Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms

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Abbreviated title: Cardiovascular consequences of obstructive sleep apnoea

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Summary

Obstructive sleep apnoea syndrome is a growing health concern, affecting nearly one billion people worldwide; it is an independent cardiovascular risk factor, associated with incident obesity, insulin resistance, hypertension, arrhythmias, stroke, coronary artery disease and heart failure. Obstructive sleep apnoea-related cardiovascular and metabolic co-morbidities are a major concern for prognosis and the complexity of obstructive sleep apnoea integrated care. Continuous positive airway pressure, the first-line therapy for the treatment of obstructive sleep apnoea, is highly effective at improving symptoms and quality of life, but has limited effect on co-morbidities. Deciphering the molecular pathways involved in obstructive sleep apnoea metabolic and cardiovascular consequences is a priority to make new pharmacological targets available, in combination with or as an alternative to continuous positive airway pressure. Intermittent hypoxia, a landmark feature of obstructive sleep apnoea, is the key intermediary mechanism underlying metabolic and cardiovascular complications. Experimental settings allowing intermittent hypoxia exposure in cells, rodents and healthy humans have been established to dissect the molecular mechanisms of obstructive sleep apnoea-related co-morbidities. The main objective of this review is to recapitulate the molecular pathways, cells and tissue interactions contributing to the cardiometabolic consequences of intermittent hypoxia. Sympathetic activation, low-grade inflammation, oxidative stress and endoplasmic reticulum stress are triggered by intermittent hypoxia, and play a role in cardiometabolic dysfunction. The key role of hypoxia-inducible factor-1 transcription factor will be detailed, as well as the underestimated and less described importance of mitochondrial functional changes in the intermittent hypoxia setting.

KEYWORDS

Obstructive sleep apnoea;

Intermittent hypoxia;

Cardiovascular consequences;

Hypoxia-inducible factor-1

Abbreviations: AHI, apnoea-hypopnoea index; CPAP, continuous positive airway pressure; ER, endoplasmic reticulum; HIF-1, hypoxia-inducible factor-1; IH, intermittent hypoxia; OSA, obstructive sleep apnoea.

Obstructive sleep apnoea syndrome: A systematic chronic disease

Epidemiology and diagnostic criteria

A diagnosis of obstructive sleep apnoea (OSA) is established by using the criteria recommended in the International Classification of Sleep Disorders, third edition (ICSD-3) [1]. OSA diagnosis requires either evocative symptoms or related medical/psychiatric co-morbidities coupled with at least five predominantly obstructive respiratory events (i.e. obstructive and mixed apnoeas, hypopnoeas or respiratory effort-related arousals) per hour of sleep during polysomnography. Alternatively, an index of obstructive respiratory events of 15/hour is a diagnostic criterion, even in the absence of associated symptoms or co-morbidities [1]. Severe OSA is, by consensus, defined by a threshold of more than 30 abnormal respiratory events per hour of sleep.

OSA is one of the most common chronic diseases, affecting nearly one billion people worldwide, and places a significant burden on individuals and society [2]. It is estimated that more than 30 million people are underdiagnosed in Europe [2]. Many recent studies have highlighted an increase in the worldwide prevalence of OSA, paralleling the obesity and type 2 diabetes epidemics [3]. OSA is now well recognized as an independent risk factor for cardiovascular and metabolic diseases but is largely underdiagnosed in patients in these at-risk populations [3]. OSA is independently associated with the prevalence and incidence of hypertension, stroke, coronary artery disease, heart failure and atrial fibrillation [3, 4]. OSA is also associated with metabolic disorders, such as obesity, insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease and metabolic syndrome [3]. Deciphering the mechanisms involved in OSA-associated cardiometabolic consequences is a major challenge for the field.

Physiopathology of OSA

OSA is characterized by the occurrence of repeated complete or incomplete pharyngeal collapses during sleep, producing intermittent hypoxia and sleep fragmentation [3]. The mechanisms underlying pharyngeal collapses are complex and multifactorial. Several factors influence the stability of the upper airway. Apnoeas and hypopnoeas occur in the context of anatomical reductions of the upper airway calibre as a result of obesity or maxillofacial or pharyngeal soft tissue abnormalities. The decrease in pharyngeal dilator activity at sleep onset triggers apnoeas and hypopnoeas that are ended by microarousals, allowing restoration of muscle activity and upper airway reopening. Other

factors, such as pharyngeal neuropathy, impairing protection of upper airway reflexes, or rostral fluid shift from the legs to the neck during sleep, are potent contributors to pharyngeal collapse [3].

