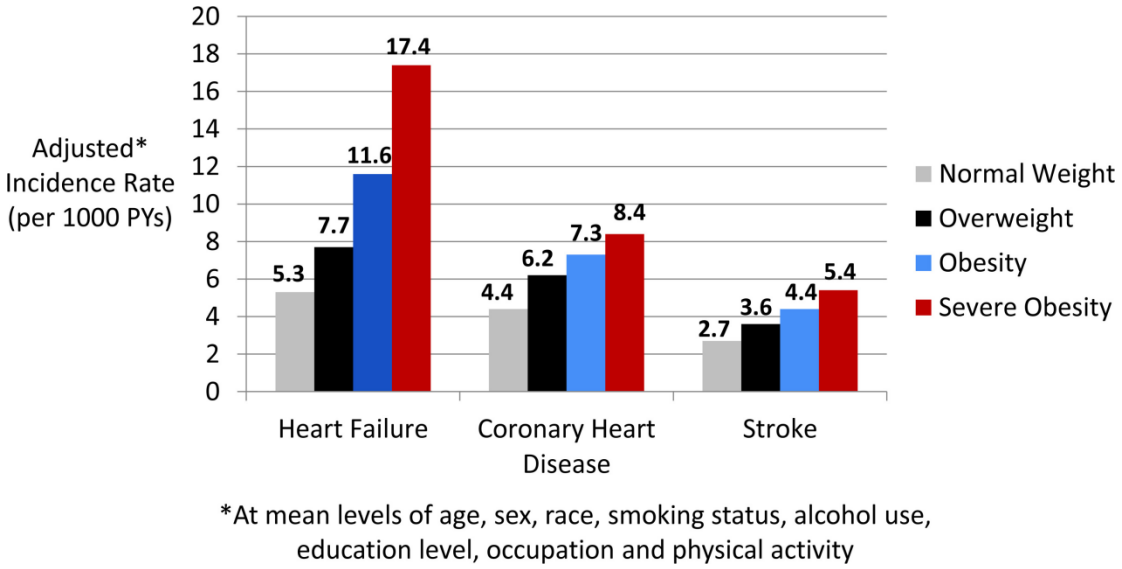


Fig.13. Association of BMI categories with adjusted incidence rates for different CVD subtypes. Incidence rates were calculated at mean levels of age, sex, race, smoking status, alcohol use, education level, occupation, and physical activity within the study population. BMI indicates body mass index; CVD, cardiovascular disease; PY, person-year. Over ≈23 years of follow-up, there were 2235 HF events, 1653 CHD events, and 986 strokes. For each subtype of CVD, higher BMI was associated with a greater adjusted incidence of events at mean levels of demographic variables, smoking, alcohol use, and physical activity[126].

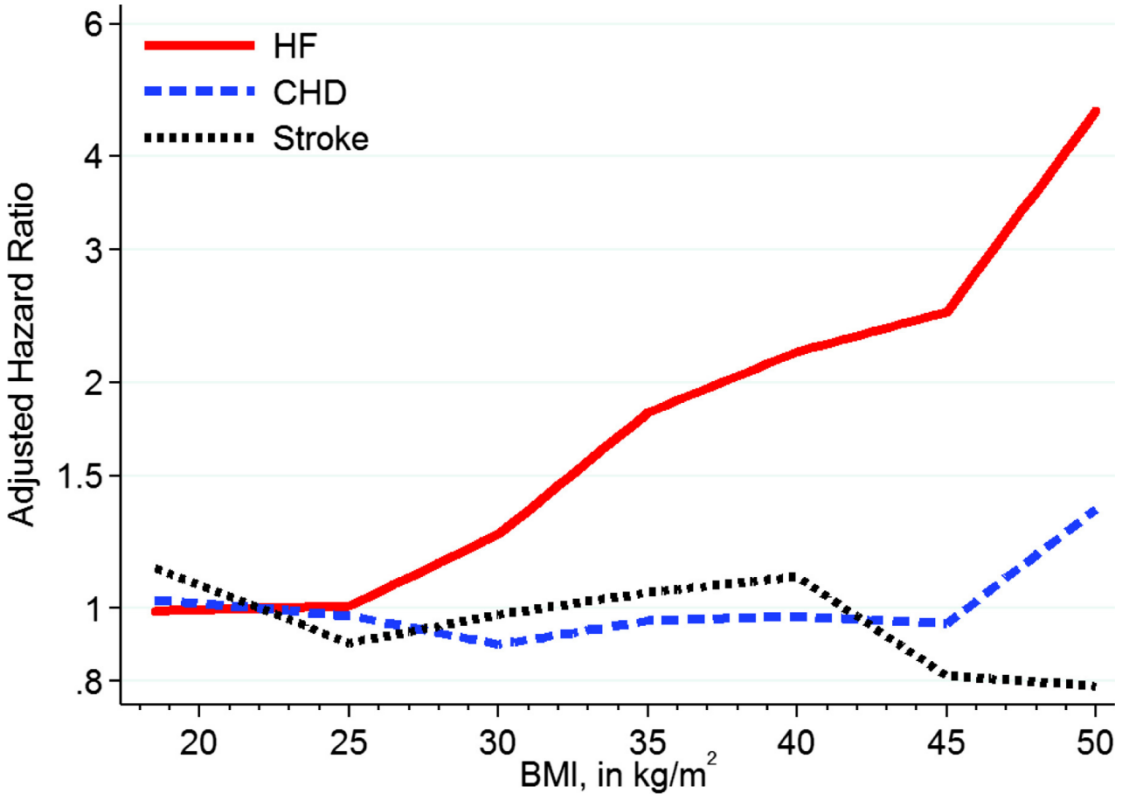


Fig.14 Relationship of continuous BMI with incident cardiovascular disease subtypes in linear spline models after multivariable adjustment. Linear spline with knots at the BMI values of 25, 30, 35, 40, and 45 and reference at BMI of 22. Adjusted for age, race, sex, alcohol use, smoking status,

occupation, education level, physical activity, diabetes mellitus, systolic blood pressure, antihypertensive medication use, HDL-C and LDL-C, and estimated glomerular filtration rate. BMI indicates body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol[126].

A statistically significant association has been observed between higher BMI and incident HF (HR for severe obesity 2.27, 95% CI 1.94–2.64), but no significant associations were seen for incident CHD and stroke. Similarly, in the fully adjusted model, every 5-U increase in BMI was associated with a 29% higher risk of incident HF, whereas no significant associations were seen for CHD and stroke[126].

Table 9. WHO recommended BMI and WC thresholds as indicators of CVD risk[127].

Classification	**Body mass index (kg/m2)**	**Disease risk (relative to normal weight and waist circumference)**	
Caucasian populations		Men <102 cm	Men >102 cm
		Women <88 cm	Women >88 cm
Underweight	<18.5	Very high	—
Healthy weight	18.5–24.9	—	High
Overweight	25.0–29.9	Increased	High
Obesity class I	30.0–34.9	High	Very high
Obesity class II (morbid obesity)	35.0–39.9	Very high	Very high
Obesity class III (severe obesity)	≥40.0	Extremely high	Extremely high
South Asian, Chinese and Japanese populations		Men <90 cm	Men >90 cm
		Women <80 cm	Women >80 cm
Underweight	<18.5	Low (increased risk of other clinical problems)	Average
Healthy weight	18.5–22.9	Average	Increased
Overweight (at risk)	23.0–24.9	Increased	Moderate

Classification	Body mass index (kg/m2)	Disease risk (relative to normal weight and waist circumference)	
Obesity class I	25.0–29.9	Moderate	Severe
Obesity class II	≥30.0	Severe	Very Severe

Adapted from: World Health Organization. Waist circumference and waist–hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008 and World Health Organization. Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. 2000.

Cardiovascular complications of obesity

Increased mortality from heart disease occurs with increasing obesity in both men and women specially with BMIs greater than or equal to 27-29 and varies among ethnic groups. For instance, the risk of heart disease associated with a high BMI is greater for whites than for blacks[128].

Cardiovascular abnormalities/changes associated with obesity[129][130][131]:

Electrocardiographic

- Increased heart rate
- Increased PR interval
- Increased QRS interval
- Decreased QRS voltage* (although sometimes increased)
- Increased QTc interval
- Abnormal signal-averaged electrocardiogram late potentials
- ST–T-wave abnormalities
- Left-axis deviation*
- Flattening of the T waves (inferolateral leads)*
- Left atrial abnormalities
- False positive criteria for inferior myocardial infarction*

Haemodynamic

- Increased heart rate (in physically inactive individuals)
- Increased blood volume
- Changes in stroke volume (will increase in early stages, and decrease in later stages)
- Increased cardiac output
- Increased systemic vascular resistance (in those with hypertension and insulin resistance)
- Increased arterial pressure, including systolic and diastolic Increased left ventricular wall stress
- Increased left ventricular stiffness
- Increased end diastolic left ventricular filling pressure
- Increased pulmonary artery pressure
- Altered atrial and ventricular pressure (in those with sleep apnoea)

Structural

- Myocardial steatosis, apoptosis, fibrosis
- Left ventricular remodelling and hypertrophy

- Left atrial enlargement

Functional

- Right ventricular hypertrophy
- Increased pericardial and perivascular adipose tissue
- Hypoxia due to sleep apnoea, atherosclerosis, thrombosis
- Left ventricular diastolic and systolic dysfunction
- Coronary obstruction
- Myocardial ischemia
- Tachyarrhythmias, including atrial fibrillation, atrial flutter, ventricular tachycardia, inappropriate sinus tachycardia
- Right ventricular failure
- Deep vein thrombosis
- Pulmonary embolism

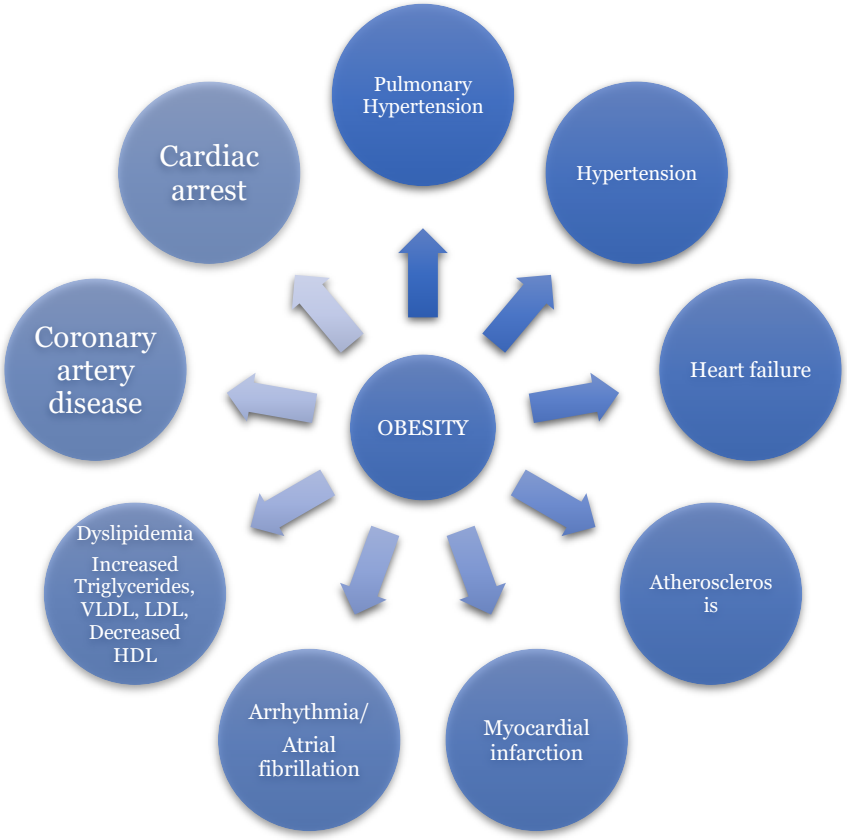


Fig.15: Cardiovascular complications of obesity

Pathogenesis of CVD in obesity:

Pathogenetic pathways linking obesity to Cardiovascular disorders:

1. Macrophage infilteration of adipose tissue
2. Baroreflex dysfunction
3. Mechanical pressure on kidney

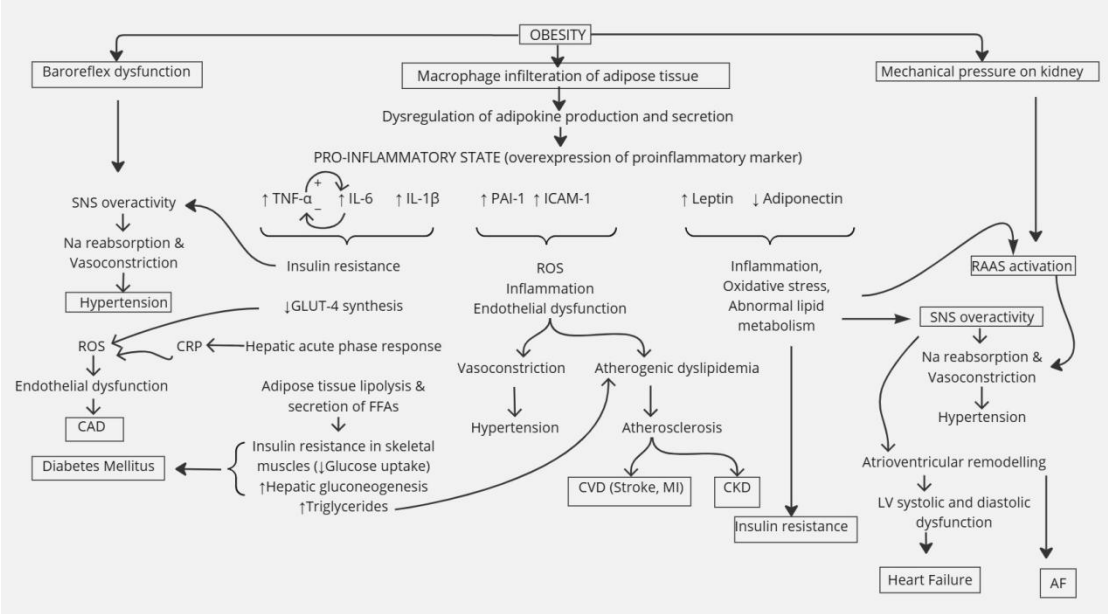


Fig.16. Pathogenesis of cardiovascular disorders in obesity.

The *inflammatory profile* associated with abdominal obesity could be the link with the development of metabolic and cardiovascular disease.

In obesity, the *macrophage infilteration of adipose tissue* results in an *overexpression of proinflammatory markers by the adipose tissue.*

The *dysregulation of adipocytokine production and secretion* in the context of abdominal obesity could be the link with the development of *metabolic and cardiovascular disease*.

More and more studies suggest that *inflammatory markers* such as tumour necrosis factor (TNF)-α and interleukin (IL)-6 may play a role in the development of metabolic complications associated with obesity such as insulin resistance.

TNF-α acts locally at the site of adipose tissue through autocrine/paracrine mechanisms having effects on insulin resistance and inducing IL-6, whereas IL-6 rather appears to be released systemically by the adipose tissue acting more as an endocrine signal that induces the hepatic acute-phase response or insulin resistance in the liver . Both TNF-α and IL-6 expression have been demonstrated to *interfere with insulin signalling in adipose tissue and in the liver* . Moreover, TNF-α as well as IL-6 are also known to promote *lipolysis* and *secretion of free fatty acids (FFA) from adipose tissue* into the circulation, a phenomenon which contributes to *insulin resistance in the skeletal muscle* and to an *increase in hepatic glucose production.*

These *adipocytokines*, in particular *IL-6*, are part of the *inflammatory cascade* which leads to the *induction of the acute-phase protein C-reactive protein (CRP)* by the liver. CRP has been shown to independently *predict cardiovascular events* in both men and women.

ICAM (Intercellular Adhesion Molecule-1) and VCAM (Vascular Cell Adhesion Molecule-1) are key adhesion molecules that become overexpressed on the surface of endothelial cells, facilitating the adhesion of white blood cells to the vessel wall, while PAI (Plasminogen Activator Inhibitor) is an enzyme that can contribute to endothelial dysfunction by inhibiting fibrinolysis and promoting platelet aggregation, all of which are considered markers for an unhealthy vascular system, often associated with conditions like atherosclerosis[132].

Central obesity *lowers adiponectin plasma levels* via *increasing proinflammatory adipokines, such as TNFalpha, leptin, and IL-1β*[133]. Obese people have a higher level of serum tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin -6 (IL-6); these all are *produced by macrophages derived from adipose tissue.*

Larsson A. et al. (2015) reported that *IL-6 and TNF-alpha* play a critical role in obesity-induced inflammation and their *levels increase parallel to the rise of BMI*[134].

NF-κB target genes present in endothelial cells are adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin, which intervene with inflammatory cytokines of the vascular wall to promote extravasations and subsequent endothelial dysfunction[135][136].

The term inflammation is associated with edema, transmigration, infiltration of leukocytes, and blood vessel and connective tissue proliferations. Inflammation has been considered as the initial stage of vascular dysfunction, progressing to vascular disease related to obesity[137].

An obese or overweight population may show strikingly different profiles of CVD risk factors based on their body fat distributions. *Excess abdominal fat tissue, independent of BMI,* has been related to *atherogenic* and *diabetogenic* factors, for example, *increased triglycerides, insulin resistance,* and *apolipoprotein B levels,* an *increased portion of LDL and VLDL*[138].

Obesity and dyslipidemias:

This increased risk of death from cardiovascular disease can be attributed to a number of factors. The first is the decreased levels of high-density lipoprotein (HDL) cholesterol associated with insulin resistance and obesity. Second is the increased concentration of plasminogen activator inhibitor-1, a factor that prevents clotting within blood vessels. Increased blood pressure associated with obesity also plays a role in the increased risk. Weight-loss studies show that all of these factors revert toward normal ranges with weight loss[139][140].

Obesity and Hypertension:

A rise in blood pressure has been documented as a function of the body mass index. Several events may account for this. The first is the increase in insulin concentration that works to increase sodium reabsorption by the renal tubule. In addition, changes in vascular resistance and cardiac function required to compensate for the higher blood flow in obese individuals contributes to the associated increase in blood pressure[139][140].

Obesity and Coronary artery disease :

Obesity is associated with elevated risk of incident coronary artery disease , involving not only epicardial vessels but also the coronary microvasculature[141][142]

Cardiovascular outcome in individual post-percutaneous coronary intervention is characterized by a lower mortality rates in overweight individuals at 6 months but, at 5- and 10-year intervals, severe obesity and high-risk coronary anatomy were associated with higher mortality[143][144].

This paradox might be due in part to earlier cardiovascular disease diagnosis and treatment in overweight or obese individuals, and it may be more relevant to focus on low body fat percentage and low BMI as predictors of adverse cardiovascular disease outcomes[145].

Obesity can lead to increased platelet activation, potentially reducing the effectiveness of antiplatelet drugs (aspirin, clopidogrel, and prasugrel), linked to factors like endothelial dysfunction, chronic inflammation, and bioactive substances produced by adipose tissue[146][147].

Obesity and Heart failure :

Obesity predisposes to heart failure due to the development of subclinical cardiac damage over time. This consists of atrioventricular re-modelling, increased filling and pulmonary pressures, and left ventricular systolic and diastolic dysfunction[152].

Pathophysiological processes affecting the myocardium and vascular system are associated with the development of HFpEF[153][154].

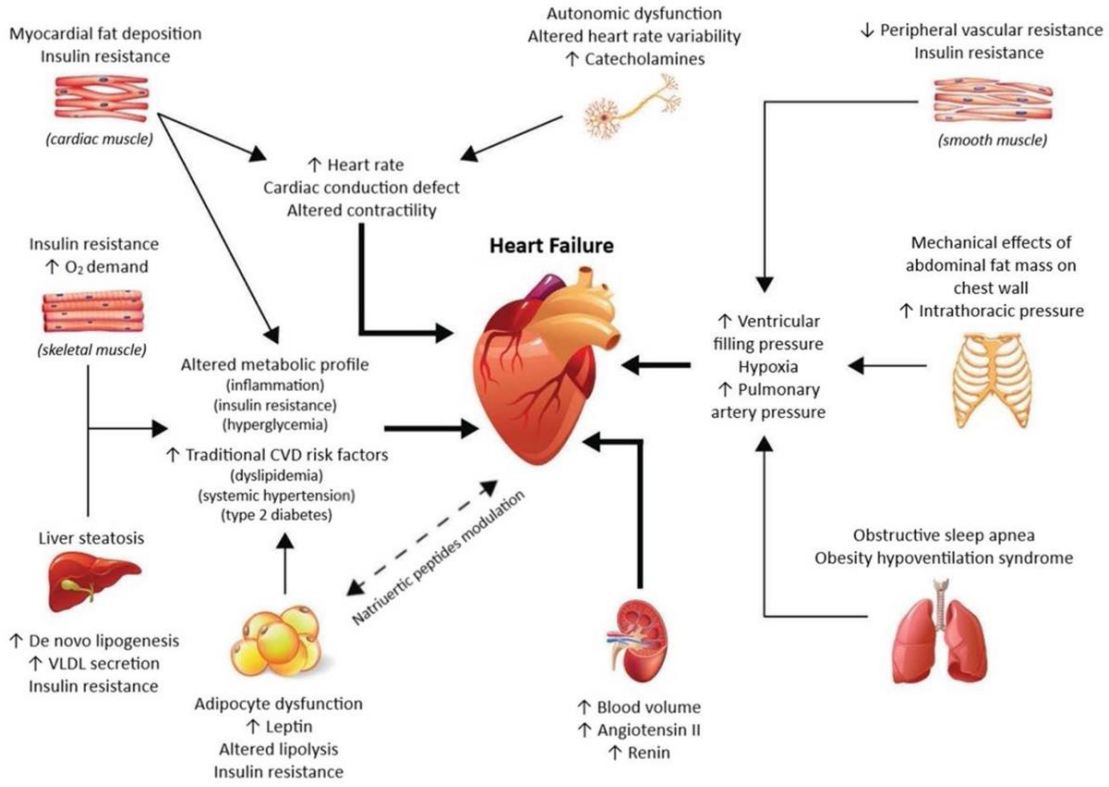


Fig.17. Pathophysiology of heart failure in obesity [155]. CVD indicates cardiovascular disease; and VLDL, very-low-density lipoprotein.

32–49% of obese people and *31–40% of overweight individuals* have a high number of *heart failures*. The span of morbid obesity is firmly connected to the advancement of a cardiovascular breakdown following 20 years of obesity; *70% are at the risk for CVD after 20 years* and *90% are at risk for CVD after 30 years*[123].

Obese patients with HFpEF are characterized by greater right ventricular dilatation and dysfunction, left ventricular remodeling, epicardial fat thickness and volume, and lower exercise capacity.

Weight loss is a key intervention in these patients due to its multiple beneficial effects[121].

Obesity and Atrial fibrillation

For every 5-unit increase in BMI , risk of AF is 29 % greater[159].

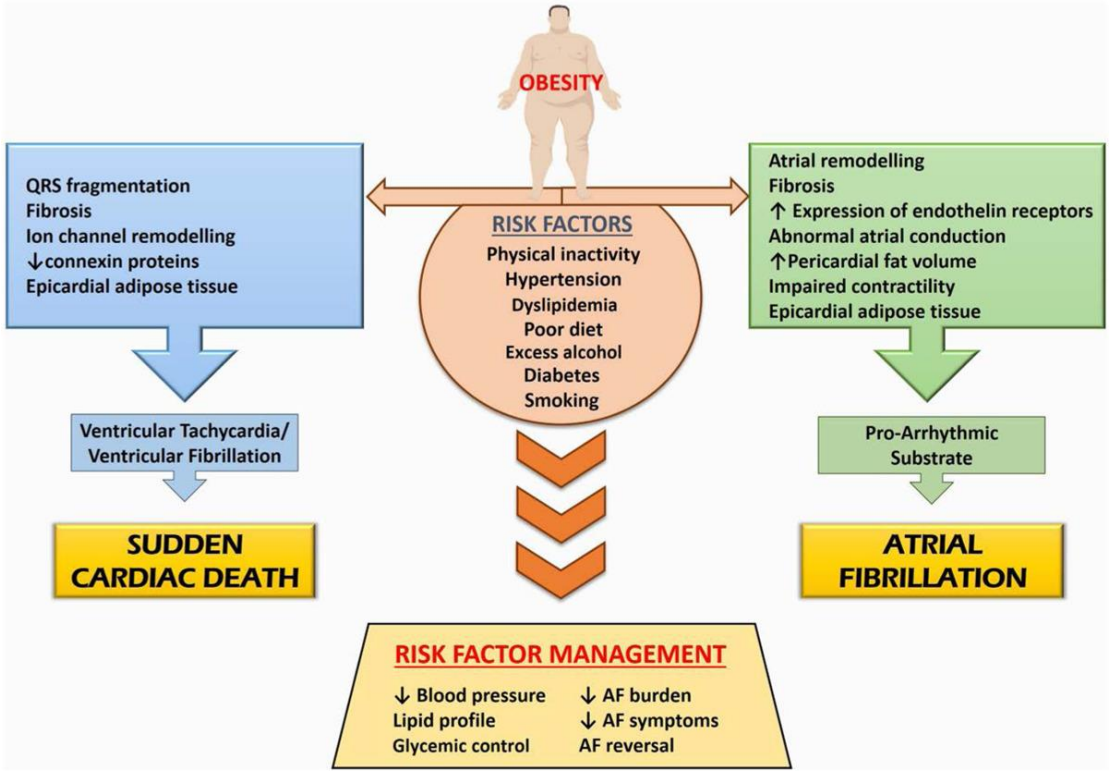


Fig. 18. Relationships between obesity and cardiac arrhythmias. AF indicates atrial fibrillation[141].

