Sleep Medicine Reviews 46 (2019) 9–16

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Matrix metalloproteinases as possible biomarkers of obstructive sleep apnea severity – A systematic review

Aleksandra Franczak [a, c], Iwona Bil-Lula [c], Grzegorz Sawicki [b, c], Mark Fenton [a, e], Najib Ayas [d, e], Robert Skomro [a, e, f, *]

[a] Division of Respiratory, Critical Care and Sleep Medicine, University of Saskatchewan, Saskatoon, Canada
[b] Department of Pharmacology, College of Medicine, University of Saskatchewan, Saskatoon, Canada
[c] Department of Medical Laboratory Diagnostics, Division of Clinical Chemistry, Wroclaw Medical University, Wroclaw, Poland
[d] University of British Columbia, Vancouver, B.C. Canada
[e] Canadian Sleep and Circadian Network
[f] Division of Angiology, Wroclaw Medical University, Wroclaw, Poland

ARTICLE INFO

Article history:
Received 28 January 2019
Received in revised form
18 March 2019
Accepted 25 March 2019
Available online 30 March 2019

Keywords:
Obstructive sleep apnea
Sleep disordered breathing
Matrix metalloproteinase
Oxidative stress
Cardiovascular disease
Systematic review

SUMMARY

Obstructive sleep apnea is an underdiagnosed sleep-related breathing disorder affecting millions of people. Recurrent episodes of apnea/hypopnea result in intermittent hypoxia leading to oxidative stress. Obstructive sleep apnea is considered an independent risk factor for cardiovascular disease but the exact pathophysiology of adverse cardiovascular outcomes of obstructive sleep apnea has not been fully elucidated. Matrix metalloproteinases (MMPs) have been associated with both oxidative stress and cardiovascular diseases. Hypoxic conditions were shown to influence MMP expression, secretion and activity. Moreover, matrix metalloproteinases contribute to ischemia/reperfusion injury. Therefore, action of matrix metalloproteinases can provide a possible molecular mechanism linking obstructive sleep apnea with oxidative stress and cardiovascular disease. The aim of this paper was to review the current evidence of association between matrix metalloproteinases and obstructive sleep apnea with focus on hypoxemia and severity of obstructive sleep apnea.

Introduction

Obstructive sleep apnea – clinical characteristics, prevalence and cardiovascular complications

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. It is characterized by recurrent episodes of airflow cessation (apnea) or reduction (hypopnea), caused by the decrease of upper airway dilating muscle activity during sleep superimposed on a narrow upper airway. These abnormalities impair normal ventilation during sleep and result in hypoxemia and sleep fragmentation as a consequence of frequent respiratory-related arousals leading to poor sleep quality, daytime somnolence and adverse effects on quality of life [1]. Cognitive complaints, fatigue and mood disorders are frequently observed. Furthermore, OSA is associated with worse work performance and higher risk of motor vehicle crashes [2].

OSA has been considered a major public health problem [3]. It affects all age groups but increases in prevalence with age. The prevalence of OSA is estimated as 13% among adult males and 5.6% among adult females [4]. OSA rates have been increasing worldwide along with the prevalence of obesity [5].

Despite the high prevalence and increased social awareness of OSA, this disorder still remains under-diagnosed. OSA is a condition with an insidious onset which can contribute to its delayed diagnosis. Data from a Canadian cross-sectional survey showed that only 5.1% of those at higher risk for OSA reported being referred to a sleep laboratory [6]. The delay in diagnosis and treatment leads to development of numerous complications. It has been shown that patients with untreated OSA are at higher risk of neurocognitive impairment, Alzheimer's disease and a wide range of cardiovascular conditions [7,8] such as systemic and pulmonary hypertension, heart failure, atherosclerosis, coronary artery disease and stroke [9,10]. The mechanisms which have been suggested to contribute to these adverse outcomes include sympathetic nervous

* Corresponding author. Room 553 Elis Hall, Royal University Hospital, Saskatoon, Saskatchewan, S7N 0W8, Canada. Fax: +1306 844 1532.
E-mail address: r.skomro@usask.ca (R. Skomro).

https://doi.org/10.1016/j.smrv.2019.03.010

Glossary of terms

AHI	apnea-hypopnea index
BMI	body mass index
CIH	chronic intermittent hypoxia
CRP	C-reactive protein
CVD	cardiovascular disease
ELISA	enzyme-linked immunosorbent assay
IL-6	interleukin 6
MMPs	matrix metalloproteinases
NF-κB	nuclear factor kappa B
ODI	oxygen desaturation index
RDI	respiratory disturbance index
ROS	reactive oxygen species
siRNA	small interfering RNA (ribonucleic acid)
SNP	single nucleotide polymorphism
SpO_2	blood oxygen saturation
SpO_2 <90%	time of blood oxygen saturation below 90%

system activation, inflammation, endothelial dysfunction and oxidative stress [8].

OSA as model of chronic intermittent hypoxia

The narrowing or collapse of upper airway is frequently associated with a repetitive transient decrease in arterial oxygen saturation [11]. Therefore, one of the hallmarks of OSA is CIH (chronic intermittent hypoxia). The hypoxic events and arousals can lead to sympathetic nervous system activation, which contributes to peripheral vasoconstriction and triggers an increase in arterial blood pressure and heart rate. Systemic hypertension can in turn promote cardiac hypertrophy, diastolic dysfunction and potentially lead to congestive heart failure. Furthermore, increased negative intrathoracic pressure, caused by the airway occlusion and resultant increased respiratory effort, generates an additional mechanical stress (increases in both pre-load and after-load) on the heart resulting in progression of cardiac remodeling. In addition to vasoconstriction, hypoxia leads to oxidative stress, inflammation and endothelial dysfunction, all of which are important element of atherosclerosis development. The adverse effect of CIH on the cardiovascular system may be a reason of premature death of OSA patients, mainly by a greater risk of myocardial infarction [12].

The exact pathophysiology of the adverse consequences of OSA is not fully-understood and is likely multi-factorial. However, it has been hypothesised that matrix metalloproteinases (MMPs) may be important markers of chronic intermittent hypoxia.