Sleep apnoea diagnosis requires sleep studies (polysomnography) in the laboratory or under ambulatory conditions to assess sleep and cardiorespiratory variables. During respiratory event scoring in polysomnography analysis, an apnoea is defined as a reduction of the air flow by > 90% for at least 10 seconds. Obstructive hypopnoeas are characterized by airflow reductions of ≥ 30%, associated with a decrease in arterial oxygen saturation of > 3% and/or a microarousal (Fig. 1).

Polysomnography is the gold-standard method to record respiratory events during sleep, and allows calculation of the apnoea-hypopnoea index (AHI), defined by the number of apnoeas and hypopnoeas per hour of sleep. Only half of the patients with OSA are symptomatic, and a significant percentage of subjects are referred and treated with the goal of limiting their cardiometabolic risk. OSA is an heterogeneous condition, and phenotypic subgroups have been recognized that vary considerably in age, sex, symptoms, obesity, co-morbidities and environmental risk factors [5].

The recommendations of the American Academy of Sleep Medicine for sleep apnoea diagnosis [6] can be summarized as follows: (1) polysomnography is the standard diagnostic test for the diagnosis of OSA in adult patients in whom there is a concern regarding OSA, based on a comprehensive sleep evaluation, assessing symptoms and associated co-morbidities that characterize “at-risk populations”; (2) questionnaires and prediction algorithms should not be used alone to diagnose OSA in adults; (3) home sleep apnoea testing by respiratory polygraphy can be used for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate a high pretest probability of moderate-to-severe OSA; (4) if a single home sleep apnoea test is negative or inconclusive, polysomnography should be performed as a second step for the diagnosis of OSA.

OSA treatment options

As OSA is clearly associated with metabolic and cardiovascular conditions, effective treatment of OSA may therefore represent an important target for improving cardiometabolic risk. However, the effect of continuous positive airway pressure (CPAP), the first-line therapy for OSA, on cardiovascular or metabolic consequences is limited, and is still a matter of debate [3, 4]. Recently, the SAVE randomized trial, which included more than 2500 patients with moderate-to-severe OSA, demonstrated a positive effect of CPAP on neurocognitive function (anxiety, daytime sleepiness), but

failed to show a significant impact on the incidence of late cardiovascular events [7]. Whereas the majority of respiratory physicians limit their intervention to prescribing CPAP, there is a need to offer multiple treatment modalities to patients with OSA if their cardiovascular and metabolic risk profile is to be modified successfully. There is also an urgent need to combine pharmacological interventions guided by mechanistic insights with CPAP, to act synergistically.

Clinicians should adapt treatment modalities to the different clinical phenotypes and clusters of co-morbidities. From this perspective, the three main tools available to clinicians are positive airway pressure therapies (CPAP and/or non-invasive ventilation), oral appliances [8], body weight loss strategies and rehabilitation programmes to increase physical activity [9]. Among alternatives to CPAP, mandibular advancement devices have emerged as the leading alternative to CPAP. Mandibular advancement devices and CPAP are similarly effective in terms of their impact on symptoms, quality of life and attainment of reductions in blood pressure and cardiovascular morbidity. Although CPAP has a greater effect on AHI reduction, adherence is better with mandibular advancement devices. As recently supported by the American Thoracic Society consensus guidelines, additional therapies for body weight reduction must be recommended for overweight or obese patients with OSA initiated on CPAP. Moreover, weight loss and CPAP have synergistic effects on weight and metabolic variables compared with each intervention alone. Level of physical activity is another lifestyle characteristic that is associated with sleep-disordered breathing, and may be corrected by lifestyle intervention programmes. Evidence supports a combined treatment strategy in obese patients with OSA. Finally, the severity of OSA is influenced by body position, referred to as position-dependent OSA. Patients with position-dependent OSA can be treated by devices for positional therapy, providing a subtle vibrating stimulus that prevents them from adopting a supine position [10].

Cardiovascular consequences of OSA and intermittent hypoxia

As mentioned previously, OSA is well recognized as an independent risk factor for cardiovascular disease. In line with this statement, OSA is also well recognized as being associated with metabolic disorders, which are themselves tightly associated with cardiovascular pathologies. Whereas sleep fragmentation and respiratory efforts are contributing factors for OSA-associated pathologies, several clinical studies associate AHI with cardiovascular events. Moreover, preclinical studies performed on animal models showed that intermittent hypoxia (IH), mimicking the repetition of oxygen saturation-

desaturation cycles, is the main mechanism responsible for cardiovascular and metabolic OSA-associated complications.

As a major risk factor for the induction of cardiovascular disease, the first part of this section focuses on the main metabolic alterations in patients with OSA, induced by IH and well recognized as being associated with cardiovascular pathologies.

