Respiratory diseases and vascular failure

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Abstract:
Patients with chronic respiratory diseases (e.g., chronic obstructive pulmonary disease, interstitial pneumonia, and sleep apnea syndrome) have common risk factors for atherosclerosis, including advanced age, smoking, chronic inflammation, and continuous or intermittent hypoxia. Previous epidemiological studies have revealed that patients with these diseases have an increased risk of atherosclerosis and vascular events. These comorbidities are also associated with poor survival; however, the impact of the treatment for vascular diseases on the prognosis of patients with respiratory diseases remains unclear. Further investigation is required to elucidate the mechanisms and establish treatment strategies for vascular failure associated with respiratory diseases.

Key words:
Chronic obstructive pulmonary disease, Coronary artery disease, Endothelial dysfunction, Interstitial pneumonia, Sleep apnea syndrome

1. Introduction

Atherosclerosis is considered an inflammatory disease initiated by endothelial dysfunction followed by adhesion of leukocytes or platelets to the endothelium, formation of cytokines and growth factors, migration and proliferation of smooth-muscle cells, and thickening of the artery wall1). Smoking, hypertension, glucose intolerance, hyperlipidemia, and obesity are known risk factors for atherosclerosis, and chronic inflammation and hypoxemia can also accelerate the disease2). Patients with chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD), bronchial asthma, interstitial lung disease (ILD), and sleep apnea syndrome (SAS) share common risk factors for atherosclerosis, including advanced age, smoking history, chronic inflammation, oxidative stress caused by intermittent hypoxia, and enhanced sympathetic activity (Figure 1). It is recognized that these respiratory diseases are associated with an increased risk of developing atherosclerosis and vascular events (Table 1). This article summarizes the current knowledge regarding the pathophysiology, epidemiology, and clinical impact of vascular failure characterized by respiratory diseases.

2. COPD

2-1. COPD and comorbidity
COPD is characterized by an airflow limitation that is not fully reversible. The airflow limitation is typically progressive and associated with an abnormal inflammatory response to noxious particles or gasses within the lungs3). COPD is the fourth leading cause of death in Japan and is often observed in combination with other respiratory diseases, such as interstitial pneumonia (combined pulmonary fibrosis and emphysema [CPFE]) or bronchial asthma (Asthma-COPD Overlap Syndrome [ACOS]).

COPD is recognized as a systemic disease, since it is often accompanied by a variety of comorbidities, including cardiovascular disease, osteoporosis, depression, malnutrition, diabetes, and lung cancer. More than 95% of patients with COPD have at least 1 comorbidity, and over 50% have 4 or more coexisting diseases4). COPD is more prevalent in smokers, men, and patients who also have other risk factors for atherosclerosis (e.g., chronic inflammation and hypoxemia). Therefore, atherosclerosis is also an important comorbidity associated with COPD.

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Vascular Failure in Respiratory Diseases

Table 1. Previous reports on vascular function and events in respiratory diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vascular Function/Events</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>COPD</td>
<td>Increased arterial stiffness, Exaggeration of atherosclerosis, Increased frequency of CAD</td>
<td>Ref. 5, 6</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Increased frequency of CAD, Increased frequency of stroke, but not CAD</td>
<td>Ref. 7-23</td>
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<tr>
<td>Interstitial lung disease</td>
<td>Endothelial dysfunction, Increased frequency of CAD</td>
<td>Ref. 34, 37, 38, 39, 40</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>Endothelial dysfunction, Increased frequency of CAD, Increased frequency of cerebral</td>
<td>Ref. 51, 52, 53</td>
</tr>
<tr>
<td></td>
<td>infarction</td>
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Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

2-2. Endothelial Dysfunction and the Development of Atherosclerosis in COPD

The endothelium acts to maintain vascular homeostasis through multiple complex interactions with cells within the vasculatures. Moreover, it regulates vascular tension by controlling vasodilators and vasoconstrictors and maintains blood fluidity through the production of factors that regulate platelet activity and the coagulation and fibrinolytic system. In addition, the endothelium can produce cytokines and adhesion molecules that regulate the inflammatory process. Endothelial dysfunction is considered to be an initial step in the development of atherosclerosis, followed by morphological changes, such as plaque formation and further progression, resulting in cardiovascular events. Flow-mediated dilation (FMD) and reactive hyperemia peripheral arterial tonometry (RH-PAT) are widely used to assess vascular endothelial function. Vascular assessments using aortic pulse wave velocity (PWV) and carotid ultrasonography have revealed that increased arterial stiffness and atherosclerosis are observed even in mild cases of COPD compared to healthy individuals or smokers without COPD.