MMPs as markers of intermittent hypoxia

MMPs are proteolytic enzymes, which take part in remodeling of extracellular matrix and have also been shown to have a biological action within the cell as well [13]. They are essential for the wide range of physiological processes; their dysregulation may contribute to development of pathological conditions including CVD (cardiovascular disease) [14]. They have been shown to play a role in development of dilated cardiomyopathy, cardiac remodeling after myocardial infarction and atherosclerotic plaque rupture [15]. Recent evidence suggests that MMPs contribute not only to long-term remodeling processes but also to acute ischemia-reperfusion injury in the heart [16].

MMPs are synthesized as inactive zymogens by inflammatory cells, fibroblasts and endothelium. They are activated by the disruption of bond between a cysteine thiol residue and the active zinc ion site. This can be achieved by two mechanisms. First, several proteases (such as plasminogen, kallikrein, tissue plasminogen activator, trypsin as well as MMPs themselves) can cause proteolysis of the propeptide domain. Secondly, reactive oxygen species (ROS) can directly change a protein conformation exposing catalytic site of MMP [17]. Oxidative stress during ischemia/reperfusion or asphyxia causes an increase in MMPs action and leads to adverse cardiovascular consequences [18–20]. Recurrent episodes of apneas/hypopneas in OSA cause a desaturation-reoxygenation sequence that resembles ischemia/reperfusion injury which is associated with excessive production of reactive oxygen species (ROS) and upregulation of oxidative stress markers and impaired antioxidant capacity in OSA [21]. In addition, the results of studies on human and animal cell cultures have shown that MMPs expression, secretion and activity are induced by hypoxic conditions [22,23], which resemble those present in OSA patients, thus suggesting a potential role of MMPs in OSA.

ROS, generated during CIH, can directly activate MMPs. Moreover, the MMPs activity can also be affected at the transcriptional level. CIH-mediated NF-κB (nuclear factor kappa B) pathway activation is an example of such regulation [24,25]. NF-κB upregulates not only numerous inflammatory cytokines and adhesion molecules, but also plays a role in the regulation of MMPs transcription [26,27]. Bond et al. have also shown that NF-κB is necessary to upregulate MMPs secretion by vascular smooth muscle cells [26]. The activation of NF-κB along with MMPs action can be a molecular mechanism linking OSA with oxidative stress, inflammation and in turn cardiovascular complications. The potential modes of action of MMPs in response to chronic intermittent hypoxia are summarized in Fig. 2.

Moreover, some studies report different single nucleotide polymorphisms (SNP) in the promoter region of MMPs in OSA patients [28–30], which may influence MMPs expression. However, the results of these studies are inconsistent. It was shown that MMP-9 SNP (1562C/T) was associated with higher risk of OSA in Chinese [29], but not in Turkish population [30]. Moreover, another study in Turkish population showed that allele frequencies of MMP-9 1626C/T SNP significantly differ between OSA patients with CVD compared to those without CVD. However, MMP-9 genotype was not associated with MMP-9 level in serum [28]. MMP-2 SNP (−1306C/T) has not been shown to be associated with risk of OSA [29].

The aim of the review

OSA can be considered a model of chronic intermittent hypoxia (CIH). Therefore, based on several lines of aforementioned evidence that MMPs play a role in hypoxia and CVD, it could be hypothesized that MMPs can be biomarkers of severity of hypoxemia, severity of OSA and may potentially be useful biomarkers of cardiovascular complications in OSA.

Considering the complexity of cardiovascular comorbidities in OSA, finding biomarkers which allow detection of patients at higher risk is a great challenge for sleep apnea research and clinical management. Although a lot of effort has already been expended in searching for possible biomarkers, the results are still inconclusive. Blood-based markers of inflammation (interleukin 6 (IL-6), C-reactive protein (CRP), high sensitivity CRP and tumor necrosis factor-α), hemodynamic cardiac stress (N-terminal-B-type natriuretic peptide), myocardial injury (cardiac troponins) as well as indicators of antioxidant capacity and oxidative stress (thioredoxin, superoxide dismutase, malondialdehyde) have been proposed [31–35]. In this paper, we have reviewed the available literature about MMPs in this regard.