Metabolic disorders

Metabolic syndrome combines metabolic disorders, such as obesity, dyslipidaemia and insulin resistance, with a cardiovascular alteration, such as arterial hypertension or coronary artery disease. It is now widely recognized that sleep disorders, and particularly OSA, play a major role in the development of metabolic syndrome [11].

Accordingly, patients with OSA are insulin-resistant, and there is an increase in the prevalence of type 2 diabetes in patients with OSA, regardless of body mass index [12]. The severity of insulin resistance is directly correlated with nocturnal hypoxia in non-obese patients with OSA [13]. In a preclinical model, we recently demonstrated that 2 weeks of exposure to IH induced systemic insulin resistance associated with canonical insulin signalling pathway impairment in liver, adipose tissue and striated skeletal muscle in mice [14].

Lipid metabolism disturbances, characterized by hypercholesterolaemia, triglyceride increase, high density lipoprotein reduction and lipid peroxidation, are also found in patients with OSA. The desaturation index, another indicator of the severity of nocturnal hypoxia, has been identified as an independent contributing factor for hypercholesterolaemia and hypertriglyceridaemia [15]. Accordingly, the lipid profile of mice exposed to IH is also modified. Indeed, 4 weeks of IH induces an increase in total cholesterol, triglycerides and triglyceride-rich lipoprotein [16].

In line with the high prevalence of metabolic disorders in patients with OSA, several clinical studies have demonstrated a strong link between OSA and cardiovascular pathologies, such as arterial hypertension, coronary artery disease, arrhythmias and heart failure. A linear correlation was demonstrated between OSA severity (i.e. AHI) and vascular alteration, coronary artery disease, arrhythmias and heart failure [17].

Vascular remodelling, arterial hypertension and atherosclerosis

OSA is associated with vascular remodelling and endothelial dysfunction. In humans, the severity of vascular alterations is correlated with AHI [18]. In animal models, intima-media thickness was increased in the aorta from mice exposed to IH [19, 20], and this was associated with endothelial dysfunction, characterized by endothelial barrier alterations [21] and impairment of endothelium-dependent relaxation [22]. In addition, there is a linear relationship between AHI and the elevation of blood pressure, regardless of the associated confounding factors [23]. The role of IH in the development of hypertension has been demonstrated in many animal models [24, 25], as well as in healthy volunteers exposed to IH [26]. For example, several studies have investigated the link between IH-induced chemosensibility alterations [26], sympathetic nervous overactivity and hypertension [27]. The endothelin system has also been well described as playing a key role in IH-induced hypertension in rodents [24, 25] and humans [28].

In addition to vascular remodelling, patients with OSA present early signs of atherosclerosis development [18]. Exposure to 2 weeks of IH induces chronic low-grade inflammation associated with vascular remodelling [29]. Consequently, IH has also been shown to accelerate the development of atherosclerosis, certainly through its impact on the inflammatory process [19]. Whereas OSA and IH are associated with vascular remodelling, arterial hypertension and early atherosclerosis, moderate-to-severe OSA is also associated with an increased risk of coronary artery disease, arrhythmias and stroke, as well as with a high prevalence of heart failure.

Arrhythmia

OSA is linked to arrhythmias, such as atrial fibrillation or ventricular arrhythmias [30]. In addition, this OSA-associated increase in arrhythmia occurrence has been correlated with an increase in sudden cardiac death that occurs predominantly during sleep in patients with OSA, but not in the general population. Interestingly, OSA severity (i.e. nocturnal hypoxaemia) is directly correlated with the risk of nocturnal sudden cardiac death, independent of other well-established risk factors [31].

Proarrhythmogenic mechanisms have been identified in patients with OSA, such as sympathoactivation and alterations in ventricular repolarization (e.g. increased QTc and T_{peak}–T_{end} intervals [32]) and, in rodents, we have also reported that IH increases the duration of the T_{peak}–T_{end} interval and increases myocardial infarction-associated lethal ventricular fibrillation [33]. Finally, recent

studies have reported that 7 or 30 days of IH also generate atrial remodelling and arrhythmias in rodents [34].

Myocardial infarction and stroke

One-month and 3 months after myocardial infarction, patients with OSA have an increase in right ventricular end-diastolic volume [35]. We confirmed in rats and mice that chronic exposure to IH is responsible for the increase in myocardial sensitivity to ischaemia/reperfusion [23, 36]. In addition, and because of the prevalence of atrial fibrillation, OSA is recognized to be a risk factor for stroke occurrence [37]. In rodents, IH was demonstrated to induce neuronal alterations associated with stroke vulnerability [38], but no study has investigated the impact of IH in a cerebrovascular accident model.