Pathogenetic mechanisms linking Sleep apnea with Cardiovascular disease risk.[18][19][21][23][43][180]

The pathogenesis of cardiovascular disease in OSAS is *not completely understood*, but is thought to be *multifactorial in origin*.

Proposed mechanisms by which OSAS predisposes to cardiovascular disease include sympa
thetic excitation, vascular endothelial dysfunction and metabolic dysregulation, as well as oxidative stress and inflammation induced by cyclical intermittent hypoxia .

Taken together, the main hallmarks of OSA, including IH, recurrent arousals, intrathoracic pressure swing, sympathetic hyperactivity, oxidative stress and coagulation abnormalities may participate in CVD pathogenesis.

There are three immediate sequelae of obstructive events in OSA

1. *progressive asphyxia &* intermittent arterial blood gas abnormalities,
2. *autonomic and behavioral arousal*
3. *increasingly negative intrathoracic pressure*

Apnoea leads to *hypoxia* and *increasingly strenuous respiratory efforts* until the patient overcomes the resistance. The combination of central hypoxic stimulation (triggers increased inspiratory effort and activation of ventilatory reflexes) and the effort to overcome obstruction wakes the patient transiently from sleep allowing the dilating muscles to re-open the airway. These awakenings are so brief that patients have no recollection of them and remain unaware of them . After a series of loud deep breaths that may wake their bed partner, the patient rapidly returns to sleep, snores and becomes apnoeic once more. This cycle of apnoea and awakening may repeat itself many hundreds of times per night. This leads to severe sleep fragmentation , *sleep deprivation* with consequent daytime sleepiness and impaired

intellectual performance , secondary variations in blood pressure, which may predispose over time to cardiovascular disease.

These events may turn on various signaling mechanisms including activation of neurohormones, elevated sympathetic tone, endothelial dysfunction, hypercoagulopathy, oxidative stress, metabolic defect (e.g., insulin resistance, leptin resistance and altered hepatic metabolism) , release of inflammatory mediators which lead on to structural alterations of the cardiac chambers .

With each *obstructive event*, the combination of progressive asphyxia, increasingly negative intrathoracic pressure, autonomic and behavioural arousals leads to acute *cardiac* and *cerebrovascular* perturbations, including :

1) *increased afterload of both the left and right ventricles*,
2) *decreased left ventricular compliance*,
3) *increased pulmonary artery pressure*,
4) *decreased coronary artery blood flow*, and
5) *increased myocardial oxygen demand.*

The episodes of upper airway collapse are typically terminated when ventilatory reflexes are activated and cause arousal, thus stimulating an increase in neuromuscular activity and opening of the airway.

The *abrupt arousal at the termination of obstructive event*s is associated with

1. *peripheral vasoconstriction*
2. *increase in the heart rate* and in *systemic blood pressure*, even as cardiac output continues to fall.

Intermittent hypoxia[250][251]

Intermittent hypoxia (IH) is a distinguished character of OSA featured by repeated short desaturation cycles following quick reoxygenation. Notably, IH is considered as a “double-edged sword” in cardiometabolic processes.Episodes of intermittent hypoxia in OSA can range anywhere from 5 to more than 100 events per hour.

OSA causes intermittent periods of hypoxia followed by reoxygenation. Recurrent episodes of hypoxia stimulate the carotid chemoreceptors and results in secondary rise in blood pressure from sympathetic activation .

Although acute hypoxia is capable of activating responses that can lead to acute nocturnal cardiac event , the chronicity in recurrent sympathetic activation and its consequent vasoconstriction over many year, can cause unique profile of biological consequences in OSA patients[197].

There is increasing evidence indicating that mild OSA patients exposed to short period of mild IH may trigger an adaptive response through a cardioprotective preconditioning process. However, patients with moderate to severe OSA who frequently experience short cycles of IH with extended desaturations suffer from multiple deleterious reactions .

For this reason, intermittent hypoxia is thought to be a major culprit in patients with OSA that can lead to CVD.

Intermittent hypoxia has shown to increase the levels of angiopoietin-like 4 (Angptl4), a potent inhibitor of lipoprotein lipase. This change decreases the body’s clearance of lipoprotein and increases fasting serum levels of triglycerides and very low density lipoprotein cholesterol.[197]

In addition, hypoxia-inducible factor-1 (HIF-1), a transcription factor that modulates the body’s response to ischemic injuries has been shown to be up regulated in hypoxia, further demonstrating the evidence of

molecular genetic association between hypoxia and ischemic CVD, secondary to impaired lipoprotein turnover[252].

Hypoxia-sensitive transcription factors hypoxia-inducible factor-1 and nuclear factor-kB appear to play a key role in mediating the inflammatory and cardiovascular consequences of OSAS. IH participates in the progression of CVD in OSA by activating inflammatory signaling pathways which involve the hypoxia-sensitive transcription factors hypoxia-inducible factor-1 (HIF-1) and NF-κB[253].

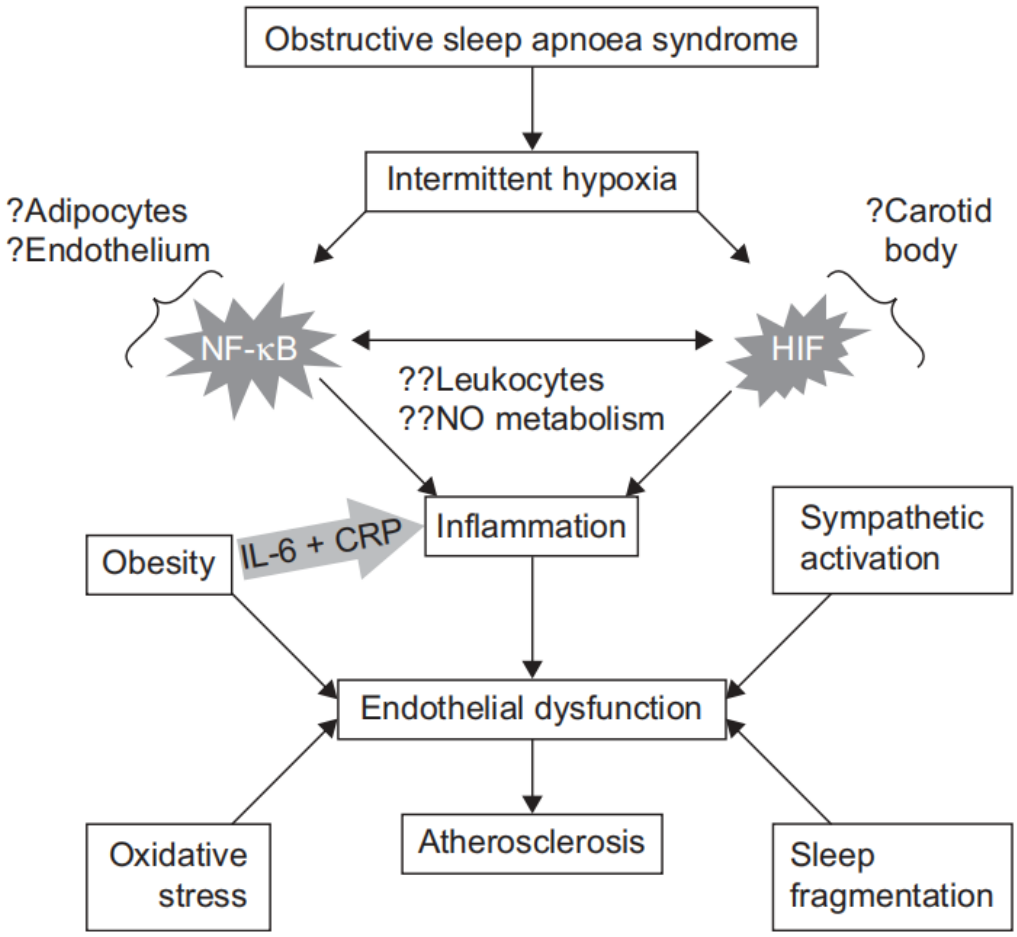


Fig.19. Activation and interaction of inflammatory pathways in response to intermittent hypoxia in obstructive sleep apnoea syndrome (OSAS). Proposed mechanisms by which OSAS predisposes to the development of endothelial dysfunction and cardiovascular disease include sympathetic excitation, vascular endothelial dysfunction, oxidative stress and inflammation. Intermittent hypoxia, the characteristic feature of OSAS, activates inflammatory mechanisms directly through the hypoxia-sensitive transcription factors nuclear factor (NF)-kB and hypoxia inducible factor (HIF)-1. The co-existence of obesity in OSAS augments the pro-inflammatory state through increased production of interleukin (IL)-6 and C-reactive protein (CRP) by adipose tissue. There are differences in the response to intermittent hypoxia between body tissues, with NF-kB having its largest apparent influence in endothelial cells, and adipocytes and HIF-1 playing a key role in the carotid body response. Activation of leukocytes and nitric oxide (NO) involvement in the inflammatory response to intermittent hypoxia in OSAS may be regulated by cross-talk between the NF-kB and HIF-1 pathways.

HYPOXIA-RESPONSIVE TRANSCRIPTION FACTORS IN OSAS

Nuclear factor-kB

The eukaryotic transcription factor nuclear factor (NF)-kB is a key mediator of the inflammatory response[254].

NF-kB exists in most cells in an *inactive form* bound to the inhibitor, *IkB*, which

retains it in the cytoplasm. IkB is targeted for ubiquitin mediated degradation upon sensation of an *appropriate endogenous or exogenous inflammatory stimulus*[255] .

NF-kB is released from IkB and translocates to the nucleus, where it can upregulate transcription of specific pro-inflammatory genes responsible for encoding of inflammatory cytokines, chemokines and surface adhesion molecules. NF-kB plays a *central role in the inflammatory response* and orchestrates expression of a range of factors, including cytokines (TNF-a, IL-6 and IL-8), adhesion molecules (intercellular adhesion molecule-1) and enzymes (cyclo-oxygenase-2)

Hypoxia-inducible factor-1

Hypoxia-inducible factor (HIF)-1 is a heterodimeric transcription factor consisting of a constitutively expressed β-subunit and an α-subunit that contains an oxygen-dependent degradation (ODD) domain[258].

Under normoxic cellular conditions, the ODD domain is hydroxylated in an oxygen-dependent manner, rendering the a-subunit vulnerable to proteasomal degradation.

Therefore, HIF-1 is suppressed in normoxia. However, in hypoxia, HIF-1 is stable and active, capable of binding to the regulatory regions of its target genes and inducing their expression.

HIF-1 is the major regulator of oxygen homeostasis within the cell, affecting and regulating dozens of genes as cellular oxygen concentrations change. In general, such factors allow an adaptation to hypoxia that is directed towards increasing tissue perfusion and oxygenation and, hence, overcoming the initial hypoxic insult. In normoxia, most cells produce ATP via oxidative phosphorylation and HIF-1 regulates the shift to increased glycolysis and anaerobic metabolism at low oxygen tensions [259].

By binding to the hypoxia response element in the EPO gene, HIF-1 activates its transcription, increasing red blood cell production and enhancing blood oxygen-carrying capacity [260].

Through VEGF transcription, HIF-1 regulates migration of mature endothelial cells towards hypoxic areas of tissue, thereby promoting angiogenesis.

Elevated serum levels of HIF-1 gene products, such as EPO and VEGF, have been demonstrated in OSAS patients, particularly patients with severe nocturnal hypoxaemia.

However, *not all HIF-1-mediated effects are protective.* HIF-1 promotes enhanced survival of myeloid inflammatory cells, such as granulocytes, monocytes and macrophages, resulting in their functional longevity and potentiation of inflammation[261].

Therefore, HIF-1 may also be viewed as a *pro-inflammatory contributor* to the hypoxic response by promoting inflammatory cell survival. Delayed neutrophil apoptosis has recently been demonstrated in OSAS patients; however, the mechanisms that underlie this response remain unexplained [262].

Interaction between the NF-kB and HIF-1 pathways

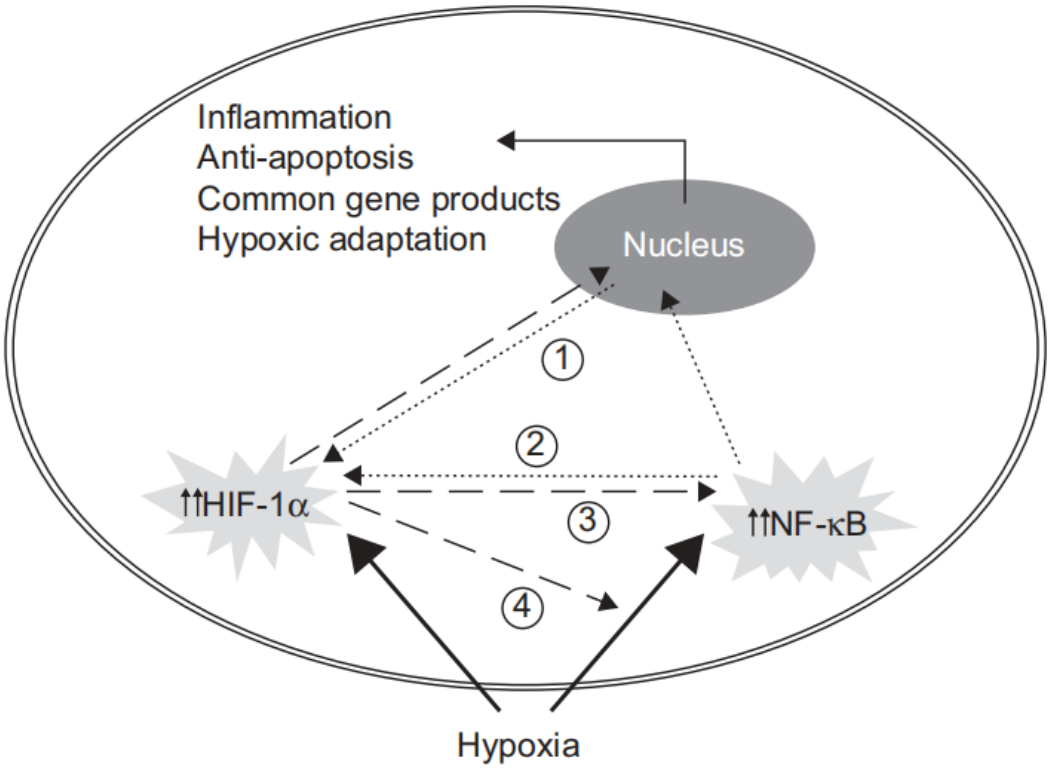


Fig. 20. Interaction between hypoxia-inducible factor (HIF)-1a and nuclear factor (NF)-kB in hypoxia. Tissue hypoxia leads to the activation of the transcription factors HIF-1a and NF-kB. Activation of HIF-1a facilitates an adaptive response to hypoxia, whereas upregulation of NF-kB leads to inflammatory and anti-apoptotic gene expression. HIF-1a and NF-kB also share some gene products, e.g. inducible nitric oxide synthase. NF-kB regulates basal levels of HIF-1 gene expression and upregulation of HIF-1 transcription occurs through a NF-kB-dependent mechanism (1 and 2). Conversely, hypoxic induction of NF-kB transcription is dependent on the presence of HIF-1a (3) and HIF-1a is directly involved in regulating apoptosis through the modulation of NF-kB signalling (4).

There is an active NF-kB binding site contained in the proximal promoter site of the HIF-1 gene and *NF-kB regulates basal levels of HIF-1 gene expression*[263].
Hypoxia up-regulates HIF-1 transcription through a NF-kB-dependent mechanism .
Hypoxia upregulates HIF-1a transcription by involving *phosphatidylinositol 3-kinase* and *nuclear factor kB* in *pulmonary artery smooth muscle cells.*
Conversely, HIF-1 can also influence the NF-kB pathway. WALMSLEY et al. showed that the *hypoxic induction of NFkB transcription is dependent on the presence of HIF-1* and that *HIF-1 is directly involved in regulating neutrophil survival in hypoxia through the modulation of NF-kB signalling.*
Overexpression of HIF-1 results in *increased NF-kB activity* and an *enhanced inflammatory response*.
HIF-1 and NF-kB also share some common gene products. For example, both HIF-1 and NF-kB can enhance the bioavailability of nitric oxide (a potent vasodilator) through increased expression of iNOS.
In summary, it is likely that cross-talk between NF-kB and HIF-1 plays a *central but complex role in modulating the inflammatory response to intermittent hypoxia in OSAS*[264].

Moreover, IH likely contributes to *vascular dysfunction* ranging from initial changes in atherosclerosis to full plaque formation, and this atherosclerotic process could be further amplified in conjunction with other risk factors (such as diet rich in cholesterol)

In line with clinical data, ample evidence revealed that changes in vascular function evoked by IH (e.g., impaired endothelium-dependent vasodilation and increased vasoconstrictive reaction) occur prior to onset of atherogenic process.

In addition, IH is related to an increased susceptibility of HF in OSA patients including ventricular hypertrophy, cardiac dilatation, myocardial interstitial fibrosis and dropped stroke volume[265]

Other than these unfavorable clinical sequelae, IH may also instigate higher incidences of hypertension and myocardial infarction (MI) in OSA patients[266].

Sympathetic overactivity

It is known that sympathetic activations are caused by nocturnal intermittent hypoxia in OSA patients. The sympathetic activations in OSA patients persist during daytime wakefulness in normoxic conditions [197].This persistent sympathetic drive promotes systemic hypertension and increased cardiac sympathetic tone .In addition, sympathetic influence on renin angiotensin system is another critical factor in the pathogenesis of systemic hypertension in OSA patients. This change in autonomic regulation of blood pressure due to impaired baroreflex and renin-angiotensin system in these patients puts them at a higher risk of developing systemic HTN, persistent tachycardia and ultimately CVD.

The episodes of IH during sleep are characteristic of OSA and may trigger surges in blood pressure (BP) and sympathetic nervous system overactivity via carotid chemoreceptors[267].

Notably, with the exception of nighttime BP fluctuation, OSA patients often demonstrate a constant BP augmentation during the awakening period because of elevated sympathetic drive manifested as increased catecholamine levels in urine and plasma[268].

Even normotensive OSA patients in the absence of obesity experience increased sympathetic tone in peripheral vessels during the awakening hours. Furthermore, it has been reported that the sensitivity of peripheral chemoreflex shows a selective potentiation in OSA patients versus normotensive controls[269], while the autonomous baroreflex sensitivity of the heart reduces in OSA patients during diurnal and nocturnal periods.

Moreover, experimental studies have offered compelling support for a role of sympathetic hyperactivity in the pathogenesis of CVD in OSA patients. In animal models of OSA such as rats and dogs, BP elevation was declined once the airway obstruction was relieved, favoring the effect of sympathetic hyperactivity on hypertension progression in OSA[265][270] .

Proinflammatory state / inflammation in OSAS

There is increasing evidence that intermittent hypoxia plays a role in the pathobiology of cardiovascular complications in OSAS through activation of *pro-inflammatory pathways.* Chronic hypoxic stress can activate systemic inflammatory pathways, as OSA patients have increased level of plasma cytokines, serum amyloid-A and C-reactive protein (CRP)[197].

Obesity has also been shown to increase the level of pro-inflammatory cytokines and may cause hypercoagulable state in the bloodstream along with OSA. Adipocyte hypertrophy results in altered expression of adipokines. Adipokines play crucial role in vascular function by influencing glucose and lipid metabolism. In fact, dysregulation of adipocytes leads to altered levels in pro- and anti-

inflammatory adipokine expression. While altered adipokine expression has been demonstrated to be a predicative marker and associate with CVD in experimental in vitro and in vivo models, this impact of is less clear in humans[272].

Along with the buildup and the rupture of atherosclerotic plaques, these phenomena of pro-inflammatory and hypercoagulable state can be fatal in the development of CVDs, such as acute myocardial infarction (MI).

Endothelial dysfunction

OSA patients suffer from endothelial dysfunction due to decreased availability of nitric oxide (NO) and cell apoptosis, secondary to increased oxidative stress and systemic inflammation[197].

It is also thought that chronic hypoxic stress causes release of endothelin-1, a potent vasoconstrictor, in human endothelium.Impaired NO production compounded with increase in endothelin-1 release in the vasculature can predispose OSA patients into systemic HTN and consequent CVD. Accumulation of reactive oxygen species also likely contributes to the pathogenesis of endothelial dysfunction in OSA patients by directly forming vascular lesions and CAD[195].

Loss of balance between reactive oxygen species (ROS) and cellular antioxidant capacity leads to oxidative stress, and serves as a possible trigger for chronic intermittent hypoxemia-re-oxygenation (CIH) associated with recurring apnoea in OSA. Specifically, CIH can selectively activate the proinflammatory transcriptional regulator NF-κB, a necessary messenger connecting OSA and cardiovascular pathology, and its function may be normalized by adequate CPAP treatment. Not surprisingly, NF-κB is known to upregulate adhesion molecules including VCAM-1, E-selectin and ICAM-1 to participate in the recruitment and migration of leucocytes to inflammatory site, leading to worsened endothelial defect[201][269].

ROS accumulation is a common manifestation of OSA which can result in oxidative stress and subsequently cell injury. On one hand, ROS promotes proinflammatory factors (e.g., TNF-α, IL-6, CRP, etc.) and adhesion molecules by initiating inflammatory reaction cascades, producing abundant proinflammatory cytokines and inflammatory responses[273].

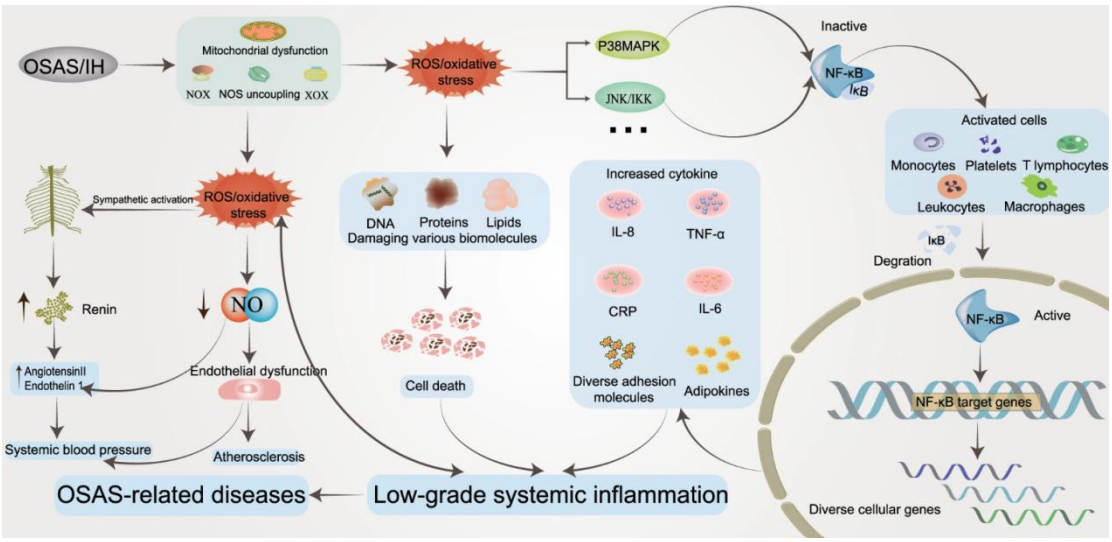


Fig.21. Schematic demonstrating the central role played by oxidative stress and inflammation in OSAS. OSAS/IH induces ROS production by inducing mitochondrial dysfunction, activating NOX and XOX,

and inducing NOS uncoupling, which results in oxidative stress. The interaction between ROS and NO further promotes oxidative stress and diminishes the bioavailability of NO, thus promoting endothelial dysfunction and inflammation, which is closely related to hypertension, atherosclerosis, and hypercoagulability. Increased ROS-dependent sympathetic activation enhances renin levels, which leads to an increase in angiotensin II, endothelin 1, and hypertension. As a second messenger, ROS can activate multiple signaling pathways (MAPK, JNK), which in turn activate ***NF-κB*** *and then induce the activation of nuclear transcription factors in a variety of cells. As the main switch of the inflammatory response, NF-κB plays an important role in the pathological process of OSAS, activating and entering the nucleus, regulating the transcription of many kinds of cells (immune cells), causing an increase in cytokines and participating in the inflammatory process of cells. In addition, elevated ROS can damage intracellular macromolecular substances (DNA) and cause cell death. Various pathological processes coordinate with each other and induce low-grade inflammation in the body, which is closely related to the occurrence and progression of a variety of diseases. ROS reactive oxygen species, NOX NADPH oxidase, NOS uncoupling nitric oxide synthase uncoupling, XOX xanthine oxidase, NOS nitric oxide synthase, JNK c-Jun N-terminal kinase, MAPK mitogen-activated protein kinase, NF-κB nuclear factor kappa B*[274].

On the other hand, pronounced endothelial dysfunction develops in response to ROS-evoked risk factors such as activation of transcription factors, inflammatory cell growth and migration and endothelial cell damage[275]. Moreover, ROS overproduction triggers membrane peroxidation, protein degeneration and DNA mutation, leading to abnormal cell function and ultimately irreversible cell damage or death[276].Furthermore, impaired endothelial cells stimulate the release of inflammatory factors and induce the aggregation of inflammatory cell to the vascular endothelium, triggering atherogenesis and higher incidence of acute coronary syndrome.