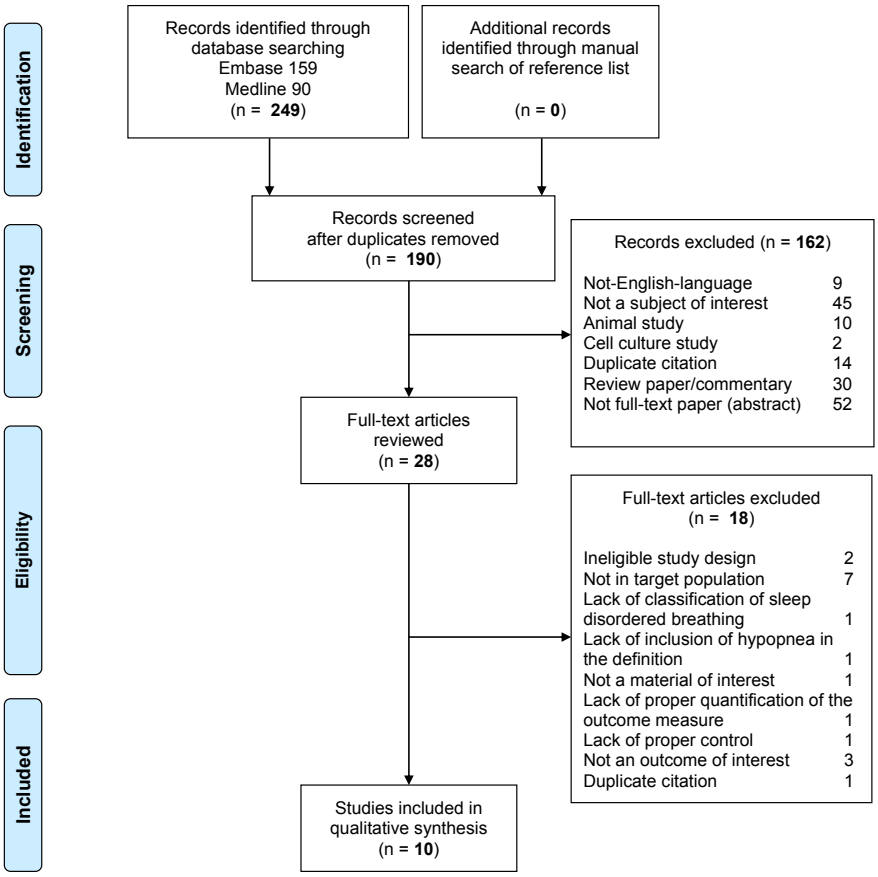

Fig. 1. Flow diagram.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA Checklist [36]. Our PICO question was: In patients with diagnosed moderate to severe OSA (P), will the severity of OSA (I) be associated with elevated levels of MMPs in biological samples (O) in comparison with patients without OSA or those with mild OSA (C)? Only studies involving human OSA subjects (adult and children) published in English were included. We have reviewed EMBASE (05/12/2018) and Medline (via Ovid – including in-process and other non-indexed citations; 05/12/2018) – see search details in Appendix 1. Duplicates were removed through EndNote, and then titles and abstracts were reviewed manually by two authors (AF, RS). After initial screening, two investigators (AF, RS) reviewed independently the full-text manuscripts. References from the retrieved manuscripts were verified manually by two authors (AF, RS) to see if we missed any articles suitable for inclusion in this review. The process for selecting studies is provided in the flow chart (see Fig. 1). The study quality was assessed with the modified Newcastle-Ottawa Scale (see Appendix 2).

Results

Our search results revealed overall 249 articles. After excluding studies which did not meet our criteria (see Fig. 1) 10 manuscripts were reviewed (see Table 1). All of these concerned MMP-9 and MMP-2.

MMP-9 in adult OSA patients

Our review identified eight publications that addressed the question of MMP-9 levels and activity in adult OSA patients. In all those articles, MMP-9 was analyzed in blood (serum, plasma, monocytes isolated from peripheral blood). The vast majority of results (five out of eight) showed that an increased blood MMP-9 level was associated with OSA and its increase was more notable in patients with severe OSA [22,37–40].

Tamaki et al. have shown that the production of MMP-9 by peripheral blood monocytes of patients with both severe and mild/moderate OSA was significantly higher compared to control; however there were no difference between severe and mild/moderate OSA [38].

Nevertheless, Bonanno et al. did not report any significant association between serum MMP-9 level and OSA, however, in severe OSA, a trend to increase MMP-9 level was observed [41]. Maeder et al. [42] and Volná et al. [43] also did not report any significant differences in blood MMP-9 concentrations in regards to OSA severity (defined by AHI (apnea-hypopnea index)).

The results of the study carried out by Hopps et al. provided some evidence of association between MMPs and oxidative stress in OSA. In this study a positive correlation between plasma levels of MMP-9 and lipid as well as protein peroxidation markers was found [44]. ROS can activate MMPs and indeed, Tazaki et al. showed that serum MMP-9 activity was elevated in patients with OSA compared to controls. Moreover, that activity was positively correlated with AHI [39].

A positive correlation between MMP-9 and level of hypoxemia expressed as ODI (oxygen desaturation index) and/or SpO_2 <90%

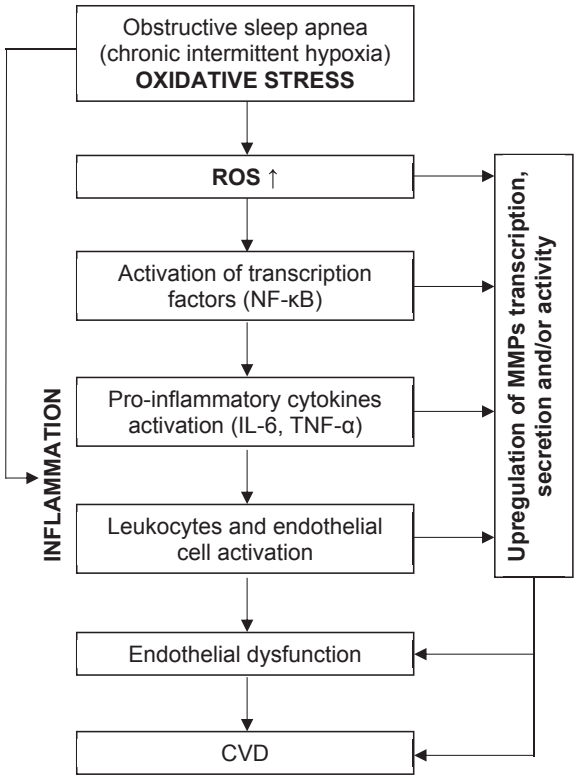

Fig. 2. Potential MMP (matrix metalloproteinases) modes of action in response to chronic intermittent hypoxia. CVD, cardiovascular disease; IL-6, interleukin 6; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α.

(time of blood oxygen saturation below 90%) was shown in five studies [22,37,39,40,43]. Moreover, a negative correlation between MMP-9 and mean oxygen saturation was found [37,43]. All these results are in accordance with findings that hypoxic condition can induce MMP-9 expression, secretion and activity [22] which indicate that oxidative stress, one of the crucial factors of CVD, may contribute to pathophysiology of OSA by stimulation of MMPs action.

Bearing in mind that MMP-9 can be upregulated by pro-inflammatory cytokines, a positive correlation between serum levels of MMP-9 and IL-6 (interleukin 6) and TNF-α found in OSA patients by Tazaki et al. is not surprising [39]. Also, Ye et al. found a positive correlation between serum MMP-9 concentration and CRP level [40]. Moreover, Wang et al. [22] suggested that MMP-9 may be a predictor of CVD in OSA patients. During up to five-year long follow-up of 35 patients without hypertension, 12 of them developed hypertension and three patients had left ventricular hypertrophy. Increased serum level of MMP-9, OSA severity (defined by AHI) and decreased lowest SpO_2 were risk factors for new hypertension onset. All patients who developed left ventricular hypertrophy had an elevated serum levels of MMP-9.

In summary, the preponderance of evidence suggests that circulating MMP-9 level is increased in patients with OSA and this increase is related to OSA severity [22,37–40], inflammation [39,40] and/or severity of hypoxemia [22,37,39,40,43].