Heart failure

Epidemiological studies have shown significant independent associations between OSA and heart failure [39]. In addition, observational studies have shown that survival is generally reduced in patients with heart failure with OSA compared with those without OSA [40]. Furthermore, as described above, despite effective reperfusion after acute myocardial infarction, patients with OSA have more severe coronary artery disease, prolonged myocardial ischaemia, lower myocardial rescue potential and greater ventricular deterioration than patients without OSA [41, 42]. All of these factors predispose to the development of heart failure, and contribute to increase mortality and/or recurrence of infarction. In rodent models, it has also been demonstrated that IH induces cardiac remodelling (hypertrophy, apoptosis and fibrosis) and contractile dysfunction [43], which participate in the development of heart failure.

The presence of sleep-disordered breathing is associated with increased mortality in patients with heart failure. However, positive airway pressure therapies are not recommended in all phenotypes of cardiac failure. The results of the large randomized Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial [44] reported a neutral primary endpoint result when adaptive servo ventilation was added to optimal medical therapy in patients with heart failure with reduced left ventricular ejection fraction, and mortality was actually higher in patients randomized to adaptive servo ventilation. Thus,

CPAP should be used cautiously, and adaptive servo ventilation therapy is currently contraindicated in this specific population.

Molecular and cellular mechanisms

A bidirectional relationship seems to exist between OSA and cardiovascular pathologies, but the mechanisms involved are still not very well described. The results of large-cohort studies of patients with OSA, coupled with preclinical studies performed on different experimental models of IH (cells, rodents, healthy volunteers) have highlighted that sympathetic activation, inflammation and oxidative stress are involved in the deleterious response to IH.

Sympathetic activation

Several clinical studies have shown an increase in circulating or urinary catecholamine concentration correlated with AHI in patients with OSA [45]. Sympathetic activation has been shown to be involved in OSA-associated heart failure [46] as well as in OSA-associated atrial fibrillation [47]. Healthy subjects exposed to 1 or 2 weeks of IH also showed signs of sympathetic activation characterized by an increase in sympathetic peroneal muscle nerve activity and a decrease in baroreflex sensitivity [26]. In preclinical studies, carotid body denervation, adrenal medulla removal and administration of adrenergic receptor antagonists have highlighted the role of the sympathetic nervous system in the metabolic and cardiovascular consequences of IH [11]. Moreover, sympathetic overactivation and chemoreceptor sensitivity reduction have been observed in mice exposed to IH [48]. In fact, studies evaluating the efficiency of sympathetic nervous system inhibitors and renin-angiotensin system modulators have demonstrated that neurohormonal activation is not the only mechanism responsible for the deleterious cardiometabolic effects of OSA [47].

Inflammation

OSA is associated with low-grade systemic inflammation, characterized by the presence of circulating markers of inflammation, such as C-reactive protein, cytokines (e.g. interleukin 6, tumour necrosis factor α) and adhesion molecules (e.g. intercellular adhesion molecule-1, vascular cell adhesion molecule-1, selectins). The levels of cytokines and adhesion molecules are correlated with the severity of nocturnal hypoxaemia [45]. Experimental models of OSA have confirmed that IH plays a major role

in inducing inflammation. Indeed, many studies have demonstrated both systemic and localized inflammation, characterized by the activation of nuclear factor kappa B (the main proinflammatory transcription factor) [20], an increase in the expression of proinflammatory cytokines and chemokines [19] and the recruitment of macrophages and their polarization in a proinflammatory M1 profile [12] in different tissues (vessels, heart, adipose tissue, liver). Indeed, it has been clearly established that inflammation induced by IH contributes to metabolic dysfunction [11], vascular remodelling and the development of atherosclerosis [29]. Although inflammation seems to be an important contributor to IH-induced metabolic and cardiovascular pathologies, the number of studies demonstrating an interesting effect of CPAP on this variable is low [45]. Moreover, no anti-inflammatory treatment has been shown to improve cardiovascular and metabolic disorders in patients with OSA [49].

Oxidative stress

OSA is now well characterized as a disrupter of the pro/antioxidant balance. Patients with OSA display a high level of superoxide anion in circulating leukocytes, an increase in nicotinamide adenine dinucleotide phosphate oxidase expression, an increase in lipid peroxidation or a decrease in antioxidant defences. These disturbances seem closely related to the repetition of hypoxia-reoxygenation cycles. Indeed, in rodent models, chronic IH also induced oxidative stress characterized, for example, by superoxide anion production, an increase in nicotinamide adenine dinucleotide phosphate oxidase expression and lipid peroxidation in vessels, heart and brain [50]. In rodents, the role of oxidative stress has also been demonstrated by the beneficial effects of antioxidant treatment during IH. For example, the endothelial dysfunction, vascular remodelling and increase in blood pressure and myocardial infarction size induced by IH were abolished by antioxidant treatment [25]. However, antioxidant treatment failed to improve the cardiometabolic consequences of OSA [51].