It is noteworthy that sleep deprivation evoked by sleep apnoea and disturbed circadian rhythm is associated with increased CVD morbidity and mortality, with a significant contribution from endothelial dysfunction. Fluctuation in sleep duration causes endothelial cell damage partially by vascular inflammation, oxidative stress within vasculature and loss of the bioavailability for nitric oxide. Upregulation of systemic inflammation and alteration in oxidative environment leads to microcirculation dysfunction and vascular remodeling including angiogenesis, vessel stiffening and atherogenesis[273][276]. Moreover, sleep deprivation may also provoke endothelial dysfunction through autonomic disorder, manifested as sympathetic nervous system (SNS) hyperactivity. Once hyperactivated, SNS can enhance vascular smooth muscle tension and promote vascular contraction pathways, predisposing to endothelial dysfunction [277].

Intrathoracic pressure changes

In OSA, the upper respiratory tract is completely or partially obstructed during sleep, causing repetitive episodes of apnoea and hypopnea. The intrathoracic negative pressure rapidly elevates to resist airway occlusion, resulting in further intensified respiration effort. On one hand, pressure changes lead to the increased pressure difference between inside and outside of cardiac lumen to stimulate sympathetic nerve. Indeed, elevated transmural pressure of left ventricle and aorta compromise hemodynamics, ventricular function and stability of autonomic nerve[278].On the other hand, rapid elevation of intrathoracic negative pressure may decrease left atrial volume, increase left ventricular afterload and

end-systolic volume of left ventricle, resulting in decreased left ventricular ejection fraction and cardiac output. As a result, reduced coronary blood flow ensues, leading to myocardial ischemia.Repetitive inspiratory effort against closed upper airway generates intrathoracic pressure change that subsequently causes an increase in transmural gradients across the atria, ventricles and aorta[197].
In addition, repeated changes of thoracic pressure and fluctuation in the returned blood volume may irritate baroreceptors on aortic body and carotid sinus, as well as stimulate sympathetic excitability. Long-term repetitive sympathetic excitation and myocardial ischemia can cause HF, whereas pulmonary vasoconstriction evoked by hypoxia contributes to PH, resulting in aggravated right ventricular afterload and the development of HF[279].

Circardian rhythm

Disruption in circadian rhythm and sleep homeostat has also shown its association with CVD. In OSA patients, insufficient duration, quality and timing of sleep, in addition to intermittent hypoxia can promote the development of CVD[280] .
It is also interesting to note that people of African descent, who have a higher prevalence of CVD than others also have more disrupted sleep pattern[280].

Recurrent arousals

Furthermore, Launois and colleagues noted that only respiratory arousals resulted in blood pressure surges compared with non-respiratory cases in a porcine model, offering a rational explanation to the inconsistency among various research groups[281].Therefore, recurrent arousals should play an additional role in the onset and development of CVD in OSA, although further translational studies are needed to elucidate its specific function.

Blood coagulation abnormalities.

Increased cardiovascular risk in OSA patients may be associated with blood coagulation abnormalities and platelet activation[282].
Blood viscosity and plasma fibrinogen elevation as well as decreased fibrinolysis are noted in patients with OSA. Meanwhile, OSA is also associated with elevated levels of thrombin-antithrombin complex, clotting factors XIIa and VIIa[283]
Additionally, platelet activation and aggregability, platelet coagulation and other potential thrombosis markers are all increased in OSA patients.
Notably, although the precise mechanism of action remains elusive for platelet activation in OSA, sympathetic hyperactivity seems to play a role. It is known that IH episodes during sleep can provoke sympathetic nervous system, resulting in high levels of epinephrine and norepinephrine, while these catecholamines evoke platelet activation in a dose-dependent manner[252] .

Insulin resistance.

Insulin resistance (IR), as characterized by an impaired biological response to insulin and thus a reduced insulin-mediated glucose processing, has been implicated in the pathogenesis of coronary artery disease (CAD) in OSA .Despite controlling obesity and other important cofounding factors of insulin level, OSA severity markers (minimum oxygen saturation and apnoea hyponea index) are predominant contributing factors of IR[285].

Several studies concerning the linkage between IR and hypertension demonstrated IR as an independent determinant of hypertension. *OSA can worsen glucose metabolism*[285][286][287].

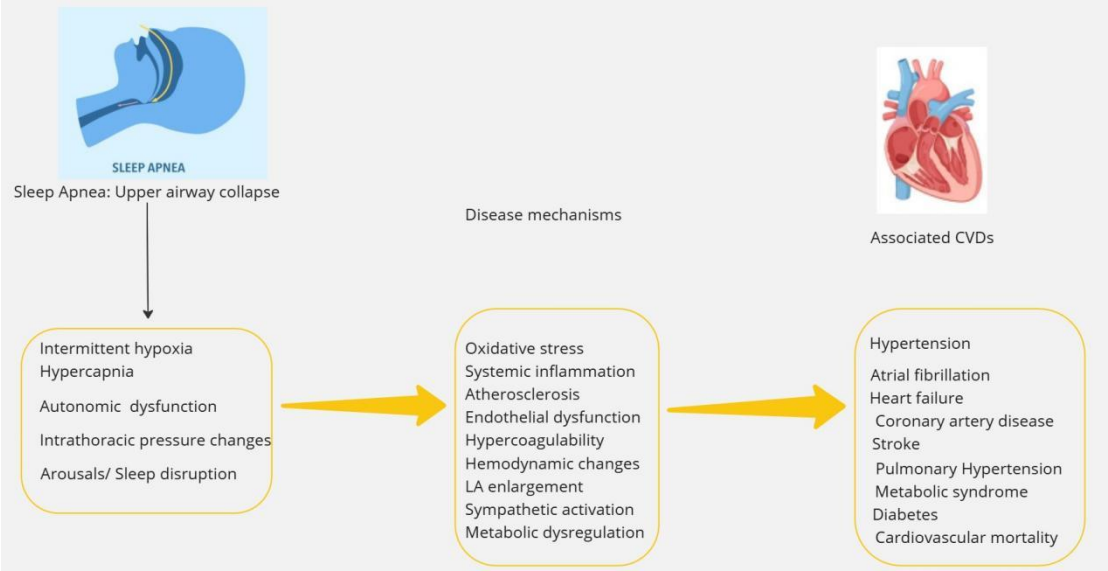


Fig.22. Pathogenetic mechanisms whereby sleep apnea leads to cardiovascular sequelae

Clinical association between Cardiovascular diseases and Sleep apnoea: Cardiovascular complications of sleep apnoea

Obstructive sleep apnoea (OSA) is a serious, potentially life-threatening condition.

Clinical and epidemiological studies have reported an independent association between OSA and cardiovascular events, suggesting that OSA may lead to cardiometabolic dysregulation[99][170][171].

Several comorbidities identified in patients with severe OSA : heart disease, stroke, kidney disease, asthma, COPD, acute heart failure, chronic heart failure, hyperlipidemia, thyroid disease, cerebral infarct or embolism, myocardial infarction, and psychological comorbidities including stress and depression[30].

OSAHS is an underdiagnosed but a major contributor to cardiovascular disease in adults. Prevalence of OSA in CVD: OSA prevalence is as high as 40% to 80% in patients with hypertension, heart failure (HF), coronary artery disease, pulmonary hypertension (PH), atrial fibrillation (AF), and stroke. Despite its high prevalence in patients with heart disease and the vulnerability of cardiac patients to OSA-related stressors and adverse cardiovascular outcomes, OSA is often underrecognized and undertreated in cardiovascular practice[30][172][173].

Epidemiologic studies show that OSA is associated with a number of cardiovascular complications including[19][21][30]:

Cardiovascular mortality.

Non-ischemic cardiovascular alterations

1. Systemic hypertension,
2. Pulmonary hypertension
3. Metabolic syndrome
4. Heart failure with and without reduced ejection fraction
5. Atrial and ventricular arrhythmias (Sinus node dysfunction, AF)
6. Diabetes mellitus

Ischemic cardiovascular alterations

1. Atherosclerosis and coronary artery disease
2. Cerebrovascular: Stroke & TIA

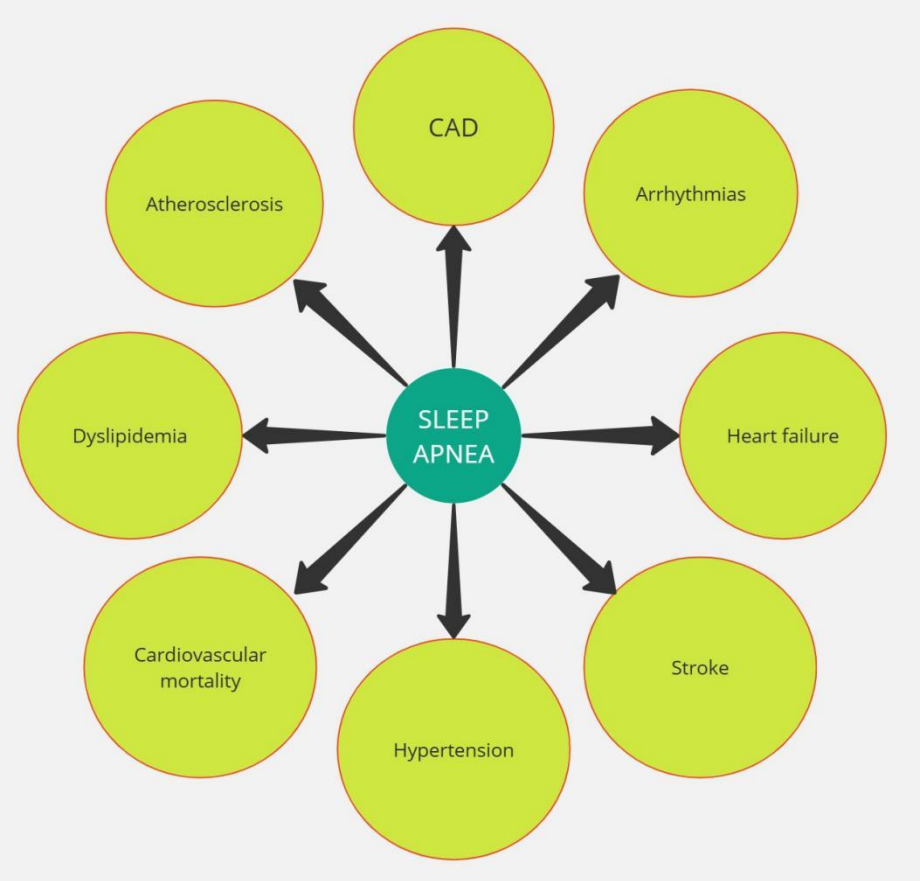


Fig. 23. Cardiovascular complications of sleep apnoea

Acute factors of OSA affecting onset of CVD

- Changes in intrathoracic pressure
- Blood gas changes
- Sympathovagal imbalance

Long term effects of OSA on atrial structural modelling

- Systemic inflammation
- Neurohumoral activation
- Persistent atrial dilation
- Obesity
- HTN

Evidence of positive linear relationship between the severity of OSA and the incidence of CVD was also shown in the Sleep Heart Health Study (SHHS), a large multi-center cross-sectional study[174].

Prevalence of obstructive sleep apnoea in comorbidities:

- Drug resistant hypertension : 70-80%
- Stroke :50-70%[175]

- CHF: 50-70 %[176],[177]
- Metabolic syndrome: > 60% [178]
- Diabetes :50-60%[179]
- Atrial fibrillation :40-50%[180]
- Coronary artery disease : 30-60%[181]
- Hypertension: 30-50%[182]

Cardiovascular mortality in OSA

OSA has constantly been related to decreased survival rate in epidemiology. E**levated mortality of all-cause and CVD were linked to severe OSA**, rather, no connection between mild or moderate OSA (AHI<30) was found[183].

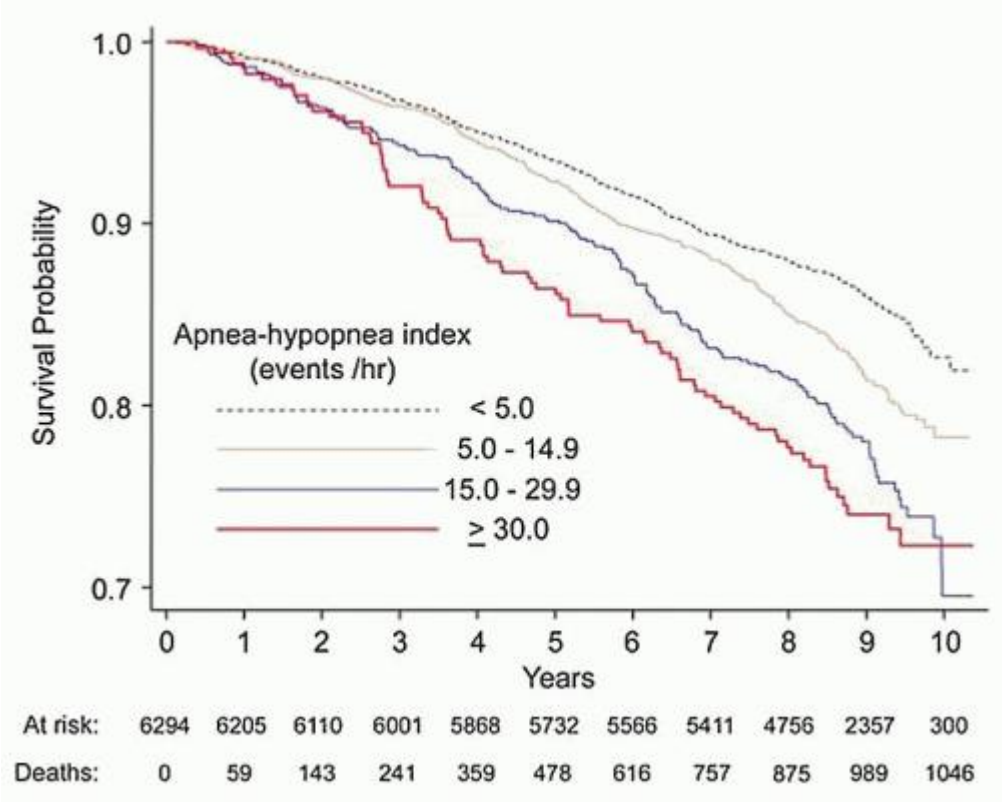


Fig. 24. *OSA severity and cardiovascular mortality: Prospective cohort analysis from the Sleep Heart Health Study showing that increased severity of OSA, based on AHI criteria, is associated with increased mortality from cardiovascular disease. (ref. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleepdisordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6(8):e1000132.)*

OSA ,Metabolic dysregulation and diabetes.

Epidemiologic studies have linked short sleep duration and disruptions of circadian rhythm with increased risk of **metabolic syndrome** and type 2 **diabetes[81]**. Experimentally induced sleep restriction combined with circadian disruption in humans led to **decreased RMR** and **increased postprandial plasma glucose** levels due to **inadequate insulin secretion[81]**.

The development of insulin resistance and pancreatic beta cell dysfunction has been linked to chronic intermittent hypoxemia observed in OSA. Even mild recurrent oxyhemoglobin desaturations (>2%) were independently associated with metabolic dysfunction[186].

An independent association between OSA, insulin resistance, and type 2 diabetes has been consistently demonstrated by a number of cross-sectional studies, observational studies, and large population-based Studies[187][188][189].

Central adiposity is linked to the development of both OSA and the metabolic syndrome, with both sharing similar pathophysiological features (eg, systemic inflammation, endothelial dysfunction).In addition, intermittent hypoxia of adipose tissue, sympathetic activation, induction of adipocytokines, and oxidative stress may promote the development of metabolic risk factors.

OSA and dyslipidemia

OSA patients had significantly *higher triacylglycerols*, *total cholesterol* and *LDL-cholesterol* compared to healthy controls. HDL cholesterol was not significantly different. Of the LDL and HDL subfractions, OSA patients had significantly *lower levels of atheroprotective LDL1 and large HDL subfractions* and significantly *higher levels of atherogenic small dense LDL3–7 and HDL8–10 subfractions*. Lipoperoxide levels in patients with OSA were significantly elevated compared to healthy individuals[190].

OSA and hypertension

OSA is highly prevalent in hypertensive patients. It is estimated that **30-50% hypertensive patients possess comorbid OSA**, and particularly, up to **80% may have OSA in patients with treatment resistant hypertension.** On the other hand, around **50% OSA patients are hypertensive** [24][191]

Sleep apnoea is associated with an increased risk of **hypertension**, and if sleep apnoea is severe, it can lead to **right-sided heart failure** and **sudden death**[81].

The most common causes of secondary hypertension are largely thought to be ***primary hyperaldosteronism*** (increased salt/water retention), ***obstructive sleep apnoea*** and ***obesity*** (the last two causing sympathetic overdrive), though the precise proportions ascribed to these and other causes vary in different studies due to advances in evaluation and diagnostics[192].

As a result of marked sympathetic activation during apnoea, sleep-disordered breathing is associated over time with *sustained hypertension* and an *increased risk of coronary events and stroke*[43].

The most compelling piece of epidemiological evidence for the causality between hypertension and OSA is supplied by the **Wisconsin Sleep Cohort Study** with a four-year follow-up.

The odds ratio of developing hypertension during follow-up period elevated linearly with **increasing apnoea hyponea index (AHI)** independent of other comorbidities[193]. From the Wisconsin cohort study, there was a dose-dependent relationship between the OSA status of an individual and the risk of developing HTN, as AHI of 15 events/hour or more showed 3-fold increase in the incidence of HTN[194].

One particularly important variant to consider is resistant HTN, defined as BP>140/90 mmHg despite being on combination of 3 or more anti-hypertensive medications titrated to their maximal doses OSA was found more frequently in the resistant HTN population, compared to controlled HTN (71% *vs.* 38%)[195][196].

This relationship was further strengthened by the evidence of decrease in daytime BP with the treatment of OSA in patients with resistant HTN[197].

Obese persons often have obstructive sleep apnoea, which may contribute to nocturnal hypertension by causing frequent arousal from sleep and resulting sympathetic activation.

Increased blood pressure in patients with OSA is **multifactorial in origin** and may depend on **sympathetic overactivity**, **systemic inflammation**, **oxidative stress**, **endogenous vasoactive factors**, and **endothelial dysfunction**[198][199]**.** Elevations in blood pressure are due to *augmented sympathetic nervous system* activation as well as alterations in the renin-angiotensin–aldosterone system and fluid balance.

A *potentiated CB chemoreceptor reflex* and associated increase in sympathetic nerve activity play major roles in the pathogenesis of sleep apnea-induced hypertension.

Early aberration resulting in persistent hypertension in OSA might be the **sympathetic-mediated hypertensive response exposing to nighttime desaturation**[200] , which was demonstrated by IH experiments in individuals without OSA or CAD. In addition, the close relationship between **noradrenaline** level and **AHI** may advocate the **potential effect of increased sympathetic tone on the onset and pathogenesis of hypertension in OSA** patients. The causal connection between hypertension and OSA is also indicated by **hyperactivation of sympathetic system persisting to wakefulness**[201]**.**

Moreover, **circulating pro-inflammatory markers** are found to be **elevated in hypertensive patients with OSA**, with the **exception of a significant rise in sympathetic activity**. These proinflammatory markers include **IL- 6**, **TNF-α**, **high-sensitivity C-reactive protein (hs-CRP)** and **asymmetric dimethylarginine**[202]**.**Among them, **TNF-α** serves as an independent inflammatory factor closely tied with **hypertension** or **OSA**[203]**.**

OSA and AF

Prevalence of SDB in patients with AF is 40% to 50%[206].

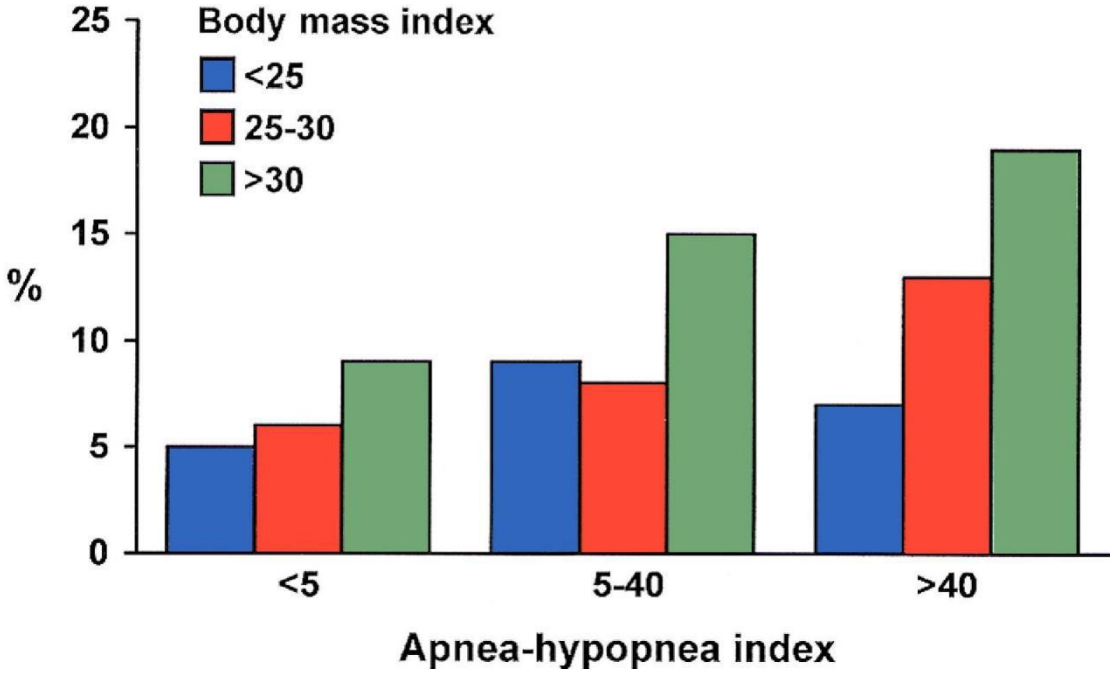


Fig.25. Incidence of atrial fibrillation based on the severity of OSA and obesity.Cumulative frequency of incident atrial fibrillation (AF) during an average 4.7 years of follow-up, based on interactions between the body mass index (BMI) and the apnea-hypopnea index (AHI). An AHI <5 represents no obstructive sleep apnoea (OSA), an AHI 5 to 40 represents mild to moderate OSA, and an AHI >40 represents

severe OSA. A BMI <25 represents normal weight, a BMI 25 to 30 kg/m2represents overweight, and a BMI >30 kg/m2represents obesity[207].

Pathogenesis of AF in OSA:

AF is the most common sustained arrhythmia associated with OSA.

There are several possible mechanisms for AF in patients with OSA. **Acute apneic episodes** lead to **hypoxia** and **hypercapnia**, **alterations in intrathoracic pressure**, **increased sympathetic tone**, and **autonomic dysregulation**. Repetitive episodes of apnoea and hypopnea during sleep result in **abrupt intrathoracic negative pressure alterations** and chronic recurrence.Chronic recurrence and abrupt negative changes in intrathoracic pressure may lead to **structural and functional atrial remodeling** and cause **atrial fibrosis** with **downregulation of connexin** and **electrophysiological alterations**[208].

In addition, **sympathetic hyperactivity** induced by apnoea during OSA can evoke **myocardial excitability**, causing the beginning of **AF** .

Indeed, the reduction in nighttime oxygen saturation has been regarded as a predictor of incident AF, and the decreasing level as well as the duration may be used to predict AF severity in patients with OSA [209].

Acute factors of OSA effecting onset of atrial fibrillation

Acute factors directly associated with obstructive respiratory events can contribute significantly to the incidence of AF in OSA, such as changes in intrathoracic pressure, changes in blood gases, and sympathovagal imbalance

Changes in intrathoracic pressure: Obstructed inspirations cause significant intrathoracic pressure variations, resulting in changes in the transmural pressure of the heart, resulting in atrial stretch. Arrhythmogenic atrial electrophysiological alterations can result from acute atrial dilation caused by thoracic pressure fluctuations[210].

Orban and colleagues used the Mueller maneuver to replicate OSA in 24 healthy young

Adults [211]. The Mueller maneuver entails forcing air into the lungs through a closed mouth and nose to create a significant negative pressure in the chest.They discovered that the left atrial volume decreased significantly during the procedure, and the LV end-systolic dimension increased, indicating that the LV ejection fraction decreased.Following the maneuver, blood flow, stroke volume, ejection fraction, and cardiac production increased above usual.

Repetitive swings in afterload burden and chamber volumes, they hypothesized, may also have outcomes for AF and coronary heart failure development within the future.

Blood gas changes: OSA causes frequent episodes of hypoxia and hypercapnia, which activate the chemoreflex and increase sympathetic nerve activity, causing tachycardia and high blood pressure, particularly at the end of apneic attacks[211][212]

Myocardial oxygen demand rises due to tachycardia and hypertension, while myocardial oxygen supply falls due to hypoxia causing recurrent myocardial ischemia while sleeping, which induces atrial and ventricular fibrosis, arrhythmias in the atrium and ventricles, as well as sudden cardiac death[211][212] [213]

Sympatho-vagal imbalance: The imbalance between the sympathetic action from apneic episodes and natural predominance of parasympathetic system during sleep, results in sympatho-vagal imbalance, a mechanism widely thought to be responsible for initiation and maintenance of AF in humans[206].