MMP-9 in OSA among children

There is only one study concerning MMP-9 in children with OSA. Kaditis et al. [45] showed that plasma MMP-9 level was correlated with CRP and BMI (body mass index), but there was no association between MMP-9 and severity of OSA. The vast majority of children (92.5%) were less than 10 y old. The AHI ranged from <1 episode/hour in patients without OSA to approximately three episodes/hour in mild OSA and 13 episodes/hour in moderate-to-severe OSA patients. The ODI ranged from 0.9 ± 0.6 to 15.6 ± 14.1 episodes/hour, depending on the OSA severity. There were no significant differences between MMP-9 level in children with and without OSA, which is in contrast to most studies in adults. This finding could be explained by the fact that children with OSA often do not have as advanced hypoxemia as adult patients. Therefore, the molecular CIH-dependent mechanisms of MMPs stimulation in children OSA patients may not be activated. The authors concluded that the primary reason for elevated MMP-9 level in blood of children with OSA may be inflammation which results from factors other than hypoxemia.

MMP-2 in adult OSA patients

Current literature on the subject of MMP-2 is more limited and inconclusive. Our search revealed only four published papers concerning MMP-2 in adults with OSA and no studies in children. MMP-2 was analyzed in serum or plasma in three manuscripts [37,41,43] and one article investigated the presence of MMP-2 in superior pharyngeal constrictor muscle specimens (however, MMP-2 protein was not detectable [46]). Only one study [37] reported an increased MMP-2 plasma level in OSA patients; however, without any correlation with OSA severity (defined by AHI) [37]. Another study showed no association between OSA and blood levels of MMP-2 [43]. Interestingly, Bonanno et al. reported that MMP-2 level was lower in patients with severe OSA (here defined as respiratory disturbance index (RDI) >30) compared to subjects with RDI <30 [41]. In summary, the evidence linking MMP-2 and OSA severity is scarce with limited data in adults and no studies in children with OSA.

Discussion

OSA is the most common sleep-related breathing disorder, which still remains underdiagnosed [6]. It leads to numerous cardiovascular complications which affect quality and length of patients' life [21]. Given that, early diagnosis is crucial to implement proper therapy early in the course of the disease to prevent adverse consequences related to OSA severity - decreasing incidence of CVD events among others. However, solely clinical criteria are insufficient to identify patients at higher risk for cardiovascular events. This review suggests that MMP-9 may be promising biomarker in this regard.

The preponderance of evidence suggests an association between MMPs (particularly MMP-9) and severity of OSA. Five out of eight studies that examined relationship between MMP-9 and OSA showed that MMP-9 level was elevated in patients with OSA in comparison with patients without OSA or those with less severe OSA [22,37–40]. Additionally, another study [41] reported a trend to increase MMP-9 level in severe OSA, however, without statistical significance (this may have been due to the lack of statistical power). Moreover, data from the reviewed studies suggests that MMP-9 may be potentially an indicator of level of hypoxemia, as in a few studies MMP-9 level was found to positively correlate with ODI and SpO_2 <90% [37,39,40,43].

The literature on the subject of MMP-2 in OSA is limited to four papers, therefore drawing any conclusions about MMP-2 association with OSA is difficult. However, there is the strong evidence of association between MMP-2 and oxidative stress in animal studies [14,27,47] and thus future studies of MMP-2 in larger samples of OSA patients should be considered, given the fact that recurrent episodes of apnea/hypopnea result in intermittent hypoxia and in turn lead to oxidative stress [21].

Table 1
Overview of studies of MMPs in OSA.

Author, reference number	Study design	Number of subjects	Type of diagnostic study[a]	Type of MMPs	Material	OSA definition	Compared groups	The direction of changes in MMP level[b]		Comment
								MMP-2	MMP-9	
Bonanno et al. [41]	Cross-sectional	50	Type 1	MMP-2 MMP-9	Serum	RDI $\geq$ 5	Severe (RDI >30) vs non-severe	↓	↑[c]	
Dantas et al. [46]	Case-control	51	Type 1	MMP-1 MMP-2	Superior pharyngeal constrictor muscle specimens	AHI $\geq$ 5	Cases vs controls	MMP-2 was not detectable (IHC).		Variable MMP-1 expression (IHC) within the same muscle fiber and between patients.
Hopps et al. [37]	Case-control	79	Type 3	MMP-2 MMP-9	Plasma	AHI $\geq$ 5	Severe (AHI >30) vs controls	↑	↑	MMP-9 positively correlated with AHI, ODI and negatively correlated with mean SpO_2.
							Severe vs mild/moderate	N	↑	
							Mild/moderate (5 $\leq$ AHI <30) vs controls	↑	↑	
Kaditis et al. [45]	Case-control	106	Type 1	MMP-9	Plasma	AHI $\geq$ 1	Moderate/severe (AHI>5) vs mild (1 $\leq$ AHI <5) vs control		N	Study in children.
Maeder et al. [42]	Cross-sectional	71	Type 1 or type 3	MMP-9	Plasma	AHI > 5	Moderate/severe (AHI $\geq$15) vs mild/no (AHI <15)		N	
Tamaki et al. [38]	Case-control	46	Type 1	MMP-9	Blood monocytes	AHI $\geq$ 10	Severe (AHI $\geq$30) vs controls		↑	
							Mild/moderate (AHI <30) vs controls		↑	
Tazaki et al. [39]	Case-control	62	Type 1	MMP-9	Serum	AHI $\geq$ 5	Moderate/severe (AHI $\geq$20) vs controls		↑	MMP-9 level and activity positively correlated with AHI and SpO_2 <90%.
							Moderate/severe vs mild (5 < AHI <20)		↑	
							Mild vs controls		↑	
Volná et al. [43]	Cross-sectional	51	Type 3	MMP-2 MMP-9	Serum	AHI > 5	Severe vs moderate vs mild vs controls	N	N	MMP-9 level positively correlated with ODI and SpO_2 <90% and negatively correlated with mean SpO_2.
Wang et al. [22]	Cohort retrospective	47	Type 3	MMP-9	Serum	AHI $\geq$ 5	Moderate (15 $\leq$ AHI <30) vs mild (5 $\leq$ AHI <15)		↑	MMP-9 level positively correlated with AHI, ODI and mean atrial pressure.
							Severe (AHI >30) vs mild		↑	
Ye et al. [40]	Case-control	76	Type 1	MMP-9	Serum	AHI $\geq$ 5	Moderate/severe (AHI $\geq$20) vs controls		↑	MMP-9 positively correlated with AHI and SpO_2 <90%.
							Moderate/severe vs mild (5 $\leq$ AHI <20)		↑	
							Mild vs controls		↑	

Legend: AHI, apnea-hypopnea index; CRP, C-reactive protein; IHC, immunohistochemical analysis; MMP, matrix metalloproteinase; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RDI, respiratory disturbance index; SpO_2, blood oxygen saturation; SpO_2 <90%, time of blood oxygen saturation below 90%.