Other mechanisms

Although sympathetic activation, inflammation and oxidative stress seem to participate in the development of OSA-associated cardiovascular pathologies, it appears that these mechanisms do not represent interesting therapeutic targets to efficiently improve metabolic and cardiovascular

consequences of OSA compared with CPAP. Thus, it is essential to investigate other mechanisms that could be more specific to the chronic IH stimulus.

Among them, hypoxia-inducible factor-1 (HIF-1) represents an attractive strategy. In particular, HIF-1 is strongly induced by oxidative stress, one of the main consequences of the repetition of hypoxia-reoxygenation cycles [52].

HIF-1

HIF-1 is a major transcription factor that is activated in response to hypoxia; it is composed of two subunits: the oxygen-dependent α subunit and the β subunit. Briefly, HIF-1 activation during hypoxia depends on: (1) normoxia-induced inhibition of HIF-1α degradation by proteasomes; (2) HIF-1α nuclear translocation and dimerization with HIF-1β to bind the hypoxia response element in the gene's promotor; (3) HIF-1 binding to co-activators such as CREB-binding protein/p300; and (4) the level of factor inhibiting HIF-1 activity.

Oxidative stress/HIF-1 axis: Role in the deleterious consequences of OSA and HI

Although HIF-1 is a well-known transcription factor regarding cardioprotective effects when activated by brief episodes of hypoxia corresponding to pre- or postconditioning, its activation by chronic exposure seems to trigger the transcription of genes that are deleterious to the cardiovascular system. Indeed, the production of superoxide anion by repeated cycles of hypoxia-reoxygenation activates the phospholipase C pathway, including calcium/calmodulin-dependent kinase and protein kinase C. This leads to stimulation of mammalian target of rapamycin-dependent HIF-1α synthesis, inhibition of prolylhydroxylase (responsible for HIF-1α degradation under normoxic conditions) followed by HIF-1α stabilization, and phosphorylation of p300 co-activator, maintaining HIF-1 [52]. A clinical study has demonstrated an increase in HIF-1α expression in the skin of patients with OSA [53]. However, to date, the deleterious consequences of HIF-1 activation have essentially been investigated in rodents exposed to IH.

For example, with partial *HIF-1α* gene deletion in mice, Peng et al. demonstrated that IH-induced sympathetic activation depends on HIF-1 activity [48]. With the same mice, we demonstrated that chronic IH is responsible for an increase in HIF-1 activity that leads to an increase in nuclear factor

kappa B activity, resulting in increased intima-media thickness [20]. We have also shown that HIF-1, by binding to the hypoxia response element of the *endothelin-1* gene, leads to an increase in myocardial preproendothelin-1 and endothelin-1. Endothelin-1 system activation was associated with a rise in blood pressure and infarct size [24]. Indeed, in both studies, administration of bosentan (a dual endothelin-1 receptor antagonist) throughout IH exposure prevented the deleterious consequences of IH. The involvement of endothelin-1 in IH-induced vascular remodelling was also demonstrated in several vascular beds by Troncoso Brindeiro et al. [25], who showed that IH-generated oxidative stress was responsible for the increase in endothelin-1 content. Based on these preclinical data and clinical studies reporting elevated endothelin-1 plasma concentrations in patients with OSA, a pilot study was done in 16 patients with moderate OSA to compare the effects of bosentan and CPAP on blood pressure elevation. Although this study demonstrated a greater hypotensive effect of bosentan on diastolic blood pressure measured over 24 hours, it did not show any significant higher beneficial effect with bosentan compared with CPAP [54]. Actually, the "HIF-1/endothelin-1 axis" does not seem to be the main and only mechanism capable of explaining the metabolic and cardiovascular consequences of OSA. Thus, understanding HIF-1 activation in the context of IH needs to be explored further.

Endoplasmic reticulum stress/HIF-1 axis: Role in the deleterious consequences of OSA and HI

Although oxidative stress has been well described as inducing sustained HIF-1 activation, other mechanisms can have the same effect. Among them, we have recently been interested in the role of endoplasmic reticulum (ER) stress. Independent of OSA, many studies have revealed that ER stress is implicated in several OSA-related conditions, such as atherosclerosis, endothelial dysfunction, type 2 diabetes and susceptibility to ischaemia-reperfusion. It has now been clearly demonstrated that chronic IH, *per se*, induces ER stress in brain [55], kidney [56] and heart [36, 57, 58]. ER stress has also been demonstrated to be activated by IH in various cell models, such as cardiomyocytes [59] and hepatocytes [60]. In addition, we and others have recently shown that ER stress inhibition during chronic IH exposure might be a beneficial therapeutic approach regarding IH cardiovascular consequences. For example, administration of adiponectin [58] or overexpression of metallothioneins [59] reduces ER stress and protects against cardiomyocyte apoptosis under IH. Similarly, we

observed that exercise training decreased infarct size enlargement and ER stress, which are both induced by IH [57]. Finally, we recently highlighted the direct role of ER stress in HIF-1 activation, as an ER stress inhibitor (tauroursodeoxycholic acid), administered during IH, abolished both HIF-1 activation and the increase in infarct size [36]. Thus, the “HIF-1/ER stress axis” could represent a new therapeutic target of interest in the management of IH-induced cardiovascular complications in patients with OSA.