Direct muscle sympathetic nerve activity recordings showed increased sympathetic activation in OSA patients during apnoea episodes. Linz et al. found that in a pig model of OSA, the negative intratracheal pressure produced by forced inspiration triggered the parasympathetic nervous system that is known to stimulate afferent vagal fibers in the thorax[214].

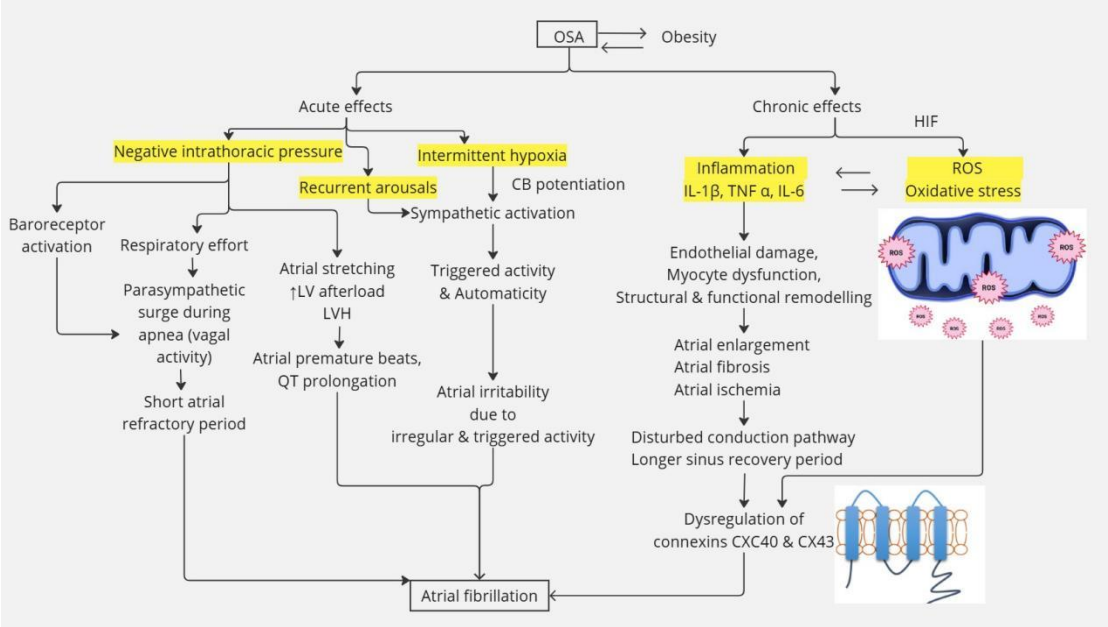


Fig.26. Pathogenetic link between Sleep apnea and Atrial fibrillation

Long-term effects of OSA on atrial structural remodeling

Long term OSA is associated with extensive atrial remodeling that disturbs local conduction pathway and causes longer sinus node recovery period[206].

Major atrial remodeling marked by 'atrial enlargement, local conduction disruptions and longer sinus node recovery,' atrial electromechanical delay, and left atrial dysfunction, is correlated with long-term OSA in patients[215].

Several mechanisms, including systemic inflammation, neurohumoral activation, and persistent atrial dilation by repeated changes in intrathoracic pressure and multiple comorbidities such as obesity and hypertension, have been considered to cause OSA-related myocardial damage.

Neurohumoral activation and inflammation: OSA is related to elevations of circulating inflammation markers, and in patients who may undergo atrial structural and electrical remodeling, neurohumoral activation, namely the circulating RAAS combined with increased oxidative stress, has been demonstrated [210].

OSA is an independent risk factor for AF in patients without other cardiac comorbidities. There is a 4-fold increase in the prevalence of AF in patients with severe OSA (AHI ≥ 30) compared with those without OSA[219].

Sleep apnoea and heart failure

Obstructive sleep apnoea and Cheyne-Stokes breathing are common in patients with **heart failure.**

Prevalence of sleep apnoea in heart failure is 50-70%. More than nearly half of HF patients (with either retained or decreased ejection fraction) have SDB[223].

OSA is highly prevalent and associated with adverse outcomes in patients with HF. The impairment degree may be dependent upon the severity of OSA[224].

Patients with HF are also at increased risk for central sleep apnoea (CSA). The overall **prevalence of sleep-disordered breathing among patients with symptomatic HF** is **40% to 60%**, with **OSA making up approximately one-third of the cases**. Most studies involving patients with HF reported roughly **equal proportions of OSA and CSA**. However, in a meta-analysis of 2570 patients with HF with reduced ejection fraction and **moderate to severe sleep apnoea, CSA represented the dominant phenotype in >70% of cases**. It was reported that the overall prevalence of OSA among HF patients fluctuates from 15% to 50%, and is more common in men compared with women with HF[196].

In patients with HF, SDB is increasingly recognized as a predictor of poor prognosis and a disease process that may speed up the decline of heart function.

Pathogenetic pathway linking sleep apnea to heart failure:

The pathophysiological effects of OSA relevant to HF are mediated by several mechanisms, including neurohormonal activation, increased oxidative stress and inflammation, acute increases in preload and afterload related to large intrathoracic pressure swings, and exacerbation of systemic hypertension.

Some patients such as those with obesity and HF with reduced ejection fraction may have a mixed picture of CSA and OSA.

Intrathoracic pressure change: During inspiration, in cases of OSA, the negative intrathoracic pressure created by the respiratory muscles attempting to inspire against a closed airway increases venous return to the right heart, increases preload, and causes the septum to move to the left, which may compromise the role of the left ventricle (LV). During episodes of negative intrathoracic pressure, which raises the afterload, enhanced preload further compromises the capacity of the failing LV to cope by increasing transmural pressure[225].

Intermittent hypoxia: Sleep apnoea associated hypoxia is an independent predictor of damaged ventricular diastole and myocardial contractility. It can also contribute to oxidative stress and myocardial impairment, en route to myocardial dysfunction manifested as lower left ventricular ejection fraction (LVEF) and systolic/diastolic dysfunction[226].

Sympathetic activation : Apnea and hypopnea stimulate the sympathetic nervous system[225]. OSA is related to a rise in sympathetic activity, and this further contributes to extra peripheral vasoconstriction, tachycardia, and salt and water retention stimulation of the renin-angiotensinaldosterone system (RAAS)[225].

The damping of this response is considered essential for improving the long term prognosis in the neurohormonal model of HF.

In those with OSA and HF, serum catecholamines and muscle sympathetic nerve activity are higher than matched controls with HF only.Rostral nocturnal fluid shift: In men without HF, the amount of fluid displaced overnight from the legs correlated strongly with a rise in the circumference of the neck overnight and the frequency of hypopnea and obstructive apnoea per hour of sleep (i.e., AHI)[227]. Hence fluid displaced from the legs into the neck increased the tendency for pharyngeal obstruction .Therefore, it is conceivable that overnight rostral fluid displacement into the neck in patients with HF, a disorder characterized by dependent fluid retention in the legs, might also lead to OSA pathogenesis.

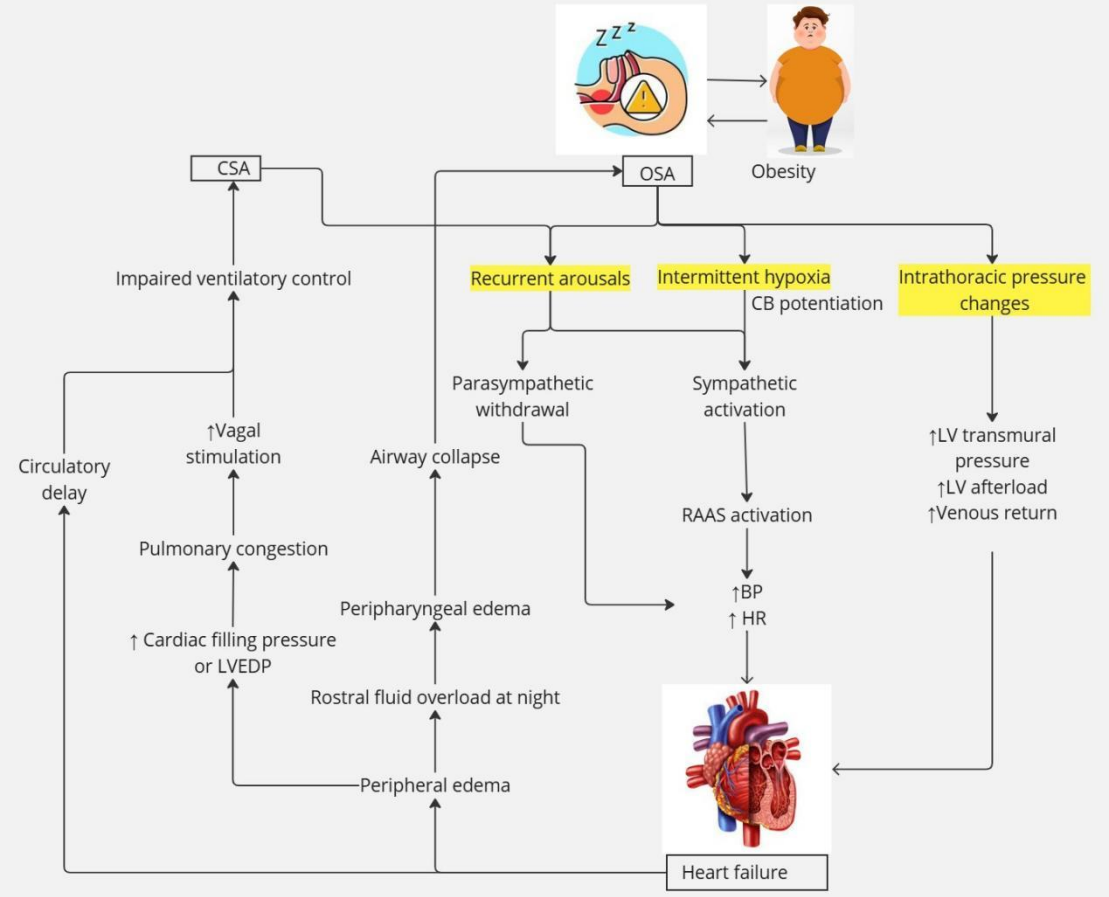


Fig.27. Pathogenetic link between Sleep apnoea and Heart failure.

In the absence of indications, such as prolonged daytime sleepiness, screening for SDB is not usually done in HF patients. Therefore, in patients with HF, sleep apnoea remains a widely underdiagnosed disorder [228].

It perhaps comes as no surprise, given the pathophysiological effects of SDB, that SDB is associated with poor outcomes in people with HF and the general population[225].

Sleep apnoea is independently associated with an increased risk of adverse outcomes, including HF related symptom progression, hospitalization, and mortality.

Meanwhile, the morbidity rate is high in patients with co-existing systolic and diastolic HF. Moreover, the result of SHHS cohort displayed that patients without HF but diagnosed with OSA are at higher risk of subsequent HF. Indeed, male patients with severe OSA are prone to HF at a higher risk of 58% compared with those without OSA[229].

Sleep apnoea and coronary artery disease

OSA independently increases the risk of coronary events.In particular, the prevalence of SDB in CAD patients is doubled compared with the general population and more than 70% patients for acute coronary heart disease are afflicted with undiagnosed OSA. Moreover, coronary artery calcification, a subclinical coronary disease indicator, is identified in 67% patients with OSA versus in 31% patients without OSA. Plaque instability and vulnerability are deemed much severer in patients with OSA than in patients without OSA[231].

Pathogenetic mechanisms :

Chronic intermittent hypoxia: Chronic intermittent hypoxia induced atherosclerosis with endothelial dysfunction are the thought to be the main causes of CAD in OSA patients. Many clinical studies have shown significant evidence to support the association between the two diseases. Severe OSA patients with AHI > 30 showed significantly higher risk of cardiovascular events, including acute coronary syndrome (ACS), myocardial infarction (MI) and stroke[232]. AHI was also found to have strong correlation with atherosclerotic volume when measured by imaging through intravascular ultrasound. The **repetitive hypoxemia and reoxygenation** elicited by OSA may result in **oxidative stress** and systemic inflammation, which contribute to **coronary atherosclerosis** and **acute myocardial infarction (MI)** events.

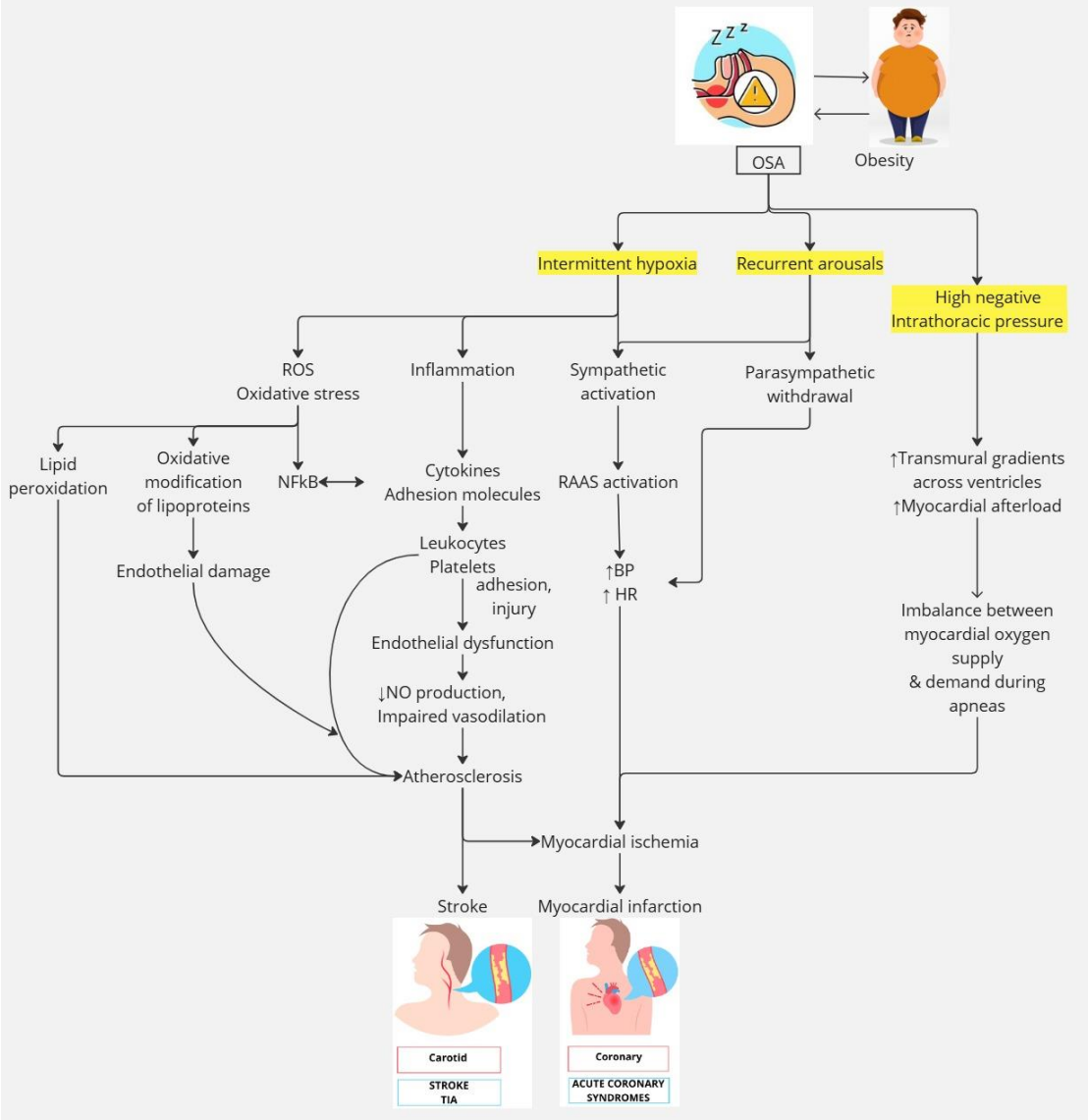


Fig. 28 Pathogenetic role of sleep apnoea in cerebrovascular diseases.

OSA has also been implicated in **coronary artery calcification**, **plaque instability**, and **plaque vulnerability** and has been associated with a **2-fold increase in risk of cardiovascular events or**

death.The **severity of hypoxemia is a major determinant of ST depression occurring during sleep**, and in patients with OSA, the onset of **MI is more likely to occur during the nighttime**.

Furthermore, OSA has been associated with a higher risk of nocturnal ischemic events and appears to trigger the incidence of sudden death at nighttime. It was reported that 32% OSA patients would suffer from MI attack between 12 AM and 6 PM compared with 7% in non-OSA patients[233].

This is likely explained by the fact that nocturnal hypoxia caused by OSA is predisposing this group of patients to nocturnal MI.

Moreover, myocardial ischemia is commonly mediated by inflammation with a key contribution from endothelin and HIF-1α. It was also reported that the incongruity between increased oxygen demand and decreased oxygen supply at night can aggregate myocardial ischemia in OSA patients[234].

High negative intrathoracic pressure: Airway obstruction during OSA can lead to recurrent high negative intrathoracic pressure that increases transmural gradients across the ventricles and thus myocardial afterload, leading to a rise in myocardial oxygen demand during the apneas, a fact that combined with the diminished oxygen supply can cause myocardial ischemia in some patients, such as patients with preexisting CAD[235]..

Sympathetic overactivity: OSA leads to an increased sympathetic activity due to hypoxia and hypercapnia, resulting in an increase in blood pressure and resting heart rate that may induce myocardial ischemia[236] The final pathogenic mechanism of an ACS is coronary artery thrombosis as a result of the loss of integrity of the covering of an atherosclerotic plaque, due to rupture or erosion, and subsequent platelet adhesion, activation, aggregation and thrombus formation . Several studies have reported increased platelet activity in OSA patients , associated with oxygen desaturation and reduced fibrinogen concentrations and fibrinolytic activity in OSA patients , among other abnormalities in the coagulation system . These alterations have also been found to be reduced after CPAP treatment[237] .

Patients with ST-segment–elevation MI who also have OSA have lower 18-month event-free survival.

Sleep apnea and Cerebrovascular Disease

OAS triggers the development of stroke and associated unfavorable clinical outcomes in patients with established stroke.

Ischemic strokes or cerebrovascular accidents were found to be higher in patients with OSA from multiple cross-sectional and prospective cohort studies .

The prevalence of OSA is higher among patients with stroke ranging from **50% to 80%** compared with normal controls. Recurrent stroke patients suffer from a higher OSA morbidity compared with those with first-time stroke (74% to 57%)[240].An association is also deciphered between deteriorative OSA severity and higher risk of stroke and death. For example, every 10-unit rise in AHI is associated with a 36% increase in the odds ratio in cerebrovascular event[241].

Poststroke, 60–80% of patients have OSA with a respiratory disturbance index (RDI) > 10. Risk of stroke in patients with OSA increases with increasing AHI, rising from 1.75 relative risk if AHI is < 12 to 3.30 if the AHI is > 36. About 54% of strokes occur at night in OSA patients, whereas stroke incidence is greatest in the first few hours after awakening in the general population[242].It is important to note that this higher risk of CVA in OSA patients are independent of other CVD risk factors whose incidence may have also been influenced by the presence of OSA, such as HTN, HF, Atrial Fibrillation(AF) and DM2.

Proposed mechanisms of pathogenesis include altered cerebral autoregulation, altered cerebral perfusion , endothelial dysfunction , pro-thrombotic/inflammatory state, hypertension, oxidative stress, hypercoagulability, atrial rhythm with thrombogenesis, resulting in embolism and mechanical stress on carotid atherosclerosis during periodic apnoea snoring . All these factors place OSA patients at a higher risk of reduced cerebral blood flow, leading to ischemic stroke[197].

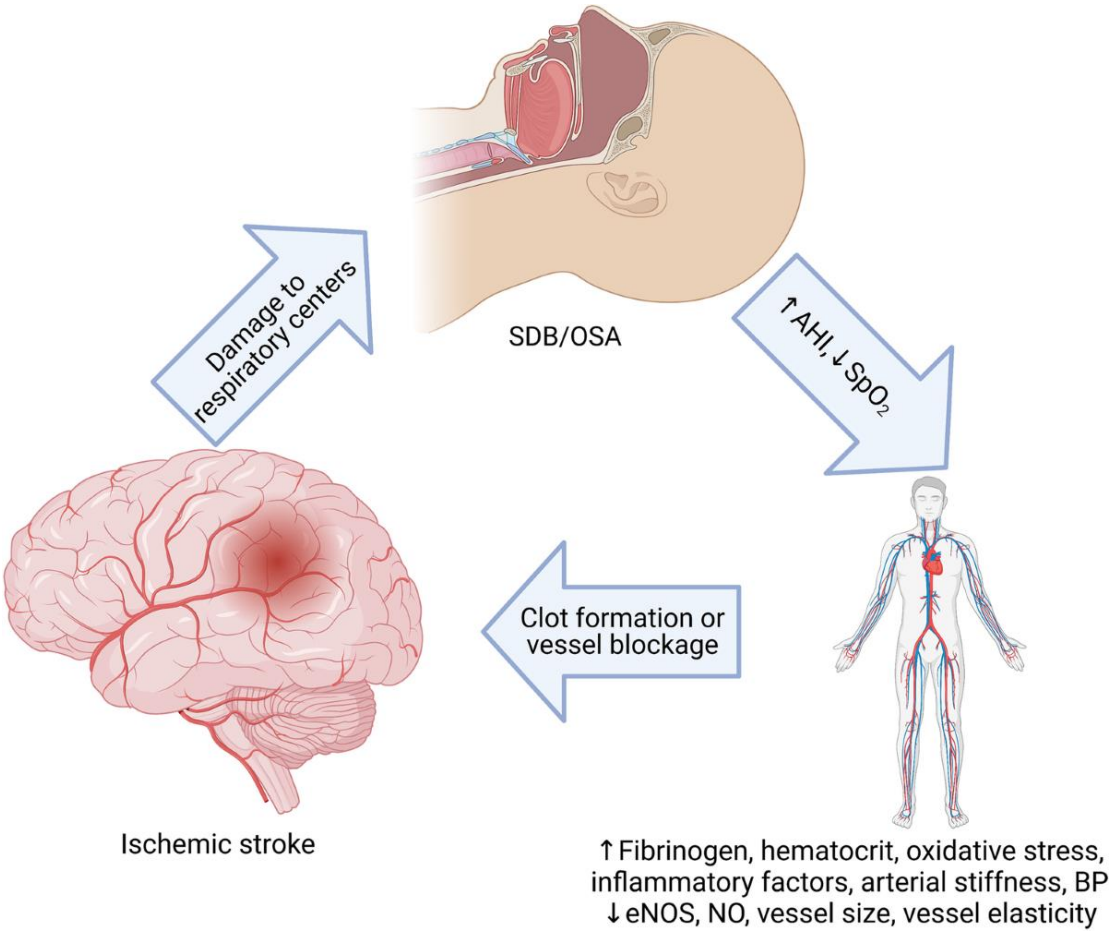


*Fig.29. Pathogenetic mechanism for sleep apnea as a cause of stroke. Ref. Mohamed, B., Yarlagadda, K., Self, Z. et al. Obstructive Sleep Apnea and Stroke: Determining the Mechanisms Behind their Association and Treatment Options. Transl. Stroke Res. **15**, 239–332 (2024). https://doi.org/10.1007/s12975-023-01123-x*

Pulmonary Hypertension

Sleep apnoea, often is overlooked as a cause of pulmonary hypertension.

OSA is closely associated with PH, with a 70%–80% prevalence of OSA in patients diagnosed with PH using right heart catheterization [245].

Patients with obesity hypoventilation syndrome are at greater risk of having PH due to the additional effect of hypercapnia, with a prevalence 59% greater than that among those with OSA alone.Based on several studies, the average prevalence of PH among those with OSA is approximately 20%. This is in contrast to the prevalence of systemic hypertension, which can be as much as 60%[246].

PH associated with OSA is usually mild in the absence of other cardiopulmonary diseases, with an average pulmonary artery pressure between 25 and 30 mmHg. Nonetheless, OSA aggravates

PH disease development and increases mortality in severe PH ascribed to other underlying cardiopulmonary causes[246].

Several risk factors for pulmonary HTN can be commonly found in OSA patients, such as high BMI, obesity-hypoventilation syndrome and nocturnal as well as daytime hypoxemia.

Pathogenesis of PH in the OSA : Main culprit is thought to be nocturnal episodic hypoxia, which reflexively triggers pulmonary arteriolar constriction resulting in sudden, reversible increase in pulmonary artery pressures, involving changes in endothelin, nitric oxide, angiopoietin-1, serotonin and NADPH-oxidase signaling cascades[246]. Angiopoietin-1 (Ang-1) originating from vascular smooth muscle cells is an endothelial selective receptor tyrosine kinase (Tie2) agonist that stabilizes the development of newly formed blood vessels and promotes quiescence and structural integrity of mature vessels. Hypoxia disrupts the constitutive Ang-1–Tie2 signaling by preventing Ang-1 from binding to the receptor. Consequently, loss of Tie2 signaling destabilizes the endothelium and induces an angiogenic response in the presence of vascular endothelial growth factor[247].

The cumulative effect of intermittent hypoxia can lead to polycythemia and PH[247].

In addition, chronic hypoxia provokes proinflammatory pathways leading to pulmonary vascular remodeling and irreversible increases in pulmonary vascular resistance .

As a result of the high frequency of diurnal hypertension and intermittent surges in arterial blood pressure due to respiratory events during sleep, patients with OSA have high prevalence of left ventricular hypertrophy and dysfunction. Left ventricular dysfunction accounts for a large proportion of PH in patients with OSA. However, PH and right heart failure can develop in patients with OSA with preserved left ventricular ejection fraction[247].