[a] According to American Academy of Sleep Medicine criteria.

[b] MMP concentration, unless otherwise noted; ↑ increase; ↓ decrease; N no difference.

[c] Without statistical significance.

Study limitations

Our search has provided important insight into association between MMP level and OSA severity, however, the results of current literature on this subject are still preliminary. In most of the studies, sample sizes were small (N = 50–70), which may have affected statistical powers of the study and different indexes (AHI, RDI) were used to express OSA severity (see Table 1).

Moreover, OSA definition varied across the studies. Most studies defined OSA by an AHI ≥5/hr, however, some used the cut-off of AHI ≥10/hr or RDI ≥5/hr (see Table 1). Some of the studies used 3% desaturation to score hypopnea [43,45], others 4% [38,40–42], while Hopps et al. used a 3% or 4% drop in oxygen saturation, depending on % in reduction of breathing [37]. Three of studies did not note the cut-off for oxygen desaturation at all [22,39,46].

Furthermore, only six of studies used the gold standard for OSA diagnosis (see Table 1), and very few controlled for confounders. MMPs have been shown to have an impaired pattern in various CVDs, inflammatory diseases and metabolic syndrome [15,48]. MMP levels may depend on age and gender [49]. However, in only four studies [38–40,45] the potential confounders (age, gender, BMI, CRP concentration [45]; BMI, age [38,40]; BMI, waist circumference, waist/hip ratio [39]) were adjusted for in the analysis. Although some authors tried to address presence of confounders in the study design by excluding patients who have had CVD or systemic infections, CVD were often not well-defined [38,39,41,45] or limited to heart failure [42]. Two studies did not address the issue of confounding at all [37,44]. Hopps et al. [37] not only did not control for it, but enrolled in the study group patients with OSA and CVD, whereas control subjects were free of medical illnesses which were however not defined in detail.

Furthermore, majority of study designs were either cross-sectional or case–control in their design. Only one study was a cohort in its design to determine if MMP-9 level can be a predictor for CVD development and demonstrated possible role of MMP in development of CV complications [22]. However, numerous limitations of this study should be listed. First, sample size was small (n = 47), and cohort chosen for follow-up constituted only 35 subjects. Second, OSA diagnosis was based on cardiorespiratory study (which is not a gold standard). It is also not clear from the paper if patients enrolled for follow-up were free from CVD (if assuming so, it still remains unknown how CVD was defined).

Last but not least, there are also some methodological limitations of reviewed studies. Only one study [39] used two techniques (enzyme-linked immunosorbent assay (ELISA) and gelatin zymography) for MMP-9 measurement, whereas others used only one (ELISA or another immunoassay technique). It should be emphasized that ELISA and zymography differ significantly in regard to the principle of methodology. More precisely, immunoassay technique quantifies protein concentration based on reaction of antigen and antibody, whereas gelatin zymography is based on the gelatinolytic (proteolytic) activity of the enzyme and the latter one is more important from biological point of view. Moreover, in methods based on interaction of antigen and antibody (ELISA) there are many limitations associated with specificity and selectivity of the antibodies used for the detection of antigen, whereas zymography allows for detection of specific enzyme based on its catalytic activity and molecular weight [50,51].

Despite a number of limitations, the association between MMPs and OSA seems to be likely, especially in the light of biological plausibility. An elevated MMP-9 level in OSA patients with more severe disease compared to those with less severe or without OSA is in accordance with suggested contribution of oxidative stress and inflammation to OSA development [11], because MMPs' expression, secretion and activity may be modulated by hypoxia and inflammation [22,27]. Keeping in mind these feasible links between OSA, oxidative stress, inflammation, CVD and MMPs (see Fig. 2), MMPs seem to be promising proteins for identification OSA patients at higher risk of CVD. Apart from the above-mentioned cohort study of Wang et al. [22], additional report showed that serum MMP-9 level was significantly increased in OSA patients with CVD (coronary artery disease, hypertension and cardiac arrhythmia) compared to those without CVD [28].

The studies in animal models also provide the evidence on the CIH-modulated MMP response and its potential association with CVD. Some authors have shown that CIH induce cardiac fibrosis in rats. Fibrosis results from an imbalance in extracellular matrix turnover which can be explained by observed significant changes in MMP levels in hearts of rats subjected to CIH [27,52–54]. However, analogously to human studies, results regarding the direction of these changes are not consistent [27,52–54].

The observations from the animal studies cannot be directly applied to humans, considering the anatomical and biochemical differences between species and the limitations of animal models to mimic the human OSA pathophysiology. Only one model applied the airway obstruction which is an integral component of OSA [54]. Furthermore, MMPs were not analyzed in body fluids, but in cardiac tissue. Moreover, various time of CIH was applied which also can be an explanation of observed differences in direction of changes in MMP levels. Also, the effect of short-term hypoxia varies from the long-term effect [55] and in the above-mentioned papers the time of protocol varied from 7 d to 5 wk with different pattern of hypoxia/normoxia cycles.

However, the animal studies, similarly to the human ones reviewed in this paper, provide some evidence that CIH has an impact on MMP response. Due to MMP's substrate specificity with respect to extracellular matrix proteins, it can lead to cardiac fibrosis and in consequence, CVD. Cardiac remodeling is associated with cardiac dysfunction which may manifest itself as malignant ventricular arrhythmias, heart failure and myocardial infarction complications [15], all of which have an increased prevalence in OSA patients. In addition, patients with OSA commonly develop left ventricular hypertrophy [56].