2-3. Cardiovascular Events in COPD

A large cohort study which enrolled patients with COPD treated by the Veterans Administration Medical System found that the prevalence of coronary artery disease (CAD), congestive heart failure, and atrial fibrillation (33.6%, 24.4%, and 14.3%, respectively) were significantly higher in this patient population than in the matched non-COPD cohort (27.1%, 13.5%, and 10.4%; p<0.001). Another epidemiological study from Canada also found an increased risk of angina pectoris (odds ratio [OR]: 1.61; confidence interval [CI]: 1.47-1.76) and acute myocardial infarction (OR:...
CARDIOVASCULAR EVENTS ARE A MAJOR CAUSE OF DEATH IN PATIENTS WITH COPD. IN THE LUNG HEALTH STUDY OF 5,887 PATIENTS WITH A MILD TO MODERATE AIRFLOW LIMITATION, CARDIOVASCULAR DISEASE ACCOUNTED FOR AROUND 25% OF THE CAUSES OF DEATH\(^1\). ANOTHER STUDY FROM SWEDEN FOUND THAT IN PATIENTS WITH SEVERE COPD UNDERGOING LONG-TERM OXYGEN TREATMENT, CIRCULATORY DISEASES ACCOUNTED FOR 16% OF THE CAUSES OF DEATH, WHICH IS THE 2ND MOST FREQUENT CAUSE OF DEATH FOLLOWING RESPIRATORY ETIOLOGIES\(^2\). THIS STUDY ALSO DEMONSTRATED THAT THE MORTALITY RATIO ASSOCIATED WITH RESPIRATORY DISEASES AND LUNG CANCER DECREASED BY 2.7% AND 3.4% PER YEAR, RESPECTIVELY, Whereas THOSE ASSOCIATED WITH CARDIOVASCULAR DISEASE AND CAD INCREASED BY 2.8% AND 2.7% PER YEAR, RESPECTIVELY\(^3\).

2-4. ETHNIC DIFFERENCES IN THE VASCULAR EVENTS ASSOCIATED WITH COPD

It has been reported that there are ethnic differences regarding the prevalence of cardiovascular comorbidities associated with respiratory diseases. FOR COPD, THE PREVALENCE OF CARDIOVASCULAR DISEASES IS 16%-22% IN JAPAN AND 10%-30% IN WESTERN COUNTRIES. THE MORTALITY RATE FOR CARDIOVASCULAR PROBLEMS IN PATIENTS WITH COPD IS 4%-29% IN JAPAN AND 18%-39% IN WESTERN COUNTRIES\(^4\). THESE DIFFERENCES MIGHT BE ATTRIBUTABLE TO THE VARIATIONS IN COPD PATHOPHYSIOLOGY, ETHNIC OR GENETIC DISPARITIES IN CARDIOVASCULAR DISEASES, OR ENVIRONMENTAL ASPECTS, INCLUDING LIFESTYLE AND SOCIOECONOMIC FACTORS\(^5\).

2-5. MECHANISMS OF VASCULAR FAILURE IN PATIENTS WITH COPD

Smoking is a strong risk factor for atherosclerosis in patients with COPD; however, some epidemiological studies have shown that the link between COPD and atherosclerosis could not be explained only by smoking. For instance, the National Health and Nutrition Examination Survey (NHANES) demonstrated that the low forced expiratory volume in 1s (FEV\(_1\)) was associated with an increased risk of cardiovascular mortality, even after adjusting for other risk factors (e.g., smoking, hypertension, obesity, and diabetes)\(^6\). In NHANES, patients in the lowest FEV\(_1\) quintile exhibited the highest risk of cardiovascular mortality (relative risk: 3.36) compared with those in the highest FEV\(_1\) quintile. In addition, a meta-analysis of large cohort studies reported that a reduced FEV\(_1\) was associated with an increased cardiovascular mortality, even after statistical adjustments for smoking status (pooled risk ratio [RR]: 1.77)\(^7\).