More in-depth examination revealed the involvement of ROS generation, increased pulmonary vascular reactivity to hypoxia and right-sided preload from negative transthoracic pressure following airway obstruction in PH pathogenesis associated with OSA.

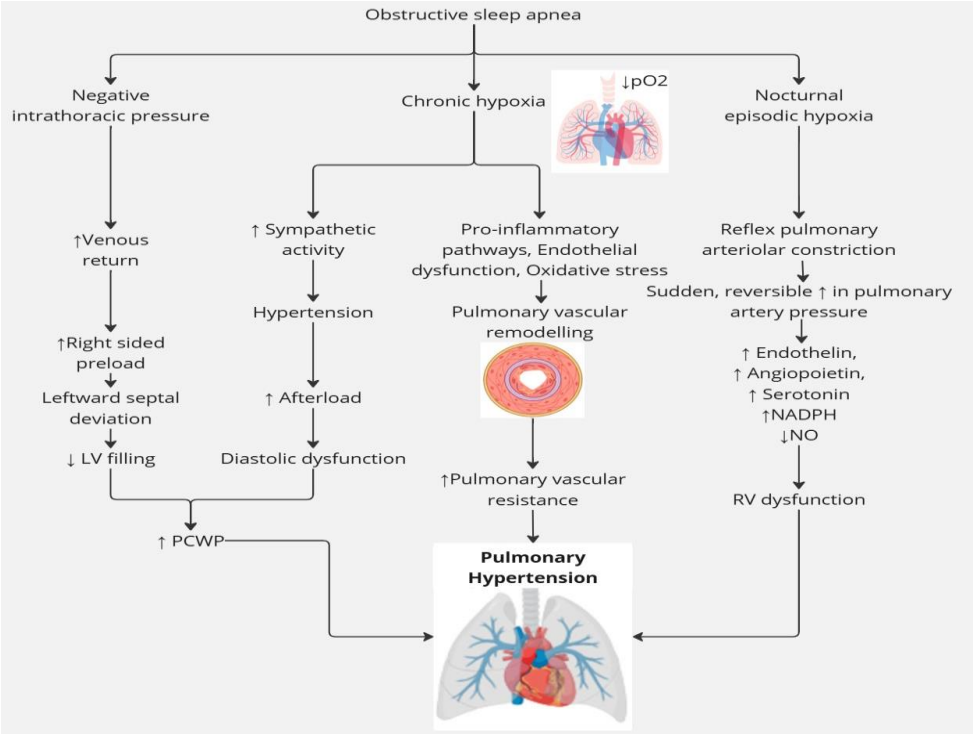


Fig.30. Link between sleep apnoea and pulmonary hypertension.

A sleep study in case of pulmonary hypertension is generally necessary only when indicated by the patient's history. Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnoea or obesity hypoventilation syndrome are observed. Moreover, OSA indirectly deteriorates PH through postcapillary PH in patients with refractory hypertension.

Notably, OSA is a condition with potential for negative feedback in which it worsens conditions that may in turn worsen the OSA (eg, OSA→hypertension→worsened OSA).

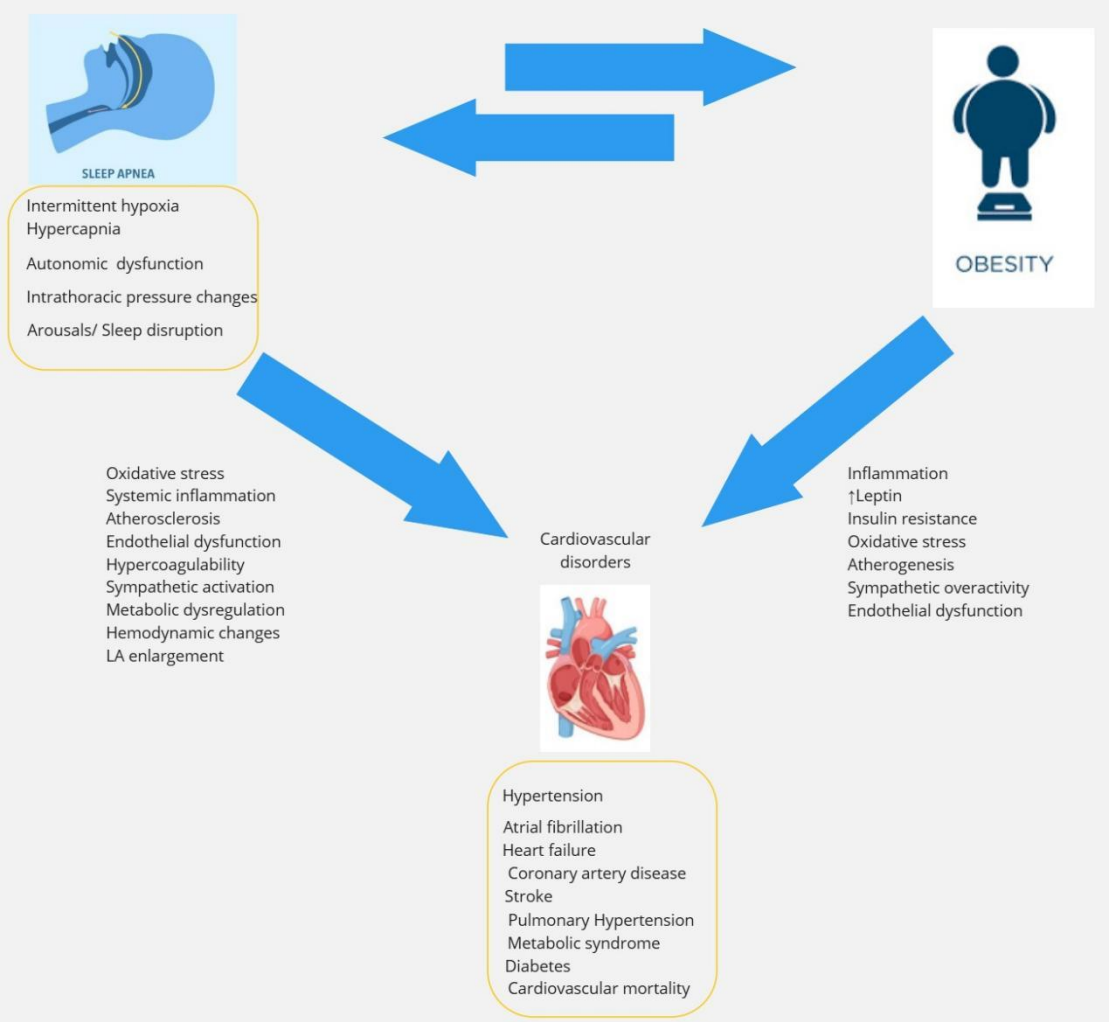


Fig. 31. **The interaction between obesity and OSA, and its cardiovascular consequences. Combination of OSA and obesity probably increases the risk for cardiovascular disorders.**

Sleep apnea screening in cardiovascular diseases

The high prevalence and comorbidity of OSA in patients with CVD, coupled with evidence of improved patient-centered outcomes, mood, and work productivity with OSA treatment in patients with CVD,provide a rationale for OSA screening.

Screening for sleep apnea[27][288]

Recommended for patients with ：

1. Resistant / poorly controlled hypertension

2. Pulmonary hypertension
3. Heart failure
4. Arrhythmias, particularly those with atrial fibrillation
5. Recurent AF after either cardioversion or ablation
6. Stroke
7. Psychiatric disorders
8. Erectile dysfunction

Evaluation for sleep apnoea in obesity and cardiovascular disorders :

Patients undergoing routine health check-up with snoring, daytime sleepiness, obesity, hypertension, motor vehicular accidents (Evidence Quality A, Strong Recommendation) and high risk cases such as congestive heart failure, diabetes mellitus, coronary artery disease, stroke, metabolic syndrome, nocturnal dysrhythmias (Evidence Quality B, Recommended) should undergo a comprehensive sleep evaluation. Additionally, patients with pulmonary hypertension and preoperative cases should also have a comprehensive sleep evaluation. Those suspected to have OSA on comprehensive sleep evaluation should be referred for a sleep study. High risk cases, even if asymptomatic, can be referred for a sleep study. Further, medical examiners evaluating drivers, air pilots, railway drivers and heavy machinery workers should be educated about OSA and should comprehensively evaluate applicants for OSA, if snoring, daytime sleepiness or obesity irrespective of the presence or absence of co morbidities are noted (Evidence Quality B, Strong Recommendation)[27].

Therapeutic potential : Treatment of sleep apnoea as a therapeutic guide to cardiovascular disorders in obesity.

Application of lifestyle modifications can reduce the incidence and consequences of obesity and sleep apnoea as well as decrease the incidence of cardiovascular disease.

The major preventable risk factors to decrease obesity are eating behaviors, smoking, alcoholism, etc.) and understanding the importance of exercise.

Adopting lifestyle changes with weight loss has shown promise in addressing metabolic syndrome and related issues such as inflammation and endothelial dysfunction[149].

The risk of OSA and associated morbidities can be reduced by controlling overweight/obesity, alcoholism, smoking, hypertension, diabetes mellitus, and hyperlipidemia[30].

In addition, treatment of sleep apnoea reduces sympathetic drive and blood pressure and also improve the associated metabolic disorders[43].

Surgery for obesity should be considered in patients with a BMI > 40 kg/m^2 and in those with a BMI > 35 kg/m^2 who have failed other attempts at weight reduction and who have health complications such as sleep apnoea, cardiac failure, uncontrolled diabetes mellitus, or severe venous stasis[289].

Bariatric surgery has consistently reduced major cardiovascular events, particularly coronary artery disease, compared to non-surgical weight management, likely due to substantial weight loss and its impact on long-term obesity[151].

Cardiovascular mortality: Treatment of sleep apnoea improves cardiovascular risk, and the failure to recognize and to treat sleep apnoea may cause failure of weight loss intervention strategies in obesity.

Treatment of OSA has been shown to reduce several markers of cardiovascular risk, improve insulin resistance, decrease the recurrence rate of atrial fibrillation, and improve various outcomes in patients with active cardiovascular disease.[19].

Using adequate nasal continuous positive airway pressure (CPAP) confers a significant **reduction in cardiovascular morbidity**[291].

In observational work examining several PAP patterns, an obvious reduction in mortality was identified with PAP, and HF patients were observed to have a greater risk reduction. Nevertheless, large randomized controlled trials (RCTs) have not shown the impact of PAP on overall survival. Explanations on this incongruity may include low mortality with comparatively short followup duration in clinical trials, preclusion of severe hypoxemia patients during nighttime, and possible confounding bias in given observational studies[184].

In an analysis from the Sleep Heart Healthy Study (SHHS), a 42% reduction in mortality was noted by PAP procedure in severe OSA patients following a 6–7 year followup period[185].

It is important to highlight here the distinct pattern of the potential effect of CPAP treatment on cardiovascular morbidity and mortality. In patients without previous cardiovascular events, treatment with CPAP led to a reduction in the risk of fatal and non-fatal cardiovascular events in men, the elderly, and women with OSA[171].

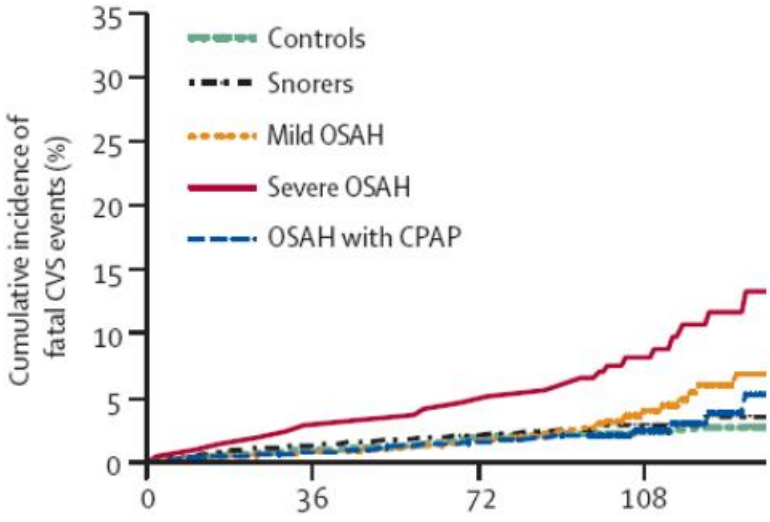


Fig.32. Cumulative incidence of fatal CVS events and Impact of obstructive sleep apnoea (OSA) treatment on primary prevention of fatal cardiovascular events in men. (ref.Marin JM, Carrizo SJ, Vincente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-1053)

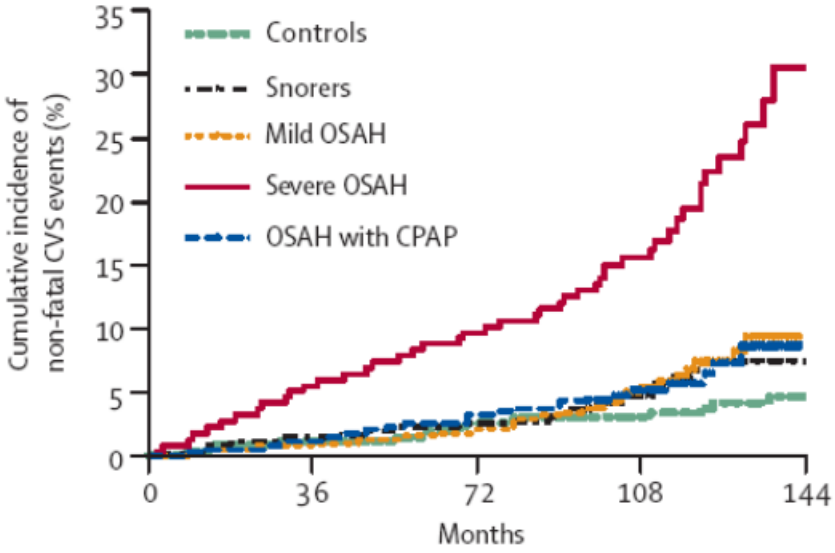


Fig.33. Cumulative incidence of non-fatal CVS events and Impact of obstructive sleep apnoea (OSA) treatment on primary prevention of non-fatal cardiovascular events in men. (ref.Marin JM, Carrizo SJ, Vincente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-1053)

CPAP is the treatment of choice in OSA patients that has been shown to be efficacious in the reduction of CVD. CPAP helps prevent episodes of airway collapse that block breathing to control levels after 6 weeks of CPAP therapy[256].

Serum TNF-a levels were higher in OSAS patients compared with controls and reverted

OSAS patients were also found to have markedly elevated monocyte NF-kB activity that decreased significantly with CPAP therapy[256]

Increased NF-kB activity has been demonstated in circulating neutrophils and raised plasma levels of the NF-kB-controlled gene products, soluble E-selectin and soluble vascular cell adhesion molecule-1 in OSAS patients, with a reduction in NF-kB activity to control levels following CPAP therapy [257].

Heart failure: A recent systematic review and meta-analysis[156] documented that weight loss improves long-term rehospitalization (>3 months), quality of life, cardiac function, and exercise capacity, and bariatric surgery reduces mortality in overweight and obese heart failure patients. The optimal way of weight loss should be selected based on the patient's condition to acquire the best prognosis. Furthermore, a healthy diet and physical activity are also suggested as a corrective action for the heart failure or as a preventive strategy to avoid its development[153].Exercise interventions in patients with heart failure lead to a reduction in adipose tissue, increased blood flow to the respiratory and skeletal muscles, and improved pulmonary function, functional capacity, left ventricular ejection fraction and mitochondrial function. Exercise training, especially aerobic and concurrent interventions, in overweight middle-aged and elderly patients is effective to promote anti-inflammatory responses[158].

Indeed, in obese patients with HFpEF, caloric restriction and aerobic exercise training significantly improve exercise capacity by increasing peak VO2 (peak oxygen consumption)[157].

Regarding pharmacological treatment, beta-blockers can lead to tiredness and reduced exercise tolerance and are associated with weight gain in individuals with overweight or obesity[121].

Sodium glucose cotransporter-2 inhibitors (SGLT2i) are recommended to reduce the risk of heart failure hospitalization and cardiovascular death, and also reduce body weight and blood pressure and improve physical function and quality of life[153].

In addition to the effects of neurohormonal modulators such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and aldosterone antagonists, SDB could be a potential therapeutic target for HF[225].

Although the appropriate treatment of CSA in patients with HF remains somewhat elusive, novel therapeutic approaches such as diaphragmatic stimulation and oxygen therapy are promising and rapidly evolving.

As per ADVENT-HF (Effect of Adaptive Servo Ventilation [ASV] on Survival and Hospital Admissions in Heart Failure) trial, ASV had no effect on the primary composite outcome or mortality but eliminated sleep-disordered breathing safely in patients with heart failure and reduced ejection fraction and sleep-disordered breathing.[230]

In the context of HF, the safety and efficacy of positive airway pressure (PAP) therapies differ between patients with predominant CSA and those with OSA. CPAP appears to be only partially effective in 50% of patients with HF attributable to residual central apneas. Although several small-scale studies have reported benefits associated with CPAP, including improved left ventricular function, reduced sympathetic tone and myocardial oxygen consumption, and lower rates of HF hospitalization and mortality, a meta-analysis of patients with OSA reported that CPAP did not have significant effects on either left ventricular ejection fraction or hospitalization rates.The 2017 American Heart Association/American College of Cardiology HF guideline identified CPAP as a possibly reasonable treatment strategy to improve sleep quality and daytime sleepiness in patients with CVD and OSA.

Treatment with CPAP increases left ventricular ejection fraction by 25–33%.[223]

Atrial fibrillation: Lifestyle changes are protective for atrial fibrillation and reduce its recurrence[162][163].

Intensive weight loss and comprehensive management of cardiometabolic risk factors lead to more significant reduction in atrial fibrillation duration, symptom severity, and intensity[160].Weight loss ≥10 % and long-term sustained weight loss are associated with reduced atrial fibrillation burden and maintenance of arrhythmia-free survival[161].

Physical activity has a central role in addition to weight loss. Indeed, improved cardiorespiratory fitness (≥2 metabolic equivalents) reduces atrial fibrillation recurrence and enhances the beneficial effect of weight loss[164].

Bariatric surgery reduces the risk of new-onset atrial fibrillation[165] and is associated with a significant reversal of the type[166] .

In terms of thromboembolism risk management, obese patients may require higher doses of vitamin K oral anticoagulants (VKAs) and extended treatment initiation periods to achieve therapeutic INR levels[167].

Instead, regarding non-vitamin K oral anticoagulants (NOACs), measurement of serum levels may be necessary in certain situations such as severely obese patients with a BMI exceeding 35 or a weight exceeding 120 kg[168]. However, this approach is discouraged for the majority of patients due to insufficient outcome data[169].

Not surprisingly, risks of coagulability and thrombosis are reported to be decreased following CPAP intervention, although further studies are needed to offer a more definitive evaluation of CPAP treatment on the hypercoagulable state in OSA[284].

In addition, this increased sympathetic trafficking is assumed to play a vital role in OSA patients afflicted with arrhythmia. Based on these opinions, CPAP treatment may provide beneficial effects on attenuating sympathetic overactivation [271].

Multiple small and mostly retrospective observational studies have assessed the ability of CPAP to reduce AF burden after ablation or cardioversion. Although limited by methodological issues and small sample size, these studies largely support the view that CPAP therapy improves AF burden. This is independent of the modality for rhythm control, including antiarrhythmic drug therapy, direct current cardioversion, or catheter ablation.

Numerous observational studies have indicated that CPAP intervention is linked to a low AF recurrence rate following ablation or electrical cardioversion, in particularly, a lower risk for the development of more permanent AF and occurrence of paroxysmal AF[220][221].

Notably, young, male gender and obese patients may benefit most from CPAP therapy. Based on this finding, AF-connected OSA presents a higher AF recurrence rate following cardioversion and a higher risk of catheter ablation failure[222].

A recent meta-analysis has also shown that patients treated with CPAP had 42% decreased risk of AF compared to ones who were not treated[216].

Recurrence of AF after radiofrequency ablation was also 25% higher amongst patients with OSA[217] .CPAP therapy was associated with lower rate of recurrent AF compared to untreated patients [218].

Overall, the data supports a reflects strong relationship between OSA and AF in their pathophysiology and a potential benefit of CPAP therapy in improving cardiovascular outcomes in patients with AF.

Insulin resistance: Several studies revealed that such glucose metabolism change is reversible with CPAP, whereas others noted the opposite outcome[286].

Indeed, CPAP treatment is more profitable to glycemic normal in non-obese individuals, while CPAP is less likely to evoke improvement on IR symptom in obese patients without weight loss[287]. CPAP treatment has shown to improve glucose control in type 2 diabetics with blood sugars not controlled with medications. This effect is achieved by increasing insulin secretion and reduced counter-regulatory hormone production[290].

Hypertension: OSAS is a common and treatable risk factor for the development of hypertension, heart failure and stroke, especially in men[290].

Among the cardiovascular comorbidities of sleep apnoea, systemic HTN has shown the strongest evidence for benefit [195] It is recommended that OSA patients with HTN, especially for those with moderate to severe symptoms, and those with resistant HTN be treated with CPAP[195].Sleeping with a nasal continuous positive airway pressure (CPAP) device is the treatment of choice because as the sleep apnoea improves, BP tends to improve as well.

Compared with the conventional therapy, CPAP treatment is associated with a 2 to 2.5 mmHg fall in systolic blood pressure (SBP) and a 1.5 to 2 mmHg drop in diastolic blood pressure (DBP) with a 24-hour blood pressure monitor, with a more pronounced response in resistant hypertensive patients[204]. Although the reduction range is relatively moderate, it was demonstrated that even a subtle reduction in blood pressure may be associated with overtly drop in cardiovascular risk. Moreover, CPAP may lower

blood pressure more significantly in patients with more severe OSA, good CPAP adherence and no hypertension drug therapeutic history[205].

CPAP adherence is associated with greater reductions in nocturnal BP. Even in patients with OSA with resistant hypertension, a 3-month treatment with CPAP (versus no CPAP) reduced 24-hour systolic, mean, and diastolic BPs by ≈3 mmHg, with a significant correlation between hours of CPAP use and BP reduction. Although the overall impact of CPAP on blood pressure levels is relatively modest (averaging 2–4 mmHg), larger improvements are observed among patients who have a high AHI, report daytime sleepiness, or who have resistant hypertension[19].

Non-CPAP therapies also may have a role in hypertensive patients with OSA. In a metaanalysis of oral appliance treatments (eg, soft-palate lifters, tongue-retaining devices, mandibular advancement appliances), BP reduction was similar to that noted in the meta-analysis of CPAP trials (2–3 mmHg). Uvulopalatopharyngoplasty may be beneficial in selected patients, with significant decreases of 4-9 mmHg reported at 6-24 months after surgery in a small randomized controlled trial.

Pulmonary hypertension:

Multiple observational studies indicated that management of OSA with CPAP offers potential benefit to PH. Following CPAP treatment, PH patients exhibit moderate decreases in pulmonary artery pressure, pulmonary vascular resistance as well as pulmonary vascular reactivity to hypoxia[248].

The available literature is limited by size and study design but suggests potential benefit associated with treatment of PH with CPAP. Observational studies have found consistent yet modest reductions in pulmonary artery pressure (≈5 mmHg) and pulmonary vascular resistance among PH patients receiving CPAP therapy.

CPAP treatment can effectively lower the pulmonary artery pressure and vascular reactivity to hypoxia, leading to treatment benefit of OSA in patients with Pulmonary HTN[249].

Atherosclerosis and CAD: In patients with obesity and coronary artery disease, a comprehensive risk assessment and multidisciplinary management are required to treat this major comorbidity. Behavior modifications, healthy diet, and increased physical activity are strongly recommended. Weight management and intentional loss are critical to significantly reduce the risk of future adverse clinical events in these type of patients[148].

Medical weight loss interventions are suggested to supplement lifestyle modifications and maintenance of weight loss over time, however clinical trials have not consistently showed the reduction of coronary artery disease rates[150].

OSA may be implicated in an increased risk of major adverse cardiovascular events after percutaneous coronary intervention. Whether CPAP therapy decreases the risk of MI remains controversial.

Reminiscent of its beneficial roles in hypertension, HF and arrhythmia, CPAP treatment might be a benchmark for favorable prognosis in CAD. It can reduce the occurrence of new cardiovascular events and cardiovascular mortality in OSA patients with CAD comorbidity compared to CPAP-intolerant ones[238].

Treating severe OSA patient has also shown significant reduction in the risk of CAD as patients who received successful CPAP therapy had lower incidence of fatal and nonfatal cardiovascular events[232].

A 4-month CPAP treatment may relive early atherosclerotic signs including thicknesses of artery and carotid intima-media as well as levels of catecholamine and hs-CRP[239].

Metabolic syndrome : In a nonrandomized study, Dorkova et al. showed that CPAP therapy reduced several components of the metabolic syndrome in patients who used CPAP for 4 h/night for 8 weeks, including blood pressure, triglyceride levels, and glucose levels, compared with patients with low adherence to CPAP (<4 h/night). More recently, Sharma et al. performed a crossover, double-blind, randomized study exploring the impact of treatment with CPAP for 3 months on components of the metabolic syndrome. In this study, treatment with CPAP (vs. sham CPAP [i.e., a placebo]) was associated with significant mean decreases in systolic blood pressure, diastolic blood pressure, serum total cholesterol levels, low-density lipoprotein cholesterol levels, triglyceride levels, and glycated hemoglobin. The prevalence of the metabolic syndrome was significantly reduced after CPAP therapy (reversal found in 11 of 86 patients [13%] undergoing CPAP therapy vs. 1 of 86 [1%] undergoing sham CPAP) . Surprisingly, treatment with CPAP also reduced BMI and visceral adiposity, which may partially explain the metabolic improvement. The reduction in BMI and visceral adiposity after the use of CPAP for the treatment of patients with OSA is in contrast to other reports.