IH-involved HIF-1 activation: New tracks

As described above, IH is a potent inducer of oxygen homeostasis perturbation, redox status alteration and HIF-1 activation. Oxygen homeostasis and redox status are strongly managed by mitochondria; however, to date, there has been no investigation into the impact of IH on mitochondria status. As previously explained, HIF-1 activation depends on oxygen homeostasis and cellular redox balance. Conversely, HIF-1 itself regulates cellular redox status by modifying mitochondrial function, especially during hypoxia (Fig. 2). Briefly, during hypoxia, several HIF-1 target genes are translated to adapt mitochondrial function [52]. In particular, HIF-1 is able to replace the mitochondrial respiratory chain complex IV subunit COX4-1 with COX4-2; it increases the expression of glucose transporter, activates glycolysis for the production of pyruvate and activates lactate dehydrogenase for the production of lactate. In parallel, HIF-1 decreases the expression of pyruvate dehydrogenase to reduce the conversion of pyruvate in acetyl coenzyme A, dropping the supply of the respiratory chain. Moreover, under HIF-1 control, the mitochondrial dynamic is modified during hypoxia. An increase in mitochondrial biogenesis can be observed. This is associated with an increase in peroxysome proliferator-activated receptor gamma co-activator 1α expression, and also with an increase in autophagy and, therefore, mitophagy. This could be initiated by HIF-1, as it is well known to increase BNIP expression, and consequently the release of beclin-1, a key protein of autophagosome constitution. In line with the interest in exploring the “mitochondria/HIF-1 axis”, preliminary results from our laboratory have shown that, under the control of HIF-1, IH alters myocardial mitochondrial function and modifies its dynamic in inducing mitophagy.

Because of the importance of mitochondrial status in the metabolic function of each organ, and consequently in metabolic and cardiovascular pathologies associated with OSA, mitochondrial

homeostasis could be an extremely interesting new target for better understanding the impact of IH on the cardiovascular system.

Conclusions

Chronic IH is the most deleterious feature of OSA. Among the mechanisms responsible for the cardiometabolic consequences of IH, the role of the sympathetic nervous system, inflammation, oxidative stress, ER stress and HIF-1 are well established. However, it seems important to explore new mechanisms, such as those involved in mitochondrial homeostasis, and perhaps to study in detail the interactions between these different key players (Central illustration). This could lead to the identification of new biomarkers of cardiovascular risk in patients with OSA and/or the proposal of new therapeutic targets, in addition to or instead of the current treatment. Currently, HIF-1 seems to be a potential therapeutic target, as it collaborates with all deleterious mechanisms involved in IH consequences. However, HIF-1 was initially well described to be a pivotal actor in the adaptation to hypoxia [52]. It is now well established that, depending on hypoxic pattern (time, depth, repetition, etc.), HIF-1 can be beneficial (i.e. pre/postconditioning) or detrimental (i.e. heart remodelling, infarct size increase, etc.). This means that the scientific community has to better investigate the mechanisms involved in the switch from adaptive to maladaptive response to HIF-1 activation, to propose specific HIF-1 modulators for patients with OSA with a high cardiovascular risk.

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The authors declare that they have no conflicts of interest concerning this article.