Systemic inflammation may be a common pathophysiology that can explain the association between COPD and atherosclerosis. In addition, COPD is characterized by both chronic lung inflammation as well as systemic inflammation associated with a variety of inflammatory markers in the blood. For instance, data from the NHANES III study revealed a significant increase in the overall cardiovascular mortality rates for individuals with high leptin and C-reactive protein (CRP) levels (RR, 1.54). Moreover, elevated leptin and CRP levels were also associated with increased all-cause mortality rates (hazard ratio [HR]: 1.80) in men, while no such association was found among women\(^8\). Another study found that patients with COPD with suspected pulmonary hypertension exhibited higher levels of serum CRP and tumor necrosis factor-alpha (TNF-\(\alpha\))\(^9\). However, it remains unclear whether such systemic inflammation in patients with COPD contributes to the development of atherosclerosis.

2-6. POTENTIAL PREVENTIVE TREATMENT FOR CARDIOVASCULAR EVENTS IN PATIENTS WITH COPD

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study followed up 5,993 patients with COPD from 37 countries over 4 years and demonstrated that tiotropium had a long-term effect on the improvement of quality of life (QOL) and prevention of acute exacerbation\(^10\). It is important to note that the incidence of cardiac events, especially congestive heart failure and myocardial infarction, was significantly lower in the tiotropium group than in the placebo group. Additionally, in the UPLIFT trial, preceding treatments (including inhaled corticosteroids) were continued; however, tiotropium was not intended to suppress inflammation; this result may suggest that medical interventions for COPD might prevent the development of cardiovascular events in patients with COPD. Other studies have shown that medical treatment for atherosclerosis and cardiac disease improved the prognosis of COPD. A retrospective study of 854 patients with COPD admitted for acute exacerbation in a Norwegian hospital found that patients being treated with statins had a significantly lower risk of mortality compared with those without statins (HR: 0.57), and the effect of statins was further enhanced by the combined use of inhaled corticosteroids (HR: 0.39)\(^11\). Furthermore, it was reported that the combined use of statins and an ACE inhibitor or angiotensin receptor blocker (ARB) decreased the risk of admission (relative risk 0.66) and all-cause mortality (RR: 0.42) due to COPD\(^12\). In the establishment of a treatment strategy for COPD, further investigation is necessary regarding the benefit of medical intervention for vascular disease.

3. BRONCHIAL ASTHMA

3-1. PATHOPHYSIOLOGY OF BRONCHIAL ASTHMA

Bronchial asthma is also an obstructive lung disease; however, it is characterized by airway inflammation, airway hyperresponsiveness, and often reversible airflow obstruc-
tion\textsuperscript{29}. The essential pathology of bronchial asthma is chronic airway inflammation dominated by eosinophils, in which continuous airway inflammation causes airway injury followed by remodeling and an irreversible airflow limitation.

3-2. Bronchial asthma and vascular failure

Previous epidemiological studies have shown that bronchial asthma is also a respiratory disease associated with an increased risk of atherosclerosis. According to a surveillance of 150,000 people who enrolled in a large managed care organization in Northern California, bronchial asthma was found to be a risk factor for the admission or death due to CAD after adjusting for cardiovascular risk factors in women (RR: 1.22), but not in men\textsuperscript{20}.

An epidemiological study of 262 patients with severe asthma who underwent daily treatment with oral steroids for more than 1 y found that there was an enhanced mortality due to CAD (RR: 1.9), especially among women (RR: 2.5)\textsuperscript{21}. A study of hospitalized patients with asthma from Australia also showed an increased mortality ratio due to CAD in elderly patients\textsuperscript{22}. The Atherosclerosis Risk in Communities Study (ARIC) conducted in the United States found that patients with asthma were at an increased risk of stroke (HR: 1.50-1.55). Moreover, participants who had experienced a wheezing attack were at a greater risk of stroke than those who had not; however, unexpectedly, the risk of CAD was not increased in participants with a history of asthma\textsuperscript{23}. Although the reason for the lack of an association between asthma and CAD in this study remains unclear, confounding factors not included in the analysis (e.g., socioeconomic background during childhood) may have affected the results.