However, none of the studies discussed in the preceding text fully controlled for physical activity and diet pre-intervention and post-intervention. Further studies are necessary to clarify these important issues.[286][292][293][294]

Stroke : Potential therapeutic benefit from the treatment of OSA is unclear at the moment as limitations in maintaining chronic CPAP treatment with CVA patients have been identified.

Nevertheless, it may be beneficial to offer CPAP treatment initially to CVA patients as it would reduce the influence and recurrence of other cardiovascular risk factors .Observational studies have provided compelling evidence to support a favorable outcome of CPAP on cerebrovascular events and stroke recovery in patients with OSA[243].

However, the adherence and tolerability of CPAP treatment are unsatisfactory in patients recovering from stroke compared with those without stroke. Better compliance for therapy and early intervention following stroke onset are considered crucial components for clinical outcome [244].

Conclusion

Obstructive sleep apnoea syndrome is a common medical disorder that is growing in prevalence worldwide. It is characterised by recurrent cycles of intermittent hypoxia and

there is increasing evidence that intermittent hypoxia plays a role in the development of cardiovascular risk in obstructive sleep apnoea syndrome patients through the activation of inflammatory pathways. Scope exists for further studies demonstrating a direct linkage between inflammation and markers of atherosclerosis and cardiovascular disease in

obstructive sleep apnoea syndrome, as currently only one study exists in the field.

The hypoxia-sensitive transcription factors hypoxia-inducible factor-1 and nuclear factor-kB appear to play a key role in mediating the inflammatory and cardiovascular consequences of the disease. Expanding our understanding of these pathways, the interaction between them and the potentiation of inflammation by intermittent hypoxia

will yield novel therapeutic targets with the scope to reduce cardiovascular risk in obstructive sleep apnoea syndrome.Obesity and OSAS adversely affect cardiovascular system and the Sleep apnoea-obesity relationship should not be ignored when considering prevention and treatment of cardiovascular disorders.Comprehensive clinical trials addressing the efficacy and efficiency of current or potential treatments on therapeutic applications in the OSAS-obesity relationship are needed.

Obesity in both the developed nations and developing nations like India, has reached its epidemic state and the prevalence of its related diseases, such as OSA and CVD are also rising. With the trend expected to rise in the future, it is important to understand the association between these two obesity-related diseases, in efforts to reduce the burden on the rising healthcare expenditure that is increasing.

Current available research work and literature suggests intermittent hypoxia, sympathetic overactivity and intrathoracic changes as chief pathophysiological mechanisms underscoring OSA-evoked CVD .

As one of the major cause of death worldwide, it is essential to recognize the pathophysiology of CVD and factors potentially contributing to its onset in obesity and sleep apnoea.

Though numerous complications have been identified concerning OSA, there are still major gaps in scientific and clinical knowledge, including exact mechanisms through which OSA causes unfavorable cardiovascular events and proper therapeutic medication for OSA. A better understanding of the mechanisms underlying OSA-related CVDs should assist better recognition and intervention of OSA anomalies. There is an urgent demand for translational studies along with large RCTs to decrease cardiovascular risks attributed to OSA.

Despite the proven tight relationship between OSA and cardiovascular complications, OSA is always underrecognized and undertreated in particular in relevance to cardiovascular field. Given the significance of early OSA identification, it is recommended that CVD patients should be screened for OSA, while all patients with OSA should be subject to immediate and intense treatment.

To-date, CPAP therapy has been proven to improve cardiovascular anomalies of OSA. Nonetheless, the exact mechanisms of this amelioration require further investigations. Follow-up sleep tests should be implemented to evaluate the effectiveness of CPAP

treatment due to its limited adherence. Moreover, innovative and valid options for therapy (e.g., mandibular devices and neural stimulation methods) as well as evidence of risk reduction are critical following steps in relieving medical and financial burdens of OSA.

References.

1. ***Alfred F. Tallia, MD, MPH Joseph E. Scherger, MD, MPH Nancy W. Dickey, MD*** *Swanson's Family medicine review Ninth edition*
2. *GBD 2019 Risk Factor Collaborators. "Global Burden of 87 Risk Factors in 204 Countries and Territories, 1990–2019: a systematic analysis for the global burden of disease study 2019". Lancet. 2020;396:1223–1249*
3. *Okunogbe et al., "Economic Impacts of Overweight and Obesity." 2nd Edition with Estimates for 161 Countries. World Obesity Federation, 2022. 3. www.who.int*
4. *NCD Risk Factor Collaboration (NCD-RisC) estimates, 2022*
5. *All India and State/UT-wise Factsheets of National Family Health Survey (NFHS) - 5, 2019-2021*
6. *Disorders of adipose tissue and obesity Chapter 18.11 Shashank R Joshi p1275 API textbook of medicine Ninth edition YP Munjal*
7. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S–209S.*
8. *J Assoc Physicians India 2009; 57: 163-70.*
9. *K.G.Sruthi, Sushil Mathew John, Sam Marconi David; Assessment of obesity in the Indian setting: A review , clinical epidemiology and global health volume 23*

10. ***Stephen O'Rahilly, I. Sadaf Farooqi Chapter 401 Pathobiology of obesity*** *p 3088 Harrison's principles of internal medicine 21st edition*
11. *KGMM Alberti et al for the IDF Epidemiology Task Force Consenssus Group: Lancet 366:1059, 2005*
12. *J Alastair Innes,Anna R Dover,Karen Fairhurst , Macleod's clinical examination. 14th edition.*
13. *Misra A, Nigam P, Hills AP, Chadha DS, Sharma V, Deepak KK, Vikram NK, Joshi S, Chauchan A, Khanna K, Sharma R, Mittal K, Passi SJ, Seth V, Puri S, Devi R, Dubey AP, and Gupta S for Physical Activity Consensus Group ; Consensus Physical Activity Guidelines for Asian Indians*
14. *Revised definition of obesity in Asian Indians living in India Anoop Misra, Naval K Vikram , Amerta Ghosh , Piyush Ranjan , Seema Gulati ; India Obesity Commission Members.*
15. *Madhu SV , Kapoor Nitin, Das Sambit, Raizada Nishant, Kalra Sanjay ; ESI Clinical Practice Guidelines for the Evaluation and Management of Obesity In India.*
16. *2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society*
17. *Shanna Tucker, Carolyn Bramante, Molly Conroy , Angela Fitch, Adam Gilden , Sandra Wittleder , Melanie Jay ' The Most Undertreated Chronic Disease: Addressing Obesity in Primary Care Settings*
18. *Sleep Related Breathing Disorders p 1764-1766 chapter 23.15 R Narasimhan, AR Gayathri. API textbook of medicine Ninth edition YP Munjal*
19. *Andrew Wellman, Daniel J. Gottlieb, Susan Redline ;* ***Sleep Apnea*** *p2204-2209 Chapter 297 Harrison's principles of internal medicine 21st edition,*
20. *ATUL MALHOTRA AND FRANK POWELL ;* ***DISORDERS OF VENTILATORY CONTROL*** *p 524 Chapter 80 Goldman cecil medicine 26th edition*
21. *BRADLEY V. VAUGHN AND ROBERT C. BASNER, Sleep Disorders p2376-2380 Chapter 377 Goldman-Cecil Medicine.*
22. *Arredondo E, Udeani G, Panahi L, Taweesedt PT, Surani S. Obstructive sleep apnoea in adults: what primary care physicians need to know. Cureus 2021, 13: e17843*
23. *McNicholas WT, Bonsigore MR, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respiratory J 2007, 29: 156–178*
24. *Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, Goldberg AN, et al. Obstructive sleep apnoea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc 2019, 8: e010440*
25. *Akashiba T, Kawahara S, Akahoshi T, Omori C, Saito O, Majima T, Horie T. Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnoea syndrome. Chest 2002, 122: 861–865*
26. *Carratù P, Di Ciaula A, Dragonieri S, Ranieri T, Matteo Ciccone M, Portincasa P, Resta O. Relationships between Obstructive Sleep Apnoea Syndrome and cardiovascular risk in a naïve population of southern Italy. Int J Clin Pract 2021, 75: e14952*
27. Consensus & Evidence-Based INOSA GUIDELINES (INdian initiative on Obstructive Sleep Apnea Guidelines) First Edition-2014

28. Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnoea? The rational clinical examination systematic review. *JAMA.* 2013;310(7):731-741

29. Krishnan V, Dixon-Williams S, Thornton JD. Where there is smoke… there is sleep apnoea: exploring the relationship between smoking and sleep apnoea. *Chest*. 2014;146(6):1673-1680

30. Mitra AK, Bhuiyan AR, Jones EA. Association and Risk Factors for Obstructive Sleep Apnea and Cardiovascular Diseases: A Systematic Review. Diseases. 2021 Dec 2;9(4):88. doi: 10.3390/diseases9040088. PMID: 34940026; PMCID: PMC8700568.

31. *Andrew Wellman, Daniel J. Gottlieb, Susan Redline ;* ***Sleep Apnea*** *p2205 Chapter 297 Harrison's principles of internal medicine 21st edition*

32. Bairam A, Uppari N, Mubayed S, Joseph V. An overview on the respiratory stimulant effects of caffeine and progesterone on response to hypoxia and apnea frequency in developing rats. *Adv Exp Med Biol* 2015, 860: 211–220

33. Balachandran JS, Patel SR. In the clinic: obstructive sleep apnea. *Ann Intern Med*. 2014;161(9):ITC1-ITC15.

34. Bixler EO, et al. Prevalence of effects of gender. *Am J Respir Crit Care Med* sleep-disordered . 2001;163(3 pt 1): breathing in women: 608-613.

35. Zancanella E, et al. Obstructive sleep apnea and primary snoring: diagnosis [published correction appears in *Braz J Otorhinolaryngol*. 2014;80(5):457]. *Braz J Otorhinolaryngol*. 2014;80(1 suppl 1):S1-S16.

36. *Andrew Wellman, Daniel J. Gottlieb, Susan Redline ;* ***Sleep Apnea*** *p2206 Chapter 297 Harrison's principles of internal medicine 21st edition*

37. Qaseem A, et al. Management of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2013;159(7):471-483.

38. Balk EM, Moorthy D, Obadan NO, et al. Diagnosis and treatment of obstructive sleep apnea in adults. Comparative Effectiveness Review no. 32. AHRQ publication no. 11-EHC052-EF. Rockville, Md.: Agency for Health Care Research and Quality; July 2011.

39. Qaseem A, et al. Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014;161(3):210-220.

40. Obstructive sleep apnea ; **Respiratory disease p 960-962 Chapter 28** *Veronica White and Prina Ruparelia ; Clinical medicine ,* Kumar and Clark

41. Bachmann, O. P. et al. Effects of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. Diabetes 50, 2579–2584 (2001).

42. Riley, R., Guilleminault, C., Herran, J. & Powell, N. Cephalometric analyses and flow-volume loops in obstructive sleep apnea patients. Sleep 6, 303–311 (1983).

43. IJ Clifton DAB Ellames , Sleep-disordered breathing , respiratory medicine, p 550 chapter 17 Davidson 24th edition

44. Lin TY, Lin PY, Su TP, Li CT, Lin WC, Chang WH, Chen TJ, et al. Risk of developing obstructive sleep apnea among women with polycystic ovarian syndrome: a nationwide longitudinal follow-up study. *Sleep Med* 2017, 36: 165–169

45. Azagra-Calero, E., Espinar-Escalona, E., Barrera-Mora, J. M., Llamas-Carreras, J. M. & Solano-Reina, E. Obstructive sleep apnea syndrome (OSAS). Review of the literature. Med. Oral. Patol. Oral. Cir. Bucal 17, e925–e929 (2012).

46. Eckert, D. J., White, D. P., Jordan, A. S., Malhotra, A. & Wellman, A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am. J. Respir. Crit. Care Med. 188, 996–1004 (2013)
47. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med* 2019, 380: 1442–1449
48. Mayer, P. et al. Relationship between body mass index, age and upper airway measurements in snorers and sleep apnoea patients. Eur. Respir. J. 9, 1801–1809 (1996)
49. White, L. H. & Bradley, T. D. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J. Physiol. 591, 1179–1193 (2013).
50. Issa, F. G. & Sullivan, C. E. Upper airway closing pressures in snorers. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 57, 528–535 (1984).
51. Issa, F. G. & Sullivan, C. E. Upper airway closing pressures in obstructive sleep apnea. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 57, 520–527 (1984).
52. Morrison, D. L. et al. Pharyngeal narrowing and closing pressures in patients with obstructive sleep apnea. Am. Rev. Respir. Dis. 148, 606–611 (1993).
53. Gleadhill, I. C. et al. Upper airway collapsibility in snorers and in patients with obstructive hypopnoea and apnoea. Am. Rev. Respir. Dis. 143, 1300–1303 (1991).
54. Gold, A. R. & Schwartz, A. R. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. Chest 110,
55. 1077–1088 (1996).
56. Kazemeini, E. et al. Critical to know Pcrit: a review on pharyngeal critical closing pressure in obstructive sleep apnoea. Front. Neurol. 13, 775709 (2022)
57. Schwartz, A. R., Smith, P. L., Wise, R. A., Gold, A. R. & Permutt, S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. J. Appl. Physiol. 64, 535–542 (1988).
58. Smith, P. L., Wise, R. A., Gold, A. R., Schwartz, A. R. & Permutt, S. Upper airway pressure-flow relationships in obstructive sleep apnoea. J. Appl. Physiol. 64, 789–795 (1988)
59. Bosi, M., Incerti Parenti, S., Fiordelli, A., Poletti, V. & Alessandri-Bonetti, G. Upper airway collapsibility in patients with OSA treated with continuous positive airway pressure: a retrospective preliminary study. J. Clin. Sleep Med. 16, 1839–1846 (2020).
60. Carberry, J. C., Jordan, A. S., White, D. P., Wellman, A. & Eckert, D. J. Upper airway collapsibility (Pcrit) and pharyngeal dilator muscle activity are sleep stage dependent. Sleep 39, 511–521 (2016).
61. Altree, T. J., Chung, F., Chan, M. T. V. & Eckert, D. J. Vulnerability to postoperative complications in obstructive sleep apnoea: importance of phenotypes. Anesth. Analg. 132, 1328–1337 (2021)
62. Younes, M. Role of arousals in the pathogenesis of obstructive sleep apnoea. Am. J. Respir. Crit. Care Med. 169, 623–633 (2004).
63. Eckert, D. J. & Younes, M. K. Arousal from sleep: implications for obstructive sleep apnoea pathogenesis and treatment. J. Appl. Physiol. 116, 302–313 (2014)
64. Xiao, S. C. et al. Neural respiratory drive and arousal in patients with obstructive sleep apnoea hypopnoea. Sleep 38, 941–949 (2015).
65. Younes, M. et al. Mechanisms of breathing instability in patients with obstructive sleep apnoea. J. Appl. Physiol. 103, 1929–1941 (2007).

66. Amatoury, J. et al. Arousal intensity is a distinct pathophysiological trait in obstructive sleep apnoea. Sleep 39, 2091–2100 (2016)
67. Campana, L., Eckert, D. J., Patel, S. R. & Malhotra, A. Pathophysiology & genetics of obstructive sleep apnoea. Indian J. Med. Res. 131, 176–187 (2010).
68. Berry, R. B. & Gleeson, K. Respiratory arousal from sleep: mechanisms and significance. Sleep 20, 654–675 (1997).
69. Gleeson, K., Zwillich, C. W. & White, D. P. The influence of increasing ventilatory effort on arousal from sleep. Am. Rev. Respir. Dis. 142, 295–300 (1990).
70. Schütz, S. G., Dunn, A., Braley, T. J., Pitt, B. & Shelgikar, A. V. New frontiers in pharmacologic obstructive sleep apnea treatment: a narrative review. Sleep Med. Rev. 57, 101473 (2021)
71. Deacon-Diaz, N. & Malhotra, A. Inherent vs. induced loop gain abnormalities in obstructive sleep apnoea. Front. Neurol. 9, 896 (2018).
72. Deacon-Diaz, N. L., Sands, S. A., McEvoy, R. D. & Catcheside, P. G. Daytime loop gain is elevated in obstructive sleep apnoea but not reduced by CPAP treatment. J. Appl. Physiol. 125, 1490–1497 (2018).
73. Panza, G. S. et al. Increased oxidative stress, loop gain and the arousal threshold are clinical predictors of increased apnoea severity following exposure to intermittent hypoxia. Nat. Sci. Sleep 11, 265–279 (2019).
74. Naughton, M. T. Loop gain in apnoea: gaining control or controlling the gain? Am. J. Respir. Crit. Care Med. 181, 103–105 (2010).
75. Waters, T. & Mehra, R. Clinical neurophysiology of apnoea. Handb. Clin. Neurol. 161, 345–352 (2019).
76. Rowley, J. A. & Badr, M. S. Central sleep apnoea in patients with congestive heart failure. Sleep Med. Clin. 12, 221–227 (2017).
77. White, D. P. Pathogenesis of obstructive and central sleep apnoea. Am. J. Respir. Crit. Care Med. 172, 1363–1370 (2005).Eckert, D. J., Malhotra, A. & Jordan, A. S. Mechanisms of apnoea. Prog. Cardiovasc. Dis. 51, 313–323 (2009)
78. Lévy, P. et al. Obstructive sleep apnoea syndrome. Nat. Rev. Dis. Prim. 1, 15015 (2015)
79. Deacon, N. L. & Catcheside, P. G. The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea. Sleep Med. Rev. 22, 3–14 (2015)
80. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A,Pickering TG, Woo M, Young T. Sleep apnoea and cardiovascular dis-ease. Circulation 118: 1080–1111, 2008. doi:10.1161/CIRCULATIONAHA.107.189420
81. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP.Pathophysiology of sleep apnea. Physiol Rev 90: 47–112, 2010.doi:10.1152/physrev.00043.2008
82. MICHAEL D. JENSEN Obesity , p.1418-1427 Chapter 207 Goldman-Cecil Medicine 26th edition.
83. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and
84. measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999, 22: 667–689
85. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, Nieto FJ, et al. Relation of sleepiness to respiratory disturbance index. *Am J Respir Crit Care Med* 1999, 159: 502–507

86. Zeidler MR, Santiago V, Dzierzewski JM, Mitchell MN, Santiago S, Martin JL. Predictors of obstructive sleep apnoea on polysomnography after a technically inadequate or normal home sleep test. *J Clin Sleep Med* 2015, 11: 1313–1318
87. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnoea. *N Engl J Med*. 2016;375:919–931. doi: 10.1056/NEJMoa1606599
88. Chiu HY, Chen PY, Chuang LP, Chen NH, Tu YK, Hsieh YJ, Wang YC, Guilleminault C. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth Sleepiness Scale in detecting obstructive sleep apnoea: a bivariate meta-analysis. *Sleep Med Rev*. 2017;36:57–70. doi: 10.1016/j.smrv.2016.10.004
89. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcántara C, Jackson CL, Williams MA, Redline S. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38:877–888. doi: 10.5665/sleep.4732
90. *Dhruva Chaudhry, Inderpaul Singh* Non-Invasive Ventilation p271-276 Chapter 7.9 API textbook of medicine.
91. Sutherland, K. and Cistulli, P. A., *Oral Appliance Therapy for Obstructive Sleep Apnoea: State of the Art*. J Clin Med, 2019. **8**(12)
92. Dedhia, R. C., Strollo, P. J., and Soose, R. J., *Upper Airway Stimulation for Obstructive Sleep Apnoea: Past, Present, and Future*. Sleep, 2015. **38**(6): p. 899–906.
93. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnoea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc*. 2008;5(2):185-192.
94. Romero-Corral, A., et al., *Interactions Between Obesity and Obstructive Sleep Apnea: Implications for Treatment*. Chest, 2010. **137**(3): p. 711–719.
95. Fritscher LG, Mottin CC, Canani S, Chatkin JM (2007) Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. Obes Surg 17: 95-99
96. Giunta J, Salifu M, McFarlane S (2016) Sleep Disorders and Cardio-Renal Disease: Implications for minority populations. Epidemiology 6: e120
97. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnoea: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479-504.
98. Bonsignore MR, McNicholas WT, Montserrat JM, Eckel J.Adipose tissue in obesity and obstructive sleep apnoea. *Eur Respir J*. 2012;39:746-767.
99. Pillar G, Shehadeh N. Abdominal fat and sleep apnoea the chicken or the egg? *Diabetes Care*. 2008;31(suppl 2):S303-S309.
100. Carter R, Watenpaugh DE. Obesity and obstructive sleep apnoea: or is it OSA and obesity? *Pathophysiology*. 2008;15:71-77.
101. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008 Aug;31(8):1071-8. PMID: 18714778; PMCID: PMC2542952.
102. Lopez PP , Stefan B , Schulman CI, Byers PM . Prevalence of sleep apnoea in morbidly obese patients who presented for weight loss surgery evaluation : more evidence for routine screening for obstructive sleep apnoea before weight loss surgery. Am Surg. (2008) 74:834-8

103. **Margaret Kay-Stacey, Eunice Torres-Rivera, Phyllis C. Zee;** sleep wake disorders ; Chapter 28 ; p900 ; Hankey's clinical neurology
104. Schwartz AR, Patil SP, Squier S, Schneider H, Kirkness JP, Smith PL. Obesity and upper airway control during sleep. J Appl Physiol (1985). 2010 Feb;108(2):430-5. doi: 10.1152/japplphysiol.00919.2009. Epub 2009 Oct 29. PMID: 19875707; PMCID: PMC2822668.
105. Imayama I, Prasad B. Role of Leptin in Obstructive Sleep Apnoea. Ann Am Thorac Soc. 2017 Nov;14(11):1607-1621. doi: 10.1513/AnnalsATS.201702-181FR. PMID: 28796527.
106. Fattal D, Hester S, Wendt L. Body weight and obstructive sleep apnoea: a mathematical relationship between body mass index and apnoea-hypopnea index in veterans. J Clin Sleep Med. 2022 Dec 1;18(12):2723-2729. doi: 10.5664/jcsm.10190. PMID: 35929587; PMCID: PMC9713905.
107. Lovin S, Bercea R, Cojocaru C, Rusu G, Mihăescu T. Body composition in obstructive sleep apnoea-hypopnea syndrome bio-impedance reflects the severity of sleep apnoea. Multidiscip Respir Med. 2010 Feb 28;5(1):44-9. doi: 10.1186/2049-6958-5-1-44. PMID: 22958677; PMCID: PMC3463035.
108. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T; American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology; American Heart Association Stroke Council; American Heart Association Council on Cardiovascular Nursing; American College of Cardiology Foundation. Sleep apnoea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008 Sep 2;118(10):1080-111. doi: 10.1161/CIRCULATIONAHA.107.189375. Epub 2008 Aug 25. Erratum in: Circulation. 2009 Mar 31;119(12):e380. PMID: 18725495.
109. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J. 2004 May;25(9):735-41. doi: 10.1016/j.ehj.2004.02.021. PMID: 15120883.
110. Arens R, Muzumdar H. Obesity and obstructive sleep apnoea syndrome in children. *J Appl Physiol*. 2010;108:436-444.
111. Rasche K, Keller T, Hader C, Leidag M, Prinz C. Impact of obstructive sleep apnoea on type 2 diabetes and vice versa. *Eur Endocrinol*. 2013;9(2):107-109.
112. Renata L. Riha, 2006. "Genetics Aspects of the Obstructive Sleep Apnea/Hypopnea Syndrome", Sleep Apnea: Current Diagnosis and Treatment, W.J. Randerath, B.M. Sanner, V.K. Somers.
113. Peter G.J.Fietze, 2006. "Physiology of the cardiovascular, Endocrine and renal systems during sleep", Sleep Apnea: Current Diagnosis and treatment
114. Gonzalez C, Almaraz L, Obeso A, Rigual R. Carotid body chemoreceptors: from natural stimuli to sensory discharges. Physiol Rev. 1994 Oct;74(4):829-98. doi: 10.1152/physrev.1994.74.4.829. PMID: 7938227.
115. Marshall JM. Peripheral chemoreceptors and cardiovascular regulation. Physiol Rev. 1994 Jul;74(3):543-94. doi: 10.1152/physrev.1994.74.3.543. PMID: 8036247.