Given MMPs possible contributions to OSA adverse cardiovascular consequences, MMPs may also become a therapeutic target. Wang et al. showed that doxycycline, administered to rats for four weeks while receiving CIH, attenuated atrial fibrosis induced by CIH by modulation of MMP-2 and MMP-9 expression [53]. In the studies on ischemia/reperfusion injury in rat hearts it was shown that doxycycline prevented MMP-2-induced troponin I degradation and improved cardiac mechanical function [13,16]. Doxycycline, analogically to other studied MMP inhibitors such as o-phenanthroline and hydroxamates, inhibits MMPs non-selectively by chelating zinc ion in catalytic site of MMPs. Currently, doxycycline is the only clinically approved inhibitor of MMPs [17]. However, in the randomized controlled trial in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass, doxycycline (20 mg) did not improve myocardial stunning following the surgery, despite the fact that the atrial MMP-2 activity was decreased. Authors suggested that higher dose of doxycycline should be considered in the next larger trials [57]. Lin et al. showed that MMP-2 siRNA (small interfering RNA), by specific inhibition of MMP-2 expression and activity, led to protection of contractile function of isolated rat cardiomyocytes subjected to chemical ischemia [58]. Due to increasing interest in the molecular therapy and precision medicine, there is a growing potential for the use of MMP-2 siRNA in clinical trials [59].

In conclusion, there are plausible biological mechanisms linking an increase in MMP levels and OSA and the preponderance of evidence from this systematic review suggests that MMPs

(especially MMP-9) is elevated in OSA patients. These studies however are limited by their study design, small subject number and lack of adjustment for confounders. Although there are a few negative studies, MMPs seem to be promising predictors of hypoxemia and severity of OSA. It is possible therefore that they may be useful markers of adverse cardiovascular outcomes in OSA which appear to be mediated by hypoxemia. However, the results of studies published on this subject are inconclusive and, thus, further research is needed to delineate the exact role of MMPs in OSA, particularly in the subset of patients with CV complications.

Future studies should be performed in larger samples of both children and adult populations, should be cross-sectional and prospective in their design, should adequately control for confounders and must be adequately powered to detect a difference in MMP levels.

Practice points

Matrix metalloproteinases are important molecules in obstructive sleep apnea research, because:

- Animal studies suggest involvement of MMP in models of CIH and their role in cardiovascular disease.
- The majority of studies suggest increased MMP levels (MMP-9 in particular) in patients with obstructive sleep apnea.
- The existing studies suggest presence of association between blood level of MMP-9 and obstructive sleep apnea severity in adults.
- Increased MMP levels in OSA patients may result from higher level of hypoxemia and therefore, MMPs could be a molecular mechanism linking OSA with oxidative stress and cardiovascular disease.
- There is very limited literature on this subject in children.
- There are no prospective studies evaluating the role of MMPs in predicting cardiovascular complications in OSA patients.
- Existing studies suffer from methodological weaknesses, especially in their approach to handling confounding.

Research agenda

- Future research should be aimed at delineating the role of matrix metalloproteinases in obstructive sleep apnea with focus on their associations with hypoxemia, severity and cardiovascular outcomes of the disease.
- Larger sample sizes are required in future studies.
- The current gold standard (i.e., in-lab PSG) should be used for diagnosis of OSA.
- Severity of the disease should be categorized according to American Academy of Sleep Medicine criteria.
- Future studies should be long term and must be powered to detect difference in MMP levels.
- More studies of MMP in children with OSA are needed.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Acknowledgements

The authors wish to acknowledge grant support from Canadian Sleep and Circadian Network.

The Canadian Sleep and Circadian Network (CSCN) is national in scope and is committed to scientific excellence in the generation of new knowledge and its translation. The CSCN was developed through a grant from the Canadian Institutes of Health Research combined with funds from partners and stakeholders. The network is inclusive, multidisciplinary and multi-thematic. It strives to facilitate effective interactions and collaborations between the scientific community, patients and stakeholders. It also has a training and career development mandate for the national sleep and circadian research community. It promotes the sharing of ideas, tools, methods and resources, and the dissemination of research outcomes. The CSCN's vision is to mobilize the healthcare community to adopt an integrated approach towards improving outcomes and treatment of patients with sleep disorders, with a first focus on obstructive sleep apnea.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.03.010.

References

[1] Ayas NT, Hirsch AAJ, Laher I, Bradley TD, Malhotra A, Polotsky VY, et al. New frontiers in obstructive sleep apnoea. Clin Sci Lond Engl 1979 2014;127:209–16. https://doi.org/10.1042/CS20140070.

[2] Skomro RP, Kryger MH. Clinical presentations of obstructive sleep apnea syndrome. Prog Cardiovasc Dis 1999;41:331–40. https://doi.org/10.1053/pcad.1999.0410331.

[3] Phillipson EA. Sleep apnea — a major public health problem. N Engl J Med 1993;328:1271–3. https://doi.org/10.1056/NEJM199304293281712.

[4] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177:1006–14. https://doi.org/10.1093/aje/kws342.

[5] Qaseem A. Management of obstructive sleep apnea in adults: a clinical practice guideline from the American college of physicians. Ann Intern Med 2013. https://doi.org/10.7326/0003-4819-159-7-201310010-00704.

[6] Evans J, Skomro R, Driver H, Graham B, Mayers I, McRae L, et al. Sleep laboratory test referrals in Canada: sleep apnea rapid response survey. Can Respir J — J Can Thorac Soc 2014;21:e4–10.

[7] Pan W, Kastin AJ. Can sleep apnea cause Alzheimer's disease? Neurosci Biobehav Rev 2014;47:656–69. https://doi.org/10.1016/j.neubiorev.2014.10.019.

[8] Ayas NT, Taylor CM, Laher I. Cardiovascular consequences of obstructive sleep apnea. Curr Opin Cardiol 2016;31:599–605. https://doi.org/10.1097/HCO.0000000000000329.

[9] Badran M, Yassin BA, Fox N, Laher I, Ayas N. Epidemiology of sleep disturbances and cardiovascular consequences. Can J Cardiol 2015;31:873–9. https://doi.org/10.1016/j.cjca.2015.03.011.

[10] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea 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). J Am Coll Cardiol 2008;52:686–717. https://doi.org/10.1016/j.jacc.2008.05.002.

[11] Sforza E, Roche F. Chronic intermittent hypoxia and obstructive sleep apnea: an experimental and clinical approach. Hypoxia Auckl NZ 2016;4:99–108. https://doi.org/10.2147/HP.S103091.

* The most important references are denoted by an asterisk.