4. ILD

4-1. Pathogenesis and clinical features of interstitial pneumonia

ILD includes a wide spectrum of fibrotic lung diseases in which the interstitium of the lungs is the primary location. The clinical course of ILD is often chronic and progressive. In particular, idiopathic pulmonary fibrosis (IPF) is the most frequent and severe form of idiopathic interstitial pneumonia, with a 5-year survival rate of ~50\%\textsuperscript{24}.

While the precise pathogenesis of IPF remains unclear, it is considered to be triggered by extrinsic stimuli, such as smoking and acid reflux which cause injury and apoptosis of alveolar epithelial cells. In response to the epithelial cell injury, increased vascular permeability, extravascular leakage of inflammatory cells, and immune activation occur, leading to myofibroblast differentiation and collagen synthesis. In IPF, these responses do not lead to complete wound healing, but result in lung fibrosis and functional impairment\textsuperscript{25}.

4-2. Vascular risk associated with interstitial pneumonia

Patients with interstitial pneumonia exhibit a variety of vascular risk factors, including advanced age, smoking, inflammation, chronic hypoxic stress, and treatment-related disorders (e.g., hypertension, diabetes mellitus, and dyslipidemia). In addition, the activation of the coagulation system is involved in the pathogenesis of IPF, and an increased platelet aggregation is also observed in some types of interstitial pneumonia\textsuperscript{26}. Furthermore, the pathogenesis of IPF shares common pathways with the process of atherosclerosis formation, which is initiated by vascular epithelial injury and characterized by fibroproliferative responses of vascular epithelial and smooth muscle cells\textsuperscript{27}. Therefore, several molecules have been reported to be involved in the pathogenesis of both pulmonary fibrosis and atherosclerosis\textsuperscript{28-30}.

Endothelin-1 (ET-1) induces potent vasoconstriction, and it has been shown to contribute to the development of atherosclerosis and vascular events in patients with diabetes. In the context of fibrosis, there are important biological mediators whose pathways interact closely with those of ET-1, including transforming growth factor-\(\beta\) (TGF-\(\beta\)), connective tissue growth factor, TNF-\(\alpha\), and a variety of cytokines, such as IL-1\textsuperscript{27}. These profibrotic mediators allow fibroblasts to differentiate into myofibroblasts, which contribute to the development of lung fibrosis. In addition, it was reported that ET-1 in the serum and bronchoalveolar lavage (BAL) was increased in IPF, and the level was associated with survival\textsuperscript{29}.

Periostin is a matricellular protein, which induces chemokines to recruit neutrophils and macrophages essential in the process of pulmonary fibrosis\textsuperscript{30}. Periostin is highly expressed in the lung tissues of patients with IPF, and its serum levels are associated with lung function\textsuperscript{31}. Periostin is also involved in the development of atherosclerosis through vascular smooth muscle cell migration\textsuperscript{32}.

On the other hand, some molecules have opposite effects to the development of lung fibrosis and atherosclerosis. Caveolin-1 is abundantly expressed in fibroblasts, endothelial cells, type I pneumocytes, and adipocytes; it also has a multitude of cellular functions, including membrane trafficking, endocytosis, lipid metabolism, and signal transduction during cellular proliferation and apoptosis\textsuperscript{32}. It was reported that caveolin-1 suppressed TGF-\(\beta\)1-induced extracellular matrix (ECM) production in cultured human lung fibroblasts, and its expression was reduced in the lung tissues, as well as primary pulmonary fibroblasts from patients with IPF\textsuperscript{30}, suggesting that its action is to ameliorate lung fibrosis. In contrast, caveolin-1 functions to accelerate the development of atherosclerosis through transporting of LDL into the vascular wall and immune modulation\textsuperscript{33}.

4-3. Endothelial dysfunction in interstitial pneumonia

Aihara et al\textsuperscript{34} assessed endothelial dysfunction using RH-
PAT in 39 patients with chronic interstitial pneumonitis/fibrosis without any specific etiology and compared the reactive hyperemia index (RHI) with 30 age-, sex-, and body mass index-matched control subjects. RHI was significantly lower in patients with interstitial pneumonia than in control subjects. The authors found that there was a significant correlation between RHI and the diffusing capacity for carbon monoxide, the difference in the alveolar-arterial oxygen pressure, 6-min walking distance, and end-exercise oxygen saturation, suggesting a possible link between pulmonary fibrosis and endothelial dysfunction. Serum intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, not serum inflammatory cytokines, were inversely correlated with RHI\(^{46}\). This result may suggest that molecules involved in the pathogenesis of pulmonary fibrosis and/or hypoxemia and oxidative stress caused by pulmonary fibrosis might contribute to the development of endothelial dysfunction in patients with pulmonary fibrosis. Further investigation is necessary to elucidate the mechanisms of vascular failure in patients with pulmonary fibrosis.