116. Koyama Y, Coker RH, Stone EE, Lacy DB, Jabbour K, Williams PE, Wasserman DH. Evidence that carotid bodies play an important role in glucoregulation in vivo. Diabetes. 2000 Sep;49(9):1434-42. doi: 10.2337/diabetes.49.9.1434. PMID: 10969826.
117. Koyama Y, Coker RH, Denny JC, Lacy DB, Jabbour K, Williams PE, Wasserman DH. Role of carotid bodies in control of the neuroendocrine response to exercise. Am J Physiol Endocrinol Metab. 2001 Oct;281(4):E742-8. doi: 10.1152/ajpendo.2001.281.4.E742. PMID: 11551850.
118. Conde SV, Ribeiro MJ, Melo BF, Guarino MP, Sacramento JF. Insulin resistance: a new consequence of altered carotid body chemoreflex? J Physiol. 2017 Jan 1;595(1):31-41. doi: 10.1113/JP271684. Epub 2016 Jun 27. PMID: 27027507; PMCID: PMC5199745.
119. Sacramento JF, Andrzejewski K, Melo BF, Ribeiro MJ, Obeso A, Conde SV. Exploring the Mediators that Promote Carotid Body Dysfunction in Type 2 Diabetes and Obesity Related Syndromes. Int J Mol Sci. 2020 Aug 3;21(15):5545. doi: 10.3390/ijms21155545. PMID: 32756352; PMCID: PMC7432672.
120. Iturriaga R. Translating carotid body function into clinical medicine. J Physiol. 2018 Aug;596(15):3067-3077. doi: 10.1113/JP275335. Epub 2017 Nov 23. PMID: 29114876; PMCID: PMC6068206.
121. Cohen JB. Hypertension in Obesity and the Impact of Weight Loss. Curr Cardiol Rep. 2017 Aug 24;19(10):98. doi: 10.1007/s11886-017-0912-4. PMID: 28840500; PMCID: PMC5606235.
122. McFarlane SI, Sica DA, Sowers JR. Stroke in patients with diabetes and hypertension. J Clin Hypertens (Greenwich). 2005 May;7(5):286-92; quiz 293-4. doi: 10.1111/j.1524-6175.2005.04379.x. PMID: 15886531; PMCID: PMC8109587.
123. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, Sattar N, Sun MC, Wittert G, Pinto FJ, Wilding JPH. Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. Eur J Prev Cardiol. 2022 Dec 7;29(17):2218-2237. doi: 10.1093/eurjpc/zwac187. PMID: 36007112.
124. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. Front Endocrinol (Lausanne). 2021 Sep 6;12:706978. doi: 10.3389/fendo.2021.706978. PMID: 34552557; PMCID: PMC8450866.
125. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996 Dec 1;94(11):2850-5. doi: 10.1161/01.cir.94.11.2850. PMID: 8941112.
126. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM, Panayiotou H, Mukerji V. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol. 1997 Sep 15;80(6):736-40. doi: 10.1016/s0002-9149(97)00505-5. PMID: 9315579.
127. Braunwald E. Heart failure. JACC Heart Fail. 2013 Feb;1(1):1-20. doi: 10.1016/j.jchf.2012.10.002. Epub 2013 Feb 4. PMID: 24621794.
128. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, Nambi V, Ballantyne CM, Solomon SD, Selvin E, Folsom AR, Coresh J. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc. 2016 Jul 28;5(8):e003921. doi: 10.1161/JAHA.116.003921. PMID: 27468925; PMCID: PMC5015307.

129. World Health Organization. Regional Office for the Western Pacific. (2000). The Asia-Pacific perspective : redefining obesity and its treatment. Sydney : Health Communications Australia. https://iris.who.int/handle/10665/206936
130. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999 Oct 7;341(15):1097-105. doi: 10.1056/NEJM199910073411501. PMID: 10511607.
131. Bray GA, Kim KK, Wilding JPH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017 Jul;18(7):715-723. doi: 10.1111/obr.12551. Epub 2017 May 10. PMID: 28489290.
132. Csige I, Ujvárosy D, Szabó Z, Lőrincz I, Paragh G, Harangi M, Somodi S. The Impact of Obesity on the Cardiovascular System. J Diabetes Res. 2018 Nov 4;2018:3407306. doi: 10.1155/2018/3407306. PMID: 30525052; PMCID: PMC6247580.
133. Bays HE, McCarthy W, Burridge K, Tondt J, Karjoo S, Christensen S, Ng J, Golden A, Davisson L, Richardson L Obesity Algorithm eBook, presented by the Obesity Medicine Association
134. Mathieu P, Lemieux I, Després JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther. 2010 Apr;87(4):407-16. doi: 10.1038/clpt.2009.311. Epub 2010 Mar 3. PMID: 20200516.
135. El-Wakkad A, Hassan Nel-M, Sibaii H, El-Zayat SR. Proinflammatory, anti-inflammatory cytokines and adiponkines in students with central obesity. Cytokine. 2013 Feb;61(2):682-7. doi: 10.1016/j.cyto.2012.11.010. Epub 2013 Jan 8. PMID: 23306429.
136. Larsson A, Carlsson L, Lind AL, Gordh T, Bodolea C, Kamali-Moghaddam M, Thulin M. The body mass index (BMI) is significantly correlated with levels of cytokines and chemokines in cerebrospinal fluid. Cytokine. 2015 Dec;76(2):514-518. doi: 10.1016/j.cyto.2015.07.010. Epub 2015 Jul 15. PMID: 26188367.
137. Mussbacher M, Salzmann M, Brostjan C, Hoesel B, Schoergenhofer C, Datler H, Hohensinner P, Basílio J, Petzelbauer P, Assinger A, Schmid JA. Cell Type-Specific Roles of NF-κB Linking Inflammation and Thrombosis. Front Immunol. 2019 Feb 4;10:85. doi: 10.3389/fimmu.2019.00085. PMID: 30778349; PMCID: PMC6369217.
138. Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol. 2009 Sep 15;78(6):539-52. doi: 10.1016/j.bcp.2009.04.029. Epub 2009 May 4. PMID: 19413999; PMCID: PMC2730638.
139. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017 Jun;13(4):851-863. doi: 10.5114/aoms.2016.58928. Epub 2016 Mar 31. PMID: 28721154; PMCID: PMC5507106.
140. Csige I, Ujvárosy D, Szabó Z, Lőrincz I, Paragh G, Harangi M, Somodi S. The Impact of Obesity on the Cardiovascular System. J Diabetes Res. 2018 Nov 4;2018:3407306. doi: 10.1155/2018/3407306. PMID: 30525052; PMCID: PMC6247580.
141. Bray GA. Etiology and pathogenesis of obesity. Clin Cornerstone. 1999;2(3):1-15. doi: 10.1016/s1098-3597(99)90001-7. PMID: 10696281.
142. George A. Bray,Etiology and pathogenesis of obesity,Clinical Cornerstone,Volume 2, Issue 3,1999,Pages 1-15,ISSN 1098-3597
143. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on

Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 May 25;143(21):e984-e1010. doi: 10.1161/CIR.0000000000000973. Epub 2021 Apr 22. PMID: 33882682; PMCID: PMC8493650.

144. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, van Dam RM, Hu FB, Visscher TL, Menotti A, Thorpe RJ Jr, Jamrozik K, Calling S, Strand BH, Shipley MJ; BMI-CHD Collaboration Investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med. 2007 Sep 10;167(16):1720-8. doi: 10.1001/archinte.167.16.1720. PMID: 17846390.
145. Terada T, Forhan M, Norris CM, Qiu W, Padwal R, Sharma AM, Nagendran J, Johnson JA. Differences in Short- and Long-Term Mortality Associated With BMI Following Coronary Revascularization. J Am Heart Assoc. 2017 Apr 14;6(4):e005335. doi: 10.1161/JAHA.116.005335. PMID: 28411242; PMCID: PMC5533024.
146. Holroyd EW, Sirker A, Kwok CS, Kontopantelis E, Ludman PF, De Belder MA, Butler R, Cotton J, Zaman A, Mamas MA; British Cardiovascular Intervention Society and National Institute of Cardiovascular Outcomes Research. The Relationship of Body Mass Index to Percutaneous Coronary Intervention Outcomes: Does the Obesity Paradox Exist in Contemporary Percutaneous Coronary Intervention Cohorts? Insights From the British Cardiovascular Intervention Society Registry. JACC Cardiovasc Interv. 2017 Jul 10;10(13):1283-1292. doi: 10.1016/j.jcin.2017.03.013. PMID: 28683933.
147. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 May 25;143(21):e984-e1010. doi: 10.1161/CIR.0000000000000973. Epub 2021 Apr 22. PMID: 33882682; PMCID: PMC8493650.
148. Beavers CJ, Heron P, Smyth SS, Bain JA, Macaulay TE. Obesity and Antiplatelets-Does One Size Fit All? Thromb Res. 2015 Oct;136(4):712-6. doi: 10.1016/j.thromres.2015.07.015. Epub 2015 Jul 16. PMID: 26205154.
149. Komócsi A, Merkely B, Hadamitzky M, Massberg S, Rizas KD, Hein-Rothweiler R, Gross L, Trenk D, Sibbing D, Aradi D. Impact of body mass on P2Y12-inhibitor de-escalation in acute coronary syndromes-a substudy of the TROPICAL-ACS trial. Eur Heart J Cardiovasc Pharmacother. 2023 Nov 2;9(7):608-616. doi: 10.1093/ehjcvp/pvad027. PMID: 37015874; PMCID: PMC10627813.
150. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4242. doi: 10.1093/eurheartj/ehz825. PMID: 31504439.

151. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 May 25;143(21):e984-e1010. doi: 10.1161/CIR.0000000000000973. Epub 2021 Apr 22. PMID: 33882682; PMCID: PMC8493650.
152. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Thomas RJ, Squires RW, Allison TG. Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. Eur J Cardiovasc Prev Rehabil. 2008 Jun;15(3):336-40. doi: 10.1097/HJR.0b013e3282f48348. PMID: 18525390.
153. Fisher DP, Johnson E, Haneuse S, Arterburn D, Coleman KJ, O'Connor PJ, O'Brien R, Bogart A, Theis MK, Anau J, Schroeder EB, Sidney S. Association Between Bariatric Surgery and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe Obesity. JAMA. 2018 Oct 16;320(15):1570-1582. doi: 10.1001/jama.2018.14619. Erratum in: JAMA. 2018 Dec 11;320(22):2381. doi: 10.1001/jama.2018.18972. PMID: 30326126; PMCID: PMC6233803.
154. Volpe M, Borghi C, Cameli M, Cianflone D, Cittadini A, Maggioni AP, Perrone Filardi P, Rosano G, Senni M, Sinagra G. Otto motivi per i quali i cardiologi non dovrebbero trascurare il problema “obesità”. Expert opinion per la pratica clinica [Eight reasons why cardiologists should not overlook the problem "obesity". Expert opinion for clinical practice]. G Ital Cardiol (Rome). 2023 Sep;24(9):677-691. Italian. doi: 10.1714/4084.40678. PMID: 37642120.
155. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Dec 21;42(48):4901. doi: 10.1093/eurheartj/ehab670. PMID: 34447992.
156. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019 Oct 21;40(40):3297-3317. doi: 10.1093/eurheartj/ehz641. Erratum in: Eur Heart J. 2021 Mar 31;42(13):1274. doi: 10.1093/eurheartj/ehaa1016. PMID: 31504452.
157. Rodriguez Flores M, Aguilar Salinas C, Piché ME, Auclair A, Poirier P. Effect of bariatric surgery on heart failure. Expert Rev Cardiovasc Ther. 2017 Aug;15(8):567-579. doi: 10.1080/14779072.2017.1352471. Epub 2017 Jul 27. PMID: 28714796.
158. Chi M, Nie Y, Su Y, Wang N, Li A, Ma T, Hou Y. Effects of weight loss in heart failure patients with overweight and obesity: a systematic review and meta-analysis. Eur J Prev Cardiol. 2023 Nov 30;30(17):1906-1921. doi: 10.1093/eurjpc/zwad284. PMID: 37652032.

159. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA. 2016 Jan 5;315(1):36-46. doi: 10.1001/jama.2015.17346. PMID: 26746456; PMCID: PMC4787295.
160. Malandish A, Gulati M. The impacts of exercise interventions on inflammaging markers in overweight/obesity patients with heart failure: A systematic review and meta-analysis of randomized controlled trials. Int J Cardiol Heart Vasc. 2023 Jun 27;47:101234. doi: 10.1016/j.ijcha.2023.101234. PMID: 37416483; PMCID: PMC10320319.
161. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. JACC Clin Electrophysiol. 2015 Jun;1(3):139-152. doi: 10.1016/j.jacep.2015.04.004. Epub 2015 Apr 20. PMID: 29759357.
162. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013 Nov 20;310(19):2050-60. doi: 10.1001/jama.2013.280521. PMID: 24240932.
163. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol. 2015 May 26;65(20):2159-69. doi: 10.1016/j.jacc.2015.03.002. Epub 2015 Mar 16. PMID: 25792361.
164. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014 Dec 2;64(21):2222-31. doi: 10.1016/j.jacc.2014.09.028. Epub 2014 Nov 24. PMID: 25456757.
165. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, Twomey D, Gallagher C, Hendriks JML, Linz D, McEvoy RD, Abhayaratna WP, Kalman JM, Lau DH, Sanders P. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace. 2018 Dec 1;20(12):1929-1935. doi: 10.1093/europace/euy117. PMID: 29912366.
166. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol. 2015 Sep 1;66(9):985-96. doi: 10.1016/j.jacc.2015.06.488. Epub 2015 Jun 22. PMID: 26113406.
167. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric Surgery and the Risk of New-Onset Atrial Fibrillation in Swedish Obese Subjects. J Am Coll Cardiol. 2016 Dec 13;68(23):2497-2504. doi: 10.1016/j.jacc.2016.09.940. PMID: 27931605; PMCID: PMC5157934.

168. Donnellan E, Wazni OM, Elshazly M, Kanj M, Hussein AA, Baranowski B, Kochar A, Trulock K, Aminian A, Schauer P, Jaber W, Saliba WI. Impact of Bariatric Surgery on Atrial Fibrillation Type. Circ Arrhythm Electrophysiol. 2020 Feb;13(2):e007626. doi: 10.1161/CIRCEP.119.007626. Epub 2020 Jan 15. PMID: 31940441.
169. Wallace JL, Reaves AB, Tolley EA, Oliphant CS, Hutchison L, Alabdan NA, Sands CW, Self TH. Comparison of initial warfarin response in obese patients versus non-obese patients. J Thromb Thrombolysis. 2013 Jul;36(1):96-101. doi: 10.1007/s11239-012-0811-x. PMID: 23015280.
170. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665. Epub 2019 Jan 28. Erratum in: Circulation. 2019 Aug 6;140(6):e285. doi: 10.1161/CIR.0000000000000719. PMID: 30686041.
171. Russo V, Paccone A, Rago A, Maddaloni V, Iafusco D, Proietti R, Atripaldi U, D'Onofrio A, Golino P, Nigro G. Apixaban in a Morbid Obese Patient with Atrial Fibrillation: A Clinical Experience Using the Plasmatic Drug Evaluation. J Blood Med. 2020 Mar 3;11:77-81. doi: 10.2147/JBM.S229526. PMID: 32184692; PMCID: PMC7061727.
172. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med. 2009 Aug;6(8):e1000132. doi: 10.1371/journal.pmed.1000132. Epub 2009 Aug 18. PMID: 19688045; PMCID: PMC2722083.
173. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005 Mar 19-25;365(9464):1046-53. doi: 10.1016/S0140-6736(05)71141-7. PMID: 15781100.
174. Arnaud C, Bochaton T, Pépin JL, Belaidi E. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. Arch Cardiovasc Dis. 2020 May;113(5):350-358. doi: 10.1016/j.acvd.2020.01.003. Epub 2020 Mar 26. PMID: 32224049.
175. Gopalakrishnan P, Tak T. Obstructive sleep apnea and cardiovascular disease. Cardiol Rev. 2011 Nov-Dec;19(6):279-90. doi: 10.1097/CRD.0b013e318223bd08. PMID: 21983316.
176. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, Bradley TD. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J. 2003 Feb;21(2):241-7. doi: 10.1183/09031936.03.00035402. PMID: 12608436.
177. Nair R, Radhakrishnan K, Chatterjee A, Gorthi SP, Prabhu VA. Sleep Apnoea-Predictor of Functional Outcome in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2019 Mar;28(3):807-814. doi: 10.1016/j.jstrokecerebrovasdis.2018.11.030. Epub 2018 Dec 14. PMID: 30554938.
178. Bhalla S, Sharma K, Yadave RD, Desai HD, Vora T, Khan E, Shah P, Jadeja D, Bhandari V. Prevalence and Patterns of Obstructive Sleep Apnea in Asian Indians With Congestive Heart Failure. Cureus. 2020 Nov 11;12(11):e11438. doi: 10.7759/cureus.11438. PMID: 33324521; PMCID: PMC7732783.

179. Kishan S, Rao MS, Ramachandran P, Devasia T, Samanth J. Prevalence and Patterns of Sleep-Disordered Breathing in Indian Heart Failure Population. Pulm Med. 2021 Jul 3;2021:9978906. doi: 10.1155/2021/9978906. PMID: 34285816; PMCID: PMC8275383.
180. Soin D, Kumar PA, Chahal J, Chawla SPS, Kaur S, Garg R, Kaur R. Evaluation of obstructive sleep apnoea in metabolic syndrome. J Family Med Prim Care. 2019 May;8(5):1580-1586. doi: 10.4103/jfmpc.jfmpc_175_19. PMID: 31198718; PMCID: PMC6559083.
181. Singh A, Chaudhary SC, Gupta KK, Sawlani KK, Singh A, Singh AB, Verma AK. Prevalence of obstructive sleep apnoea in diabetic patients. Ann Afr Med. 2021 Jul-Sep;20(3):206-211. doi: 10.4103/aam.aam_43_20. PMID: 34558450; PMCID: PMC8477286.
182. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnoea. Circulation. 2004 Jul 27;110(4):364-7. doi: 10.1161/01.CIR.0000136587.68725.8E. Epub 2004 Jul 12. PMID: 15249509.
183. Mahajan SK, Mahajan K, Sharma S. Obstructive sleep apnoea and coronary artery disease: An unholy nexus or a holy alliance? Lung India. 2022 Sep-Oct;39(5):460-465. doi: 10.4103/lungindia.lungindia_597_21. PMID: 36629208; PMCID: PMC9623863.
184. Chaudhary SC, Gupta P, Sawlani KK, Gupta KK, Singh A, Usman K, Kumar V, Himanshu D, Verma A, Singh AB. Obstructive Sleep Apnoea in Hypertension. Cureus. 2023 Apr 27;15(4):e38229. doi: 10.7759/cureus.38229. PMID: 37252498; PMCID: PMC10225023.
185. Xie C, Zhu R, Tian Y, Wang K. Association of obstructive sleep apnoea with the risk of vascular outcomes and all-cause mortality: a meta-analysis. BMJ Open. 2017 Dec 22;7(12):e013983. doi: 10.1136/bmjopen-2016-013983. PMID: 29275335; PMCID: PMC5770910.
186. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnoea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2019 Feb 15;15(2):301-334. doi: 10.5664/jcsm.7638. PMID: 30736888; PMCID: PMC6374080.
187. Lisan Q, Van Sloten T, Marques Vidal P, Haba Rubio J, Heinzer R, Empana JP. Association of Positive Airway Pressure Prescription With Mortality in Patients With Obesity and Severe Obstructive Sleep Apnoea: The Sleep Heart Health Study. JAMA Otolaryngol Head Neck Surg. 2019 Jun 1;145(6):509-515. doi: 10.1001/jamaoto.2019.0281. PMID: 30973594; PMCID: PMC6583022.
188. Stamatakis K, Sanders MH, Caffo B, Resnick HE, Gottlieb DJ, Mehra R, Punjabi NM. Fasting glycemia in sleep disordered breathing: lowering the threshold on oxyhemoglobin desaturation. Sleep. 2008 Jul;31(7):1018-24. PMID: 18652097; PMCID: PMC2491502.
189. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE; Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol. 2004 Sep 15;160(6):521-30. doi: 10.1093/aje/kwh261. PMID: 15353412.
190. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnoea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005 Dec 15;172(12):1590-5. doi: 10.1164/rccm.200504-637OC. Epub 2005 Sep 28. PMID: 16192452; PMCID: PMC2718458.
191. Resta O, Foschino-Barbaro MP, Legari G, Talamo S, Bonfitto P, Palumbo A, Minenna A, Giorgino R, De Pergola G. Sleep-related breathing disorders, loud snoring and excessive daytime

sleepiness in obese subjects. Int J Obes Relat Metab Disord. 2001 May;25(5):669-75. doi: 10.1038/sj.ijo.0801603. PMID: 11360149.

192. Kollar B, Siarnik P, Hluchanova A, Klobucnikova K, Mucska I, Turcani P, Paduchova Z, Katrencikova B, Janubova M, Konarikova K, Argalasova L, Oravec S, Zitnanova I. The impact of sleep apnoea syndrome on the altered lipid metabolism and the redox balance. Lipids Health Dis. 2021 Dec 5;20(1):175. doi: 10.1186/s12944-021-01604-8. PMID: 34865634; PMCID: PMC8647408.
193. Andrade AG, Bubu OM, Varga AW, Osorio RS. The Relationship between Obstructive Sleep Apnea and Alzheimer's Disease. J Alzheimers Dis. 2018;64(s1):S255-S270. doi: 10.3233/JAD-179936. PMID: 29782319; PMCID: PMC6542637.
194. Vikas kapil , p1138 hypertension, chapter 31 kumar and clark's clinical medicine, tenth edition
195. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000 May 11;342(19):1378-84. doi: 10.1056/NEJM200005113421901. PMID: 10805822.
196. Gonçalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, Branchi T, Moreira LB, Fuchs SC, de Oliveira AC, Fuchs FD. Obstructive sleep apnoea and resistant hypertension: a case-control study. Chest. 2007 Dec;132(6):1858-62. doi: 10.1378/chest.07-1170. PMID: 18079220.
197. Kuniyoshi FH, Pusalavidyasagar S, Singh P, Somers VK. Cardiovascular consequences of obstructive sleep apnoea. Indian J Med Res. 2010 Feb;131:196-205. PMID: 20308745.
198. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail. 2007 Mar;9(3):251-7. doi: 10.1016/j.ejheart.2006.08.003. Epub 2006 Oct 5. PMID: 17027333.
199. Drager LF, Yao Q, Hernandez KL, Shin MK, Bevans-Fonti S, Gay J, Sussan TE, Jun JC, Myers AC, Olivecrona G, Schwartz AR, Halberg N, Scherer PE, Semenza GL, Powell DR, Polotsky VY. Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4. Am J Respir Crit Care Med. 2013 Jul 15;188(2):240-8. doi: 10.1164/rccm.201209-1688OC. PMID: 23328524; PMCID: PMC3778753.
200. Pedrosa RP, Krieger EM, Lorenzi-Filho G, Drager LF. Recent advances of the impact of obstructive sleep apnoea on systemic hypertension. Arq Bras Cardiol. 2011 Aug;97(2):e40-7. English, Portuguese, Spanish. doi: 10.1590/s0066-782x2011005000017. Epub 2011 Feb 25. PMID: 21359488.
201. Kapa S, Sert Kuniyoshi FH, Somers VK. Sleep apnoea and hypertension: interactions and implications for management. Hypertension. 2008 Mar;51(3):605-8. doi: 10.1161/HYPERTENSIONAHA.106.076190. Epub 2008 Jan 28. PMID: 18227409.
202. Jouett NP, Watenpaugh DE, Dunlap ME, Smith ML. Interactive effects of hypoxia, hypercapnia and lung volume on sympathetic nerve activity in humans. Exp Physiol. 2015 Sep;100(9):1018-29. doi: 10.1113/EP085092. Epub 2015 Aug 11. PMID: 26132990.
203. Thomas JJ, Ren J. Obstructive sleep apnoea and cardiovascular complications: perception versus knowledge. Clin Exp Pharmacol Physiol. 2012 Dec;39(12):995-1003. doi: 10.1111/1440-1681.12024. PMID: 23082844.

204. Stradling JR, Craig SE, Kohler M, Nicoll D, Ayers L, Nunn AJ, Bratton DJ. Markers of inflammation: data from the MOSAIC randomised trial of CPAP for minimally symptomatic OSA. Thorax. 2015 Feb;70(2):181-2. doi: 10.1136/thoraxjnl-2014-205958. Epub 2014 Sep 2. Erratum in: Thorax. 2015 Apr;70(4):319. doi: 10.1136/thoraxjnl-2014-205958corr1. PMID: 25182045.
205. Li NF, Yao XG, Zhu J, Yang J, Liu KJ, Wang YC, Wang XL, Zu FY. Higher levels of plasma TNF-alpha and neuropeptide Y in hypertensive patients with obstructive sleep apnoea syndrome. Clin Exp Hypertens. 2010 Jan;32(1):54-60. doi: 10.3109/10641960902993087. PMID: 20144074.
206. Liu L, Cao Q, Guo Z, Dai Q. Continuous Positive Airway Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Meta-Analysis of Randomized Controlled Trials. J Clin Hypertens (Greenwich). 2016 Feb;18(2):153-8. doi: 10.1111/jch.12639. Epub 2015 Aug 17. PMID: 26278919; PMCID: PMC8031627.
207. Muxfeldt ES, Margallo V, Costa LM, Guimarães G, Cavalcante AH, Azevedo JC, de Souza F, Cardoso CR, Salles GF. Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnoea and resistant hypertension: a randomized controlled trial. Hypertension. 2015 Apr;65(4):736-42. doi: 10.1161/HYPERTENSIONAHA.114.04852. Epub 2015 Jan 19. PMID: 25601933.
208. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnoea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011 Jul 1;108(1):47-51. doi: 10.1016/j.amjcard.2011.02.343. Epub 2011 Apr 29. PMID: 21529734.
209. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnoea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007 Feb 6;49(5):565-71. doi: 10.1016/j.jacc.2006.08.060. Epub 2007 Jan 22. PMID: 17276180.
210. Patel N, Donahue C, Shenoy A, Patel A, El-Sherif N. Obstructive sleep apnoea and arrhythmia: A systemic review. Int J Cardiol. 2017 Feb 1;228:967-970. doi: 10.1016/j.ijcard.2016.11.137. Epub 2016 Nov 9. PMID: 27914359.
211. Shivalkar B, Van de Heyning C, Kerremans M, Rinkevich D, Verbraecken J, De Backer W, Vrints C. Obstructive sleep apnoea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. J Am Coll Cardiol. 2006 Apr 4;47(7):1433-9. doi: 10.1016/j.jacc.2005.11.054. Epub 2006 Mar 15. PMID: 16580533.
212. Hohl M, Linz B, Böhm M, Linz D. Obstructive sleep apnoea and atrial arrhythmogenesis. Curr Cardiol Rev. 2014 Nov;10(4):362-8. doi: 10.2174/1573403x1004140707125137. PMID: 25004989; PMCID: PMC4101201.
213. Mittal S, Golombeck D, Pimienta J. Sleep Apnoea and AF: Where Do We Stand? Practical Advice for Clinicians. Arrhythm Electrophysiol Rev. 2021 Oct;10(3):140-146. doi: 10.15420/aer.2021.05. PMID: 34777817; PMCID: PMC8576511.
214. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnoea syndrome. Am J Cardiol. 1983 Sep 1;52(5):490-4. doi: 10.1016/0002-9149(83)90013-9. PMID: 6193700.
215. Pépin JL, Lévy P. Physiopathologie du risque cardio-vasculaire au cours du syndrome d'apnées du sommeil (SAS) [Pathophysiology of cardiovascular risk in sleep apnea syndrome (SAS)]. Rev Neurol (Paris). 2002 Sep;158(8-9):785-97. French. PMID: 12386523.