[12] Hopps E, Caimi G. Obstructive sleep apnea syndrome: links betwen pathophysiology and cardiovascular complications. Clin Investig Med – Med Clin Exp 2015;38:E362–70.
[13] Wang W, Schulze CJ, Suarez-Pinzon WL, Dyck JRB, Sawicki G, Schulz R. Intracellular action of matrix metalloproteinase-2 accounts for acute myocardial ischemia and reperfusion injury. Circulation 2002;106:1543–9.
[14] Sawicki G. Intracellular regulation of matrix metalloproteinase-2 activity: new strategies in treatment and protection of heart subjected to oxidative stress. Sci Tech Rep 2013. https://doi.org/10.1155/2013/130451.
[15] Liu P, Sun M, Sader S. Matrix metalloproteinases in cardiovascular disease. Can J Cardiol 2006;22:25B–30B. https://doi.org/10.1016/S0828-282X(06)70983-7.
[16] Cheung PY, Sawicki G, Wozniak M, Wang W, Radomski MW, Schulz R. Matrix metalloproteinase-2 contributes to ischemia-reperfusion injury in the heart. Circulation 2000;101:1833–9.
[17] Krzywonos-Zawadzka A, Franczak A, Sawicki G, Woźniak M, Bil-Lula I. Multidrug prevention or therapy of ischemia-reperfusion injury of the heart-Mini-review. Environ Toxicol Pharmacol 2017;55:55–9. https://doi.org/10.1016/j.etap.2017.08.004.
[18] Wang W, Sawicki G, Schulz R. Peroxynitrite-induced myocardial injury is mediated through matrix metalloproteinase-2. Cardiovasc Res 2002;53:165–74.
[19] Sawicki G, Leon H, Sawicka J, Sariahmetoglu M, Schulze CJ, Scott PG, et al. Degradation of myosin light chain in isolated rat hearts subjected to ischemia-reperfusion injury: a new intracellular target for matrix metalloproteinase-2. Circulation 2005;112:544–52. https://doi.org/10.1161/CIRCULATIONAHA.104.531616.
[20] Doroszko A, Polewicz D, Sawicka J, Richardson JS, Cheung P-Y, Sawicki G. Cardiac dysfunction in an animal model of neonatal asphyxia is associated with increased degradation of MLC1 by MMP-2. Basic Res Cardiol 2009;104:669–79. https://doi.org/10.1007/s00395-009-0035-1.
[21] Badran M, Ayas N, Laher I. Cardiovascular complications of sleep apnea: role of oxidative stress. Oxid Med Cell Longev 2014;2014:985258. https://doi.org/10.1155/2014/985258.
[22] Wang S, Li S, Wang B, Liu J, Tang Q. Matrix metalloproteinase-9 is a predictive factor for systematic hypertension and heart dysfunction in patients with obstructive sleep apnea syndrome. BioMed Res Int 2018;2018. https://doi.org/10.1155/2018/1569701.
[23] Ben-Yosef Y, Miller A, Shapiro S, Lahat N. Hypoxia of endothelial cells leads to MMP-2-dependent survival and death. Am J Physiol Cell Physiol 2005;289:C1321–31. https://doi.org/10.1152/ajpcell.00079.2005.
[24] 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;343:591–6. https://doi.org/10.1016/j.bbrc.2006.03.015.
[25] Htoo AK, Greenberg H, Tongia S, Chen G, Henderson T, Wilson D, et al. Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. Sleep Breath Schlaf Atm 2006;10:43–50. https://doi.org/10.1007/s11325-005-0046-6.
[26] Bond M, Chase AJ, Baker AH, Newby AC. Inhibition of transcription factor NF-kappaB reduces matrix metalloproteinase-1, -3 and -9 production by vascular smooth muscle cells. Cardiovasc Res 2001;50:556–65.
[27] Wei Q, Bian Y, Yu F, Zhang Q, Zhang G, Li Y, et al. Chronic intermittent hypoxia induces cardiac inflammation and dysfunction in a rat obstructive sleep apnea model. J Biomed Res 2016;30:490–5. https://doi.org/10.7555/JBR.30.20160110.
[28] Yuksel M, Kuzu-Okur H, Velioglu-Ogunc A, Pelin Z. Matrix metalloproteinase-9 level and gene polymorphism in sleep disordered breathing patients with or without cardiovascular disorders. Balkan Med J 2013;30:8–12. https://doi.org/10.5152/balkanmedj.2012.068.
[29] Cao C, Wu B, Wu Y, Yu Y, Ma H, Sun S, et al. Functional polymorphisms in the promoter region of MMP-2 and MMP-9 and susceptibility to obstructive sleep apnea. Sci Rep 2015;5. https://doi.org/10.1038/srep08966.
[30] Yalcinkaya M, Erbek SS, Babakurban ST, Kupeli E, Bozbas S, Terzi YK, et al. Lack of association of matrix metalloproteinase-9 promoter gene polymorphism in obstructive sleep apnea syndrome. J Cranio-Maxillo-Fac Surg 2015;43:1099–103. https://doi.org/10.1016/j.jcms.2015.06.014.
[31] Maeder MT, Mueller C, Schoch OD, Ammann P, Rickli H. Biomarkers of cardiovascular stress in obstructive sleep apnea. Clin Chim Acta 2016;460:152–63. https://doi.org/10.1016/j.cca.2016.06.046.
[32] de Araújo Freitas IG, de Bruin PFC, Bittencourt L, de Bruin VMS, Tufik S. What can blood biomarkers tell us about cardiovascular risk in obstructive sleep apnea? Sleep Breath 2015;19:755–68. https://doi.org/10.1007/s11325-015-1143-9.
[33] Lira AB, de Sousa Rodrigues CF. Evaluation of oxidative stress markers in obstructive sleep apnea syndrome and additional antioxidant therapy: a review article. Sleep Breath Schlaf Atm 2016;20:1155–60. https://doi.org/10.1007/s11325-016-1367-3.
[34] Li K, Wei P, Qin Y, Wei Y. Is C-reactive protein a marker of obstructive sleep apnea? Medicine (Baltim) 2017;96. https://doi.org/10.1097/MD.0000000000006850.
[35] Svatikova A, Wolk R, Lerman LO, Juncos LA, Greene EL, McConnell JP, et al. Oxidative stress in obstructive sleep apnoea. Eur Heart J 2005;26:2435–9. https://doi.org/10.1093/eurheartj/ehi440.
[36] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097.