4-4. Vascular events in patients with interstitial pneumonia

In a population-based epidemiological study conducted in the United States, 50% of the primary cause of death for IPF was acute events, with CAD and cerebrovascular accidents accounting for 4/17 (23%) and 1/17 (6%), respectively\(^{39}\). In contrast, cardiovascular disease accounts for 3% of the cause of death of Japanese patients with IPF\(^{46}\), suggesting ethnic differences for cardiovascular events as recognized in COPD\(^{39}\).

Hubbard et al.\(^{37}\) used data from a longitudinal, primary-care dataset and investigated the cumulative incidence of first-time acute coronary syndromes in 920 patients with IPF and 3,593 control subjects. They showed that there was an increased risk of acute coronary syndrome in the period before the diagnosis of IPF (OR: 1.53) and during the follow-up period (RR: 3.14). Another study enrolled 630 patients evaluated for lung transplantation for whom coronary angiography was performed at a university hospital. This study found that fibrotic lung diseases were associated with an increased prevalence of CAD compared with nonfibrotic diseases after adjusting for traditional risk factors (OR: 2.18)\(^{46}\). In particular, the risk of developing a multivessel disease was further elevated in fibrotic diseases (OR: 4.16). A similar study from Israel enrolled 100 lung transplantation candidates and revealed that the frequency of CAD was significantly higher in patients with pulmonary fibrosis (14/49, 28.6%) than those with COPD (5/51, 9.8%), despite the fact that smokers were more prevalent among the patients with COPD\(^{46}\).

An analysis using a large UK primary care database enrolled 3,211 patients with IPF and 12,307 control subjects. It was found that the rate of first-time CAD events was significantly higher in the patients with IPF than in the control subjects (RR: 2.32); however, the incidence of stroke was only marginally higher for IPF. A high prevalence of coronary risk factors in IPF did not fully account for the increased risk of CAD, suggesting that IPF itself was a specific risk factor for CAD\(^{46}\).

4-5. Implication of IPF treatment on vascular failure

A drug targeting the common pathway of pulmonary fibrosis and atherosclerosis might be effective for the treatment of both diseases. However, an international multicenter randomized controlled study, which investigated the efficacy of bosentan, an endothelin receptor antagonist, did not report the anti-fibrotic efficacy against IPF\(^{47}\). Currently, 2 anti-fibrotic drugs with different mechanisms were found to be efficacious against IPF\(^{47}\). Further investigation is necessary to elucidate the efficacy of these drugs on vascular disease in IPF.

5. SAS

5-1. Clinical features and classification of SAS

Obstructive SAS (OSAS) is characterized by repeated episodes of breathing decline (hypopneas) or cessation (apneas) during sleep due to upper airway obstructions. These events result in repetitive decreases in oxygen saturation with rapid reoxygenation causing cyclical deoxygenation/reoxygenation\(^{48}\). SAS is classified into 2 types: 1) OSAS, in which a mechanical obstruction of the upper airway occurs intermittently and 2) central sleep apnea (CSA), in which the brain temporarily fails to signal the muscles responsible for controlling breathing, including Cheyne-Stokes respiration.

SAS is a highly prevalent disease, and a recent study from Japan showed that the frequency of mild sleep-disordered breathing (SDB) was ~30% and that of moderate to severe SDB was 8%-22% in men\(^ {39}\)-\(^ {45}\). The primary treatment for SAS is continuous positive airway pressure (CPAP).

5-2. Mechanisms of vascular failure in patients with OSAS

Hypopnea and apnea events in patients with OSAS can cause intermittent hypoxia, repeated changes in the intrathoracic pressure, and sleep fragmentation, which result in increased oxidative stress, inflammation, and activation of the sympathetic pathways. Increases in inflammatory cytokines and adhesion molecules lead to the activation of various immune cells (e.g., monocytes, lymphocytes, and endothelial cells), resulting in endothelial dysfunction and cardiovascular disease development\(^ {48}\).