216. Linz D, Hohl M, Nickel A, Mahfoud F, Wagner M, Ewen S, Schotten U, Maack C, Wirth K, Böhm M. Effect of renal denervation on neurohumoral activation triggering atrial fibrillation in obstructive sleep apnoea. Hypertension. 2013 Oct;62(4):767-74. doi: 10.1161/HYPERTENSIONAHA.113.01728. Epub 2013 Aug 19. PMID: 23959548.
217. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, Antic N, Thornton A, Saint DA, McEvoy D, Antic R, Kalman JM, Sanders P. Atrial remodeling in obstructive sleep apnoea: implications for atrial fibrillation. Heart Rhythm. 2012 Mar;9(3):321-7. doi: 10.1016/j.hrthm.2011.10.017. Epub 2011 Oct 19. PMID: 22016075.
218. Yaggi H, Mohsenin V. Obstructive sleep apnoea and stroke. Lancet Neurol. 2004 Jun;3(6):333-42. doi: 10.1016/S1474-4422(04)00766-5. PMID: 15157848.
219. Minai OA, Ricaurte B, Kaw R, Hammel J, Mansour M, McCarthy K, Golish JA, Stoller JK. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnoea syndrome. Am J Cardiol. 2009 Nov 1;104(9):1300-6. doi: 10.1016/j.amjcard.2009.06.048. PMID: 19840581.
220. Arias MA, García-Río F, Alonso-Fernández A, Martínez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J. 2006 May;27(9):1106-13. doi: 10.1093/eurheartj/ehi807. Epub 2006 Feb 23. PMID: 16497687.
221. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2006 Apr 15;173(8):910-6. doi: 10.1164/rccm.200509-1442OC. Epub 2006 Jan 19. PMID: 16424443; PMCID: PMC2662909.
222. Anter E, Di Biase L, Contreras-Valdes FM, Gianni C, Mohanty S, Tschabrunn CM, Viles-Gonzalez JF, Leshem E, Buxton AE, Kulbak G, Halaby RN, Zimetbaum PJ, Waks JW, Thomas RJ, Natale A, Josephson ME. Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients With Obstructive Sleep Apnea. Circ Arrhythm Electrophysiol. 2017 Nov;10(11):e005407. doi: 10.1161/CIRCEP.117.005407. PMID: 29133380; PMCID: PMC5726812.
223. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ; ORBIT-AF Investigators. Impact of obstructive sleep apnoea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015 May;169(5):647-654.e2. doi: 10.1016/j.ahj.2014.12.024. Epub 2015 Feb 7. PMID: 25965712.
224. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012 Apr;14(4):528-606. doi: 10.1093/europace/eus027. Epub 2012 Mar 1. PMID: 22389422.

225. Kasai T, Narui K, Dohi T, Yanagisawa N, Ishiwata S, Ohno M, Yamaguchi T, Momomura S. Prognosis of patients with heart failure and obstructive sleep apnoea treated with continuous positive airway pressure. Chest. 2008 Mar;133(3):690-6. doi: 10.1378/chest.07-1901. Epub 2008 Jan 15. PMID: 18198253.
226. Bandi PS, Panigrahy PK, Hajeebu S, Ngembus NJ, Heindl SE. Pathophysiological Mechanisms to Review Association of Atrial Fibrillation in Heart Failure With Obstructive Sleep Apnoea. Cureus. 2021 Jul 1;13(7):e16086. doi: 10.7759/cureus.16086. PMID: 34345562; PMCID: PMC8325395.
227. Pearse SG, Cowie MR. Sleep-disordered breathing in heart failure. Eur J Heart Fail. 2016 Apr;18(4):353-61. doi: 10.1002/ejhf.492. Epub 2016 Feb 11. PMID: 26869027.
228. Chen L, Zadi ZH, Zhang J, Scharf SM, Pae EK. Intermittent hypoxia in utero damages postnatal growth and cardiovascular function in rats. J Appl Physiol (1985). 2018 Apr 1;124(4):821-830. doi: 10.1152/japplphysiol.01066.2016. Epub 2017 Dec 14. PMID: 29357521.
229. Yumino D, Redolfi S, Ruttanaumpawan P, Su MC, Smith S, Newton GE, Mak S, Bradley TD. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnoea in men with heart failure. Circulation. 2010 Apr 13;121(14):1598-605. doi: 10.1161/CIRCULATIONAHA.109.902452. Epub 2010 Mar 29. PMID: 20351237.
230. Grimm W, Koehler U. Cardiac arrhythmias and sleep-disordered breathing in patients with heart failure. Int J Mol Sci. 2014 Oct 16;15(10):18693-705. doi: 10.3390/ijms151018693. PMID: 25325536; PMCID: PMC4227240.
231. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnoea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010 Jul 27;122(4):352-60. doi: 10.1161/CIRCULATIONAHA.109.901801. Epub 2010 Jul 12. PMID: 20625114; PMCID: PMC3117288.
232. Bradley TD, Logan AG, Lorenzi Filho G, Kimoff RJ, Durán Cantolla J, Arzt M, Redolfi S, Parati G, Kasai T, Dunlap ME, Delgado D, Yatsu S, Bertolami A, Pedrosa R, Tomlinson G, Marin Trigo JM, Tantucci C, Floras JS; ADVENT-HF Investigators. Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial. Lancet Respir Med. 2024 Feb;12(2):153-166. doi: 10.1016/S2213-2600(23)00374-0. Epub 2023 Dec 21. PMID: 38142697.
233. Sorajja D, Gami AS, Somers VK, Behrenbeck TR, Garcia-Touchard A, Lopez-Jimenez F. Independent association between obstructive sleep apnoea and subclinical coronary artery disease. Chest. 2008 Apr;133(4):927-33. doi: 10.1378/chest.07-2544. Epub 2008 Feb 8. PMID: 18263678; PMCID: PMC2831406.
234. Kuniyoshi FH, Garcia-Touchard A, Gami AS, Romero-Corral A, van der Walt C, Pusalavidyasagar S, Kara T, Caples SM, Pressman GS, Vasquez EC, Lopez-Jimenez F, Somers VK. Day-night variation of acute myocardial infarction in obstructive sleep apnoea. J Am Coll Cardiol. 2008 Jul 29;52(5):343-6. doi: 10.1016/j.jacc.2008.04.027. PMID: 18652941; PMCID: PMC2598735.
235. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnoea as a risk factor for coronary events or cardiovascular death. Sleep Breath. 2010 Jun;14(2):131-6. doi: 10.1007/s11325-009-0298-7. Epub 2009 Sep 24. PMID: 19777281.

236. Kosacka M, Brzecka A. Endothelin-1 and LOX-1 as Markers of Endothelial Dysfunction in Obstructive Sleep Apnea Patients. Int J Environ Res Public Health. 2021 Feb 1;18(3):1319. doi: 10.3390/ijerph18031319. PMID: 33535693; PMCID: PMC7908073.
237. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet. 2009 Jan 3;373(9657):82-93. doi: 10.1016/S0140-6736(08)61622-0. Epub 2008 Dec 26. PMID: 19101028.
238. Nauman J, Janszky I, Vatten LJ, Wisløff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA. 2011 Dec 21;306(23):2579-87. doi: 10.1001/jama.2011.1826. PMID: 22187277.
239. De Torres-Alba F, Gemma D, Armada-Romero E, Rey-Blas JR, López-de-Sá E, López-Sendon JL. Obstructive sleep apnoea and coronary artery disease: from pathophysiology to clinical implications. Pulm Med. 2013;2013:768064. doi: 10.1155/2013/768064. Epub 2013 Apr 15. PMID: 23691310; PMCID: PMC3649685.
240. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnoea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med. 2016 Sep 1;194(5):613-20. doi: 10.1164/rccm.201601-0088OC. PMID: 26914592.
241. Chen Y, Chen Y, Wen F, He Z, Niu W, Ren C, Li N, Wang Q, Ren Y, Liang C. Does continuous positive airway pressure therapy benefit patients with coronary artery disease and obstructive sleep apnoea? A systematic review and meta-analysis. Clin Cardiol. 2021 Aug;44(8):1041-1049. doi: 10.1002/clc.23669. Epub 2021 Jun 19. PMID: 34145595; PMCID: PMC8364731.
242. Kojic B, Dostovic Z, Ibrahimagic OC, Smajlovic D, Hodzic R, Iljazovic A, Salihovic D. Risk Factors in Acute Stroke Patients With and Without Sleep Apnoea. Med Arch. 2021 Dec;75(6):444-450. doi: 10.5455/medarh.2021.75.444-450. PMID: 35169372; PMCID: PMC8802685.
243. Dong R, Dong Z, Liu H, Shi F, Du J. Prevalence, Risk Factors, Outcomes, and Treatment of Obstructive Sleep Apnoea in Patients with Cerebrovascular Disease: A Systematic Review. J Stroke Cerebrovasc Dis. 2018 Jun;27(6):1471-1480. doi: 10.1016/j.jstrokecerebrovasdis.2017.12.048. Epub 2018 Mar 16. PMID: 29555400.
244. Dyken ME, Im KB. Obstructive sleep apnoea and stroke. Chest. 2009 Dec;136(6):1668-1677. doi: 10.1378/chest.08-1512. PMID: 19995768.
245. Gupta A, Shukla G, Afsar M, Poornima S, Pandey RM, Goyal V, Srivastava A, Vibha D, Behari M. Role of Positive Airway Pressure Therapy for Obstructive Sleep Apnea in Patients With Stroke: A Randomized Controlled Trial. J Clin Sleep Med. 2018 Apr 15;14(4):511-521. doi: 10.5664/jcsm.7034. PMID: 29609704; PMCID: PMC5886428.
246. Brown DL, Shafie-Khorassani F, Kim S, Chervin RD, Case E, Morgenstern LB, Yadollahi A, Tower S, Lisabeth LD. Sleep-Disordered Breathing Is Associated With Recurrent Ischemic Stroke. Stroke. 2019 Mar;50(3):571-576. doi: 10.1161/STROKEAHA.118.023807. PMID: 30744545; PMCID: PMC6389387.
247. Jilwan FN, Escourrou P, Garcia G, Jaïs X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. Chest. 2013 Jan;143(1):47-55. doi: 10.1378/chest.11-3124. PMID: 22878784.

248. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnoea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ. 2015 Jun;5(2):220-7. doi: 10.1086/679995. PMID: 26064448; PMCID: PMC4449234.
249. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnoea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ. 2015 Jun;5(2):220-7. doi: 10.1086/679995. PMID: 26064448; PMCID: PMC4449234.
250. Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2002 Jan 15;165(2):152-8. doi: 10.1164/ajrccm.165.2.2010092. PMID: 11790646.
251. Khayat R, Small R, Rathman L, Krueger S, Gocke B, Clark L, Yamokoski L, Abraham WT. Sleep-disordered breathing in heart failure: identifying and treating an important but often unrecognized comorbidity in heart failure patients. J Card Fail. 2013 Jun;19(6):431-44. doi: 10.1016/j.cardfail.2013.04.005. PMID: 23743494; PMCID: PMC3690313.
252. Li YE, Ren J. Association between obstructive sleep apnoea and cardiovascular diseases. Acta Biochim Biophys Sin (Shanghai). 2022 Jul 25;54(7):882-892. doi: 10.3724/abbs.2022084. PMID: 35838200; PMCID: PMC9828315.
253. Khayat R, Pleister A. Consequences of Obstructive Sleep Apnea: Cardiovascular Risk of Obstructive Sleep Apnoea and Whether Continuous Positive Airway Pressure Reduces that Risk. Sleep Med Clin. 2016 Sep;11(3):273-86. doi: 10.1016/j.jsmc.2016.05.002. PMID: 27542874.
254. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnoea. J Clin Invest. 1995 Oct;96(4):1897-904. doi: 10.1172/JCI118235. PMID: 7560081; PMCID: PMC185826.
255. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J. 2009 May;33(5):1195-205. doi: 10.1183/09031936.00111208. PMID: 19407053.
256. Sen R, Baltimore D. Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. Cell. 1986 Dec 26;47(6):921-8. doi: 10.1016/0092-8674(86)90807-x. PMID: 3096580.
257. Karin M. Nuclear factor-kappaB in cancer development and progression. Nature. 2006 May 25;441(7092):431-6. doi: 10.1038/nature04870. PMID: 16724054.
258. Greenberg H, Ye X, Wilson D, Htoo AK, Hendersen T, Liu SF. Chronic intermittent hypoxia activates nuclear factor-kappaB in cardiovascular tissues in vivo. Biochem Biophys Res Commun. 2006 May 5;343(2):591-6. doi: 10.1016/j.bbrc.2006.03.015. Epub 2006 Mar 13. PMID: 16554025.
259. Htoo AK, Greenberg H, Tongia S, Chen G, Henderson T, Wilson D, Liu SF. Activation of nuclear factor kappaB in obstructive sleep apnoea: a pathway leading to systemic inflammation. Sleep Breath. 2006 Mar;10(1):43-50. doi: 10.1007/s11325-005-0046-6. PMID: 16491391.
260. Semenza GL. Hydroxylation of HIF-1: oxygen sensing at the molecular level. Physiology (Bethesda). 2004 Aug;19:176-82. doi: 10.1152/physiol.00001.2004. PMID: 15304631.
261. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab. 2006 Mar;3(3):187-97. doi: 10.1016/j.cmet.2006.01.012. PMID: 16517406.

262. Fandrey J. Oxygen-dependent and tissue-specific regulation of erythropoietin gene expression. Am J Physiol Regul Integr Comp Physiol. 2004 Jun;286(6):R977-88. doi: 10.1152/ajpregu.00577.2003. PMID: 15142852.
263. Cramer T, Yamanishi Y, Clausen BE, Förster I, Pawlinski R, Mackman N, Haase VH, Jaenisch R, Corr M, Nizet V, Firestein GS, Gerber HP, Ferrara N, Johnson RS. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell. 2003 Mar 7;112(5):645-57. doi: 10.1016/s0092-8674(03)00154-5. Erratum in: Cell. 2003 May 2;113(3):419. PMID: 12628185; PMCID: PMC4480774.
264. Dyugovskaya L, Polyakov A, Lavie P, Lavie L. Delayed neutrophil apoptosis in patients with sleep apnoea. Am J Respir Crit Care Med. 2008 Mar 1;177(5):544-54. doi: 10.1164/rccm.200705-675OC. Epub 2007 Nov 15. PMID: 18006889.
265. Rius J, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, Nizet V, Johnson RS, Haddad GG, Karin M. NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. Nature. 2008 Jun 5;453(7196):807-11. doi: 10.1038/nature06905. Epub 2008 Apr 23. PMID: 18432192; PMCID: PMC2669289.
266. Taylor CT. Interdependent roles for hypoxia inducible factor and nuclear factor-kappaB in hypoxic inflammation. J Physiol. 2008 Sep 1;586(17):4055-9. doi: 10.1113/jphysiol.2008.157669. Epub 2008 Jul 3. PMID: 18599532; PMCID: PMC2652186.
267. Li YE, Ren J. Association between obstructive sleep apnoea and cardiovascular diseases. Acta Biochim Biophys Sin (Shanghai). 2022 Jul 25;54(7):882-892. doi: 10.3724/abbs.2022084. PMID: 35838200; PMCID: PMC9828315.
268. Morand J, Arnaud C, Pepin JL, Godin-Ribuot D. Chronic intermittent hypoxia promotes myocardial ischemia-related ventricular arrhythmias and sudden cardiac death. Sci Rep. 2018 Feb 14;8(1):2997. doi: 10.1038/s41598-018-21064-y. PMID: 29445096; PMCID: PMC5813022.
269. Khayat R, Patt B, Hayes D Jr. Obstructive sleep apnoea: the new cardiovascular disease. Part I: Obstructive sleep apnoea and the pathogenesis of vascular disease. Heart Fail Rev. 2009 Sep;14(3):143-53. doi: 10.1007/s10741-008-9112-z. Epub 2008 Sep 20. PMID: 18807180; PMCID: PMC2698951.
270. Thomas JJ, Ren J. Obstructive sleep apnoea and cardiovascular complications: perception versus knowledge. Clin Exp Pharmacol Physiol. 2012 Dec;39(12):995-1003. doi: 10.1111/1440-1681.12024. PMID: 23082844.
271. Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnoea. Circulation. 1999 Mar 9;99(9):1183-9. doi: 10.1161/01.cir.99.9.1183. PMID: 10069786.
272. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnoea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest. 1997 Jan 1;99(1):106-9. doi: 10.1172/JCI119120. PMID: 9011563; PMCID: PMC507773.
273. Treptow E, Pepin JL, Bailly S, Levy P, Bosc C, Destors M, Woehrle H, Tamisier R. Reduction in sympathetic tone in patients with obstructive sleep apnoea: is fixed CPAP more effective than APAP? A randomised, parallel trial protocol. BMJ Open. 2019 Apr 4;9(4):e024253. doi: 10.1136/bmjopen-2018-024253. PMID: 30948567; PMCID: PMC6500296.

274. Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT 2nd, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med. 1979 Aug 30;301(9):453-9. doi: 10.1056/NEJM197908303010901. PMID: 460363.
275. Holmer BJ, Lapierre SS, Jake-Schoffman DE, Christou DD. Effects of sleep deprivation on endothelial function in adult humans: a systematic review. Geroscience. 2021 Feb;43(1):137-158. doi: 10.1007/s11357-020-00312-y. Epub 2021 Feb 9. PMID: 33558966; PMCID: PMC8050211.
276. Lv R, Liu X, Zhang Y, Dong N, Wang X, He Y, Yue H, Yin Q. Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnoea syndrome. Signal Transduct Target Ther. 2023 May 25;8(1):218. doi: 10.1038/s41392-023-01496-3. PMID: 37230968; PMCID: PMC10211313.
277. Hensley K, Robinson KA, Gabbita SP, Salsman S, Floyd RA. Reactive oxygen species, cell signaling, and cell injury. Free Radic Biol Med. 2000 May 15;28(10):1456-62. doi: 10.1016/s0891-5849(00)00252-5. PMID: 10927169.
278. Guo R, Ma H, Gao F, Zhong L, Ren J. Metallothionein alleviates oxidative stress-induced endoplasmic reticulum stress and myocardial dysfunction. J Mol Cell Cardiol. 2009 Aug;47(2):228-37. doi: 10.1016/j.yjmcc.2009.03.018. Epub 2009 Apr 1. PMID: 19344729; PMCID: PMC2703679.
279. Tobaldini E, Costantino G, Solbiati M, Cogliati C, Kara T, Nobili L, Montano N. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. Neurosci Biobehav Rev. 2017 Mar;74(Pt B):321-329. doi: 10.1016/j.neubiorev.2016.07.004. Epub 2016 Jul 7. PMID: 27397854.
280. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, Polotsky VY, Redline S, Somers VK. Sleep Apnoea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol. 2017 Feb 21;69(7):841-858. doi: 10.1016/j.jacc.2016.11.069. PMID: 28209226; PMCID: PMC5393905.
281. Orban M, Bruce CJ, Pressman GS, Leinveber P, Romero-Corral A, Korinek J, Konecny T, Villarraga HR, Kara T, Caples SM, Somers VK. Dynamic changes of left ventricular performance and left atrial volume induced by the mueller maneuver in healthy young adults and implications for obstructive sleep apnoea, atrial fibrillation, and heart failure. Am J Cardiol. 2008 Dec 1;102(11):1557-61. doi: 10.1016/j.amjcard.2008.07.050. Epub 2008 Sep 15. PMID: 19026314; PMCID: PMC2638210.
282. Turmel J, Sériès F, Boulet LP, Poirier P, Tardif JC, Rodés-Cabeau J, Larose E, Bertrand OF. Relationship between atherosclerosis and the sleep apnoea syndrome: an intravascular ultrasound study. Int J Cardiol. 2009 Feb 20;132(2):203-9. doi: 10.1016/j.ijcard.2007.11.063. Epub 2008 Jan 24. PMID: 18221805.
283. Launois SH, Averill N, Abraham JH, Kirby DA, Weiss JW. Cardiovascular responses to nonrespiratory and respiratory arousals in a porcine model. J Appl Physiol (1985). 2001 Jan;90(1):114-20. doi: 10.1152/jappl.2001.90.1.114. PMID: 11133900.
284. Reinhart WH, Oswald J, Walter R, Kuhn M. Blood viscosity and platelet function in patients with obstructive sleep apnoea syndrome treated with nasal continuous positive airway pressure. Clin Hemorheol Microcirc. 2002;27(3-4):201-7. PMID: 12454377.
285. Steiner S, Jax T, Evers S, Hennersdorf M, Schwalen A, Strauer BE. Altered blood rheology in obstructive sleep apnoea as a mediator of cardiovascular risk. Cardiology. 2005;104(2):92-6. doi: 10.1159/000086729. Epub 2005 Jul 7. PMID: 16015032.

286. Jayaprakash TP, Ogbue OD, Malhotra P, Akku R, Khan S. Impact of snoring on the cardiovascular system and its treatment: positive and negative effects of continuous positive airway pressure in sleep apnoea. Cureus 2020, 12: e9796

287. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnoea is independently associated with insulin resistance. Am J Respir Crit Care Med. 2002 Mar 1;165(5):670-6. doi: 10.1164/ajrccm.165.5.2103001. PMID: 11874812.

288. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhiravan T, Lakshmy R, Jagia P, Kumar A. CPAP for the metabolic syndrome in patients with obstructive sleep apnoea. N Engl J Med. 2011 Dec 15;365(24):2277-86. doi: 10.1056/NEJMoa1103944. Retraction in: N Engl J Med. 2013 Oct 31;369(18):1770. doi: 10.1056/NEJMc1313105. PMID: 22168642.

289. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, Pepin JL. Impact of obstructive sleep apnoea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. Sleep Med Rev. 2015 Jun;21:23-38. doi: 10.1016/j.smrv.2014.07.004. Epub 2014 Jul 31. PMID: 25220580.

290. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive Sleep Apnoea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 Jul 20;144(3):e56-e67. doi: 10.1161/CIR.0000000000000988. Epub 2021 Jun 21. Erratum in: Circulation. 2022 Mar 22;145(12):e775. doi: 10.1161/CIR.0000000000001043. PMID: 34148375.

291. De Luca M, Angrisani L, Himpens J, Busetto L, Scopinaro N, Weiner R, Sartori A, Stier C, Lakdawala M, Bhasker AG, Buchwald H, Dixon J, Chiappetta S, Kolberg HC, Frühbeck G, Sarwer DB, Suter M, Soricelli E, Blüher M, Vilallonga R, Sharma A, Shikora S. Indications for Surgery for Obesity and Weight-Related Diseases: Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). Obes Surg. 2016 Aug;26(8):1659-96. doi: 10.1007/s11695-016-2271-4. PMID: 27412673; PMCID: PMC6037181.

292. Kasai T, Floras JS, Bradley TD. Sleep apnoea and cardiovascular disease: a bidirectional relationship. Circulation. 2012 Sep 18;126(12):1495-510. doi: 0.1161/CIRCULATIONAHA.111.070813. PMID: 22988046.

293. Rodrigo Iturriaga, Julio Alcayaga, Mark W. Chapleau and Virend K. Somers. Carotid body chemoreceptors: physiology, pathology, and implications for health and disease Physiological ReviewsVolume 101, Issue 3Jul 2021Pages739-1456

294. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnoea and metabolic syndrome. Chest. 2008 Oct;134(4):686-692. doi: 10.1378/chest.08-0556. Epub 2008 Jul 14. PMID: 18625666.

295. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR, Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. Thorax. 2012 Dec;67(12):1081-9. doi: 10.1136/thoraxjnl-2011-201420. Epub 2012 May 5. Erratum in: Thorax. 2013 Sep;68(9):879. PMID: 22561530.

296. Sivam S, Phillips CL, Trenell MI, et al. Effects of 8 weeks of continuous positive airway pressure on abdominal adiposity in obstructive sleep apnoea. Eur Respir J 2012;40:913–8