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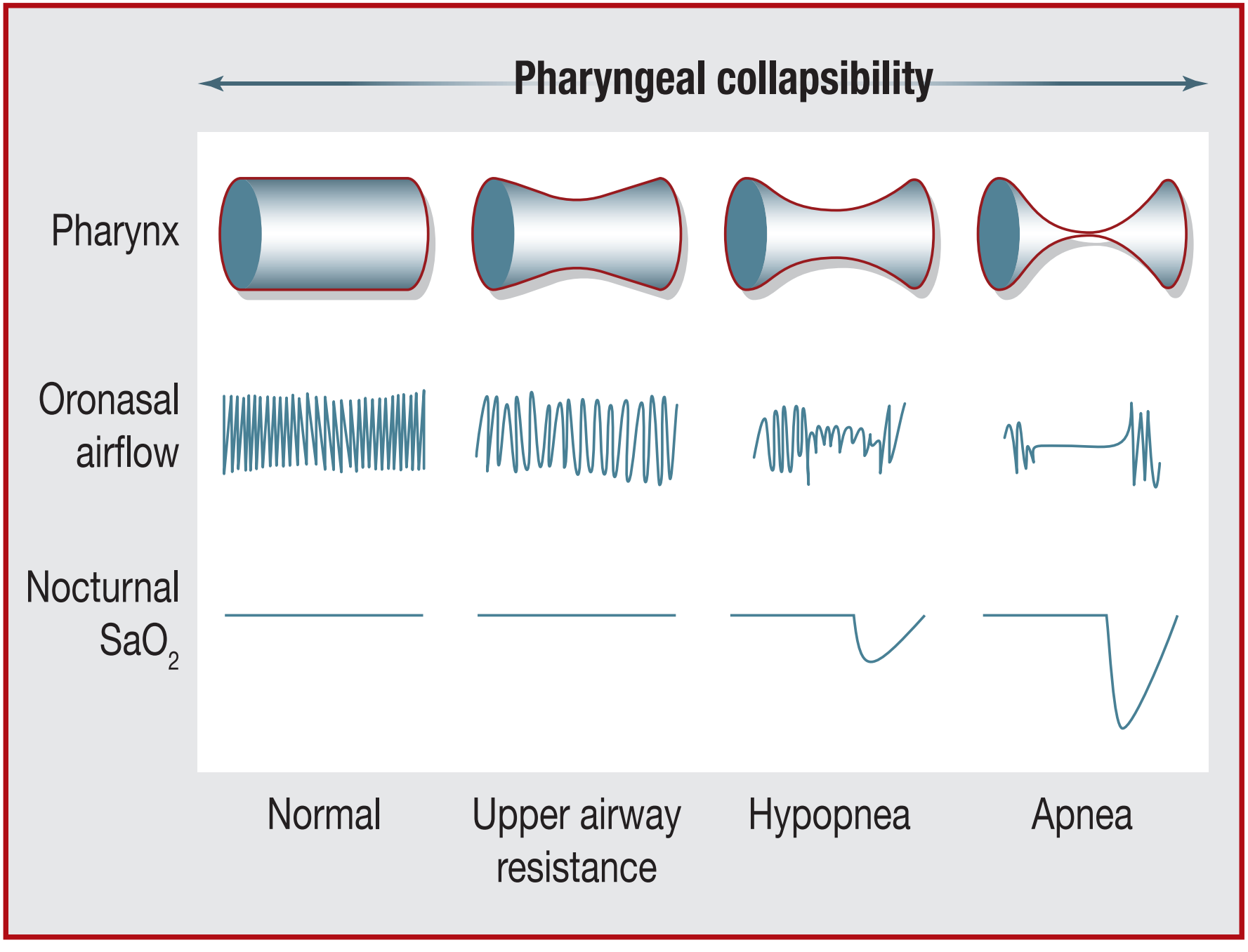
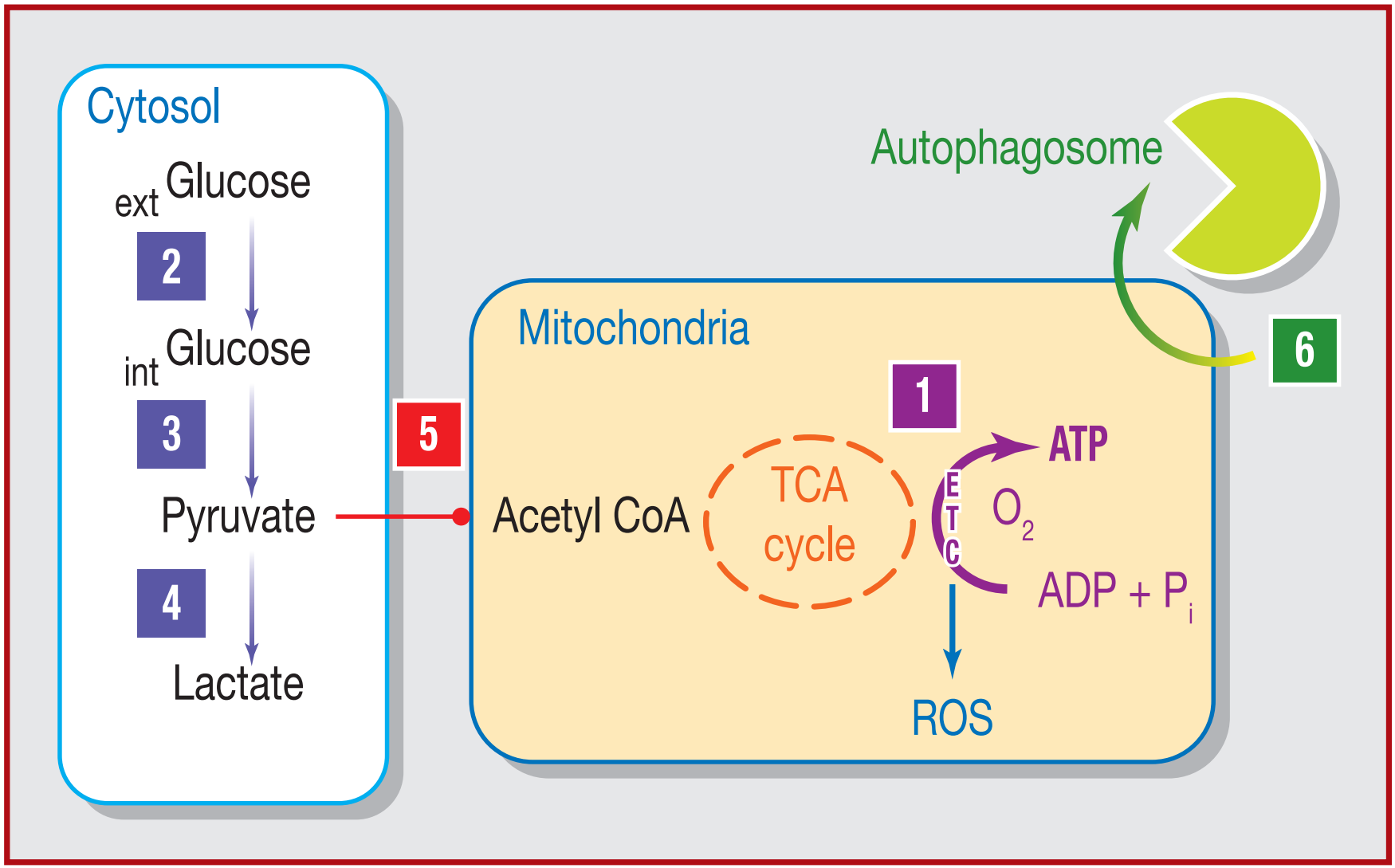
Figure legends