*[37] Hopps E, Canino B, Montana M, Calandrino V, Urso C, Lo Presti R, et al. Gelatinases and their tissue inhibitors in a group of subjects with obstructive sleep apnea syndrome. Clin Hemorheol Microcirc 2016;62:27–34. https://doi.org/10.3233/CH-151928.
*[38] Tamaki S, Yamauchi M, Fukuoka A, Makinodan K, Koyama N, Tomoda K, et al. Production of inflammatory mediators by monocytes in patients with obstructive sleep apnea syndrome. Intern Med Tokyo Jpn 2009;48:1255–62.
*[39] Tazaki T, Minoguchi K, Yokoe T, Samson KTR, Minoguchi H, Tanaka A, et al. Increased levels and activity of matrix metalloproteinase-9 in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2004;170:1354–9. https://doi.org/10.1164/rccm.200402-193OC.
*[40] Ye J, Liu H, Li Y, Liu X, Zhu J. Increased serum levels of C-reactive protein and matrix metalloproteinase-9 in obstructive sleep apnea syndrome. Chin Med J (Engl) 2007;120:1482–6.
*[41] Bonanno A, Riccobono L, Bonsignore MR, Lo Bue A, Salvaggio A, Insalaco G, et al. Relaxin in obstructive sleep apnea: relationship with blood pressure and inflammatory mediators. Respir Int Rev Thorac Dis 2016;91:56–62. https://doi.org/10.1159/000443182.
*[42] Maeder MT, Strobel W, Christ M, Todd J, Estis J, Wildi K, et al. Comprehensive biomarker profiling in patients with obstructive sleep apnea. Clin Biochem 2015;48:340–6. https://doi.org/10.1016/j.clinbiochem.2014.09.005.
*[43] Volná J, Kemlink D, Kalousová M, Vávrová J, Majerová V, Mestek O, et al. Biochemical oxidative stress-related markers in patients with obstructive sleep apnea. Med Sci Monit Int Med J Exp Clin Res 2011;17:CR491–7.
[44] Hopps E, Lo Presti R, Montana M, Canino B, Calandrino V, Caimi G. Analysis of the correlations between oxidative stress, gelatinases and their tissue inhibitors in the human subjects with obstructive sleep apnea syndrome. J Physiol Pharmacol Off J Pol Physiol Soc 2015;66:803–10.
*[45] Kaditis AG, Alexopoulos EI, Karathanasi A, Ntamagka G, Oikonomidi S, Kiropoulos TS, et al. Adiposity and low-grade systemic inflammation modulate matrix metalloproteinase-9 levels in Greek children with sleep apnea. Pediatr Pulmonol 2010;45:693–9. https://doi.org/10.1002/ppul.21251.
[46] Dantas DA da S, Mauad T, Silva LFF, Lorenzi-Filho G, Formigoni GGS, Cahali MB. The extracellular matrix of the lateral pharyngeal wall in obstructive sleep apnea. Sleep 2012;35:483–90. https://doi.org/10.5665/sleep.1730.
[47] Ali MAM, Schulz R. Activation of MMP-2 as a key event in oxidative stress injury to the heart. Front Biosci Landmark Ed 2009;14:699–716.
[48] Hopps E, Caimi G. Matrix metalloproteinases in metabolic syndrome. Eur J Intern Med 2012;23:99–104. https://doi.org/10.1016/j.ejim.2011.09.012.
[49] Kusnierova P, Vsiansky F, Pleva L, Plevova P, Safarcik K, Svagera Z. Reference intervals of plasma matrix metalloproteinases 2, 3, and 9 and serum asymmetric dimethylarginine levels. Scand J Clin Lab Invest 2015;75:508–13. https://doi.org/10.3109/00365513.2015.1057760.
[50] Kupai K, Szucs G, Cseh S, Hajdu I, Csonka C, Csont T, et al. Matrix metalloproteinase activity assays: importance of zymography. J Pharmacol Toxicol Methods 2010;61:205–9. https://doi.org/10.1016/j.vascn.2010.02.011.
[51] Ricci S, D'Esposito V, Oriente F, Formisano P, Di Carlo A. Substrate-zymography: a still worthwhile method for gelatinases analysis in biological samples. Clin Chem Lab Med 2016;54:1281–90. https://doi.org/10.1515/cclm-2015-0668.
[52] Ramirez TA, Jourdan-Le Saux C, Joy A, Zhang J, Dai Q, Mifflin S, et al. Chronic and intermittent hypoxia differentially regulate left ventricular inflammatory and extracellular matrix responses. Hypertens Res Off J Jpn Soc Hypertens 2012;35:811–8. https://doi.org/10.1038/hr.2012.32.
[53] Wang W, Zhang K, Li X, Ma Z, Zhang Y, Yuan M, et al. Doxycycline attenuates chronic intermittent hypoxia-induced atrial fibrosis in rats. Cardiovasc Ther 2018;36:e12321. https://doi.org/10.1111/1755-5922.12321.
[54] Ramos P, Rubies C, Torres M, Batlle M, Farre R, Brugada J, et al. Atrial fibrosis in a chronic murine model of obstructive sleep apnea: mechanisms and prevention by mesenchymal stem cells. Respir Res 2014;15:54. https://doi.org/10.1186/1465-9921-15-54.
[55] Pamenter ME, Powell FL. Time domains of the hypoxic ventilatory response and their molecular basis. Comp Physiol 2016;6:1345–85. https://doi.org/10.1002/cphy.c150026.
[56] Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. Chest 2003;124:594–601.
[57] Schulze CJ, Castro MM, Kandasamy AD, Cena J, Bryden C, Wang SH, et al. Doxycycline reduces cardiac matrix metalloproteinase-2 activity but does not ameliorate myocardial dysfunction during reperfusion in coronary artery bypass patients undergoing cardiopulmonary bypass. Crit Care Med 2013;41:2512–20. https://doi.org/10.1097/CCM.0b013e318292373c.
[58] Lin H-B, Cadete VJJ, Sra B, Sawicka J, Chen Z, Bekar LK, et al. Inhibition of MMP-2 expression with siRNA increases baseline cardiomyocyte contractility and protects against simulated ischemic reperfusion injury. BioMed Res Int 2014;2014:810371. https://doi.org/10.1155/2014/810371.
[59] Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee S-S. Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine. Mol Ther Nucleic Acids 2017;8:132–43. https://doi.org/10.1016/j.omtn.2017.06.005.