Intermittent hypoxia is broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia, which is in contrast with continuous hypoxemia. In CAD and cerebrovascular infarction, in addition to tissue hypoxia by ischemia, the restoration of circulation also contributes to the damage caused by inflammation and oxidative stress, which is termed as reperfusion injury.
From the perspective of tissue oxygen supply, repeated apnea-related hypoxic events in OSAS (similar to hypoxia and reperfusion injury) initiate oxidative stress, which alters the expression of genes related to energy metabolism and redox responses, and induce the production of growth factors, inflammatory cytokines, and adhesion molecules. During this process, oxygen stress is considered to be more strongly enhanced by the recovery from hypoxemia to normoxia than the continuous hypoxemia. Therefore, intermittent and continuous hypoxias have different influences.

Takahashi et al. showed that serum thioredoxin, a marker of oxidative stress, was significantly increased in patients with OSAS compared with healthy subjects and that thioredoxin was correlated with both the respiratory disturbance index (RDI) and percent time of SpO2 <90%. Oxidative stress can also contribute to the induction of heme metabolism. It was reported that an indirect serum bilirubin, a metabolite of heme metabolism, increases during sleep and can be suppressed by CPAP therapy. An animal study demonstrated that mice exposed to both chronic intermittent hypoxia and high-cholesterol diet developed atherosclerotic lesions in the aorta, whereas atherosclerosis was not observed in mice exposed to control air and high-cholesterol diet or in mice exposed to chronic intermittent hypoxia and regular diet. This result may suggest that the clinical significance of intermittent hypoxia in SAS differs depending on individual lifestyles or comorbidities.

An increased platelet aggregation and coagulation cascade can also contribute to endothelial dysfunction. Oga et al. showed that platelet aggregation was increased in moderate to severe OSAS cases and was correlated with the RDI. They also demonstrated that an increased platelet aggregation was ameliorated by CPAP treatment. Furthermore, patients with SAS are frequently obese, and many have metabolic syndrome, which greatly contributes to the development of vascular injury in patients with OSAS.

5-3. Endothelial dysfunction in OSAS

Visceral obesity and low adiponectin are known risk factors for the development of cardiovascular disease. Azuma et al. investigated the association between these factors in patients with OSAS and endothelial dysfunction using RH-PAT. They found that there was a significant negative correlation between RHI and the apnea-hypopnea index (AHI) or visceral fat area, while RHI was positively correlated with serum adiponectin. In a multivariate regression analysis, only severe OSAS remained an independent predictive factor of RHI.

5-4. OSAS and cardiovascular events

A cohort study from Spain found that untreated patients with severe OSAS had significantly increased risks of fatal (OR: 2.87) and non-fatal (OR: 3.17) cardiovascular events compared with healthy participants and that CPAP therapy reduced this risk. The Sleep Heart Health Study conducted in the United States demonstrated that hypopneas with a desaturation of at least 4% are independently associated with cardiovascular diseases.

Eguchi et al. demonstrated that nocturnal hypoxia higher than 5.6 times per hour was independently associated with a silent cerebral infarction, suggesting that OSAS is also a risk factor for vascular events in Japanese patients.

5-5. Effect of CPAP on endothelial dysfunction in patients with OSAS

A systematic review of 8 RCTs investigating the effect of CPAP therapy on endothelial dysfunction in patients with OSAS found that CPAP improved the endothelial function. In addition, the authors performed a meta-analysis on 4 RCTs involving a total of 150 patients. Compared to the control group, the CPAP therapy group had significantly improved endothelial dysfunction by 3.87% assessed using the FMD (CI: 1.93-5.80; P<0.001). The beneficial effect of CPAP on endothelial function was also confirmed by a more recent study using RH-PAT. Further investigation is necessary to elucidate whether CPAP can prevent cardiovascular events in OSAS.

6. Summary and future perspectives

Previous epidemiological studies have found an association between major chronic respiratory diseases and atherosclerosis or vascular events. The influence of vascular disease on the prognosis of respiratory diseases is not negligible; thus, the evaluation of vascular disease and its risk factors are important for the management of respiratory diseases. Further investigation is necessary regarding the effect of treatment for underlying lung diseases on comorbid vascular diseases.

Conflicts of Interest

Tomohiro Handa has no conflict of interest to disclose.

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