Figure 1. Scheme of severity of obstructive sleep apnoea respiratory events dependent on pharyngeal collapsus. Disturbances of oronasal airflow are correlated with the degree of pharyngeal obstruction. In severe cases of pharyngeal collapsus, oronasal flow is stopped. The degree of obstruction and oronasal airflow reduction are subsequently correlated with a higher decrease in nocturnal oxygen saturation (SaO_2).

Figure 2. Scheme of the mitochondrial impact of hypoxia-inducible factor-1 activation: (1) electron transport chain (ETC) structure modification; (2) increase in cellular glucose uptake; (3) glycolysis activation; (4) increase in pyruvate dehydrogenase activation and lactate production; (5) increase in pyruvate dehydrogenase kinase expression, avoiding the production of acetyl coenzyme A (CoA) and consumption in tricarboxylic acid (TCA) cycle; and (6) autophagy/mitophagy. ADP: adenosine diphosphate; ATP: adenosine triphosphate; ext: external; int: internal; P_i: inorganic phosphate; ROS: reactive oxygen species.

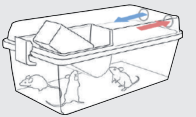
Central illustration. Mechanisms involved in deleterious consequences of obstructive sleep apnoea (OSA). Intermittent hypoxia (IH) leads to sympathetic nervous system overactivity, inflammation, oxidative stress and endoplasmic reticulum stress. Hypoxia-inducible factor-1 (HIF-1) seems to play a major role in OSA and IH consequences. Mitochondrial integrity could also be an interesting target to explain OSA-associated pathologies. Adapted from [61].

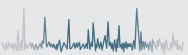

Pharyngeal collapsibility
Pharynx
Oronasal airflow
Nocturnal SaO_2
Normal
Upper airway resistance
Hypopnea
Apnea

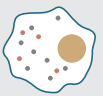

Cytosol
ext Glucose
2
int Glucose
3
Pyruvate
4
Lactate
5
Mitochondria
1
Acetyl CoA
TCA cycle
ETC
ATP
O2
ADP + Pi
ROS
Autophagosome
6

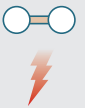
Sleep apnea syndrome

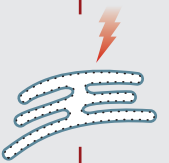
Chronic intermittent hypoxia











Sympathetic nervous system activation

Inflammation

Oxidative stress

Endoplasmic reticulum stress

Mitochondrial integrity ?

HIF-1

Arterial hypertension
Endothelial dysfunction
Atherosclerosis
Arrhythmia
Increase in infarct size
Heart failure

Metabolism disorders