Obstructive sleep apnoea, intermittent hypoxia and heart failure with a preserved ejection fraction

John E Sanderson, Fang Fang, Mi Lu, Chen Yao Ma, Yong Xiang Wei

Beijing Institute of Heart, Lung, and Blood diseases, Capital Medical University Affiliated Anzhen Hospital, Beijing, Chaoyang-qu, China

Correspondence to
Dr Fang Fang, Sleep Medical Centre, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; fangfang_ff@hotmail.com

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ABSTRACT

Obstructive sleep apnoea (OSA) is recognised to be a potent risk factor for hypertension, coronary heart disease, strokes and heart failure with a reduced ejection fraction. However, the association between OSA and heart failure with a preserved ejection fraction (HFpEF) is less well recognised. Both conditions are very common globally.

It appears that there are many similarities between the pathological effects of OSA and other known aetiologies of HFpEF and its postulated pathophysiology. Intermittent hypoxia induced by OSA leads to widespread stimulation of the sympathetic nervous system, renin–angiotensin–aldosterone system and more importantly a systemic inflammatory state associated with oxidative stress. This is similar to the consequences of hypertension, diabetes, obesity and ageing that are the common precursors to HFpEF. The final common pathway is probably via the development of myocardial fibrosis and structural changes in collagen and myocardial titin that cause myocardial stiffening. Thus, considering the pathophysiology of OSA and HFpEF, OSA is likely to be a significant risk factor for HFpEF and further trials of preventive treatment should be considered.

INTRODUCTION

Obstructive sleep apnoea (OSA) is increasingly being recognised as a global problem with almost 1 billion people affected worldwide and a possible important risk factor for a wide range of cardiovascular disorders either as a primary agent or as an exacerbating factor.[1 2] A significant body of work has now shown that the prevalence of OSA is about 40% in patients with hypertension, ischaemic heart disease, stroke, atrial fibrillation (AF) and heart failure (HF).[3 4] In addition, one study has shown that incident HF is increased in men with OSA,[4] and a recent study of risk factors for incident HF for both those with heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection fraction (HFpEF) found that the hazard ratio (HR) for OSA was 2.4.[5] For patients with HFpEF, the HR for OSA was comparable with the HRs for diabetes, coronary artery disease and blood pressure although significantly less than obesity alone, which was very high (HR=16).[5] There have been several excellent recent reviews of the relationship of OSA with cardiovascular diseases including HF, other metabolic disturbances and quality of life.[2 3 6] The purpose of this review is to assess the role of OSA in the development and progression of the earliest and more subtle form of HF, HFpEF, also previously labelled heart failure with a normal ejection fraction (HFnEF) and diastolic heart failure[7] and to propose that OSA may be a potential stimulant of changes in the extracellular matrix (ECM) and development of myocardial fibrosis and that early treatment of OSA may be particularly relevant for the prevention of HFpEF.

OSA PATHOPHYSIOLOGY

OSA is due to recurrent pharyngeal collapse during sleep. Patients generally have a compliant pharynx that is prone to collapse and many patients are obese, and fat deposition around the pharynx may be partly responsible for pharyngeal narrowing. The immediate consequences of breathing against the pharyngeal obstruction of air flow is the development of hypoxia and a marked drop in intrathoracic pressure, often to minus 60 mm Hg, which increases transmural pressure across all cardiac chambers and great vessels.[2] This drop in intrathoracic pressure increases venous return causing right ventricular distention and a left-ward shift of the interventricular septum and consequent decreased LV filling. The net result of both decreased LV filling and increased afterload is reduced stroke volume.[8] This, combined with hypoxia, causes stimulation of the sympathetic nervous system (SNS) increasing myocardial oxygen demand raising the risk of ischaemia developing and arrhythmias especially at a time of hypoxia. Activation of the renal–angiotensin–aldosterone and a host of other metabolic, inflammatory and hormonal changes are also triggered. Some or all of these can contribute to myocardial damage and the development of sustained hypertension.

Central sleep apnoea (CSA) by contrast is a consequence of HF. It is usually seen in more severe forms of HF but can occur in HF regardless of ejection fraction.[8 9] Patients with HF and CSA are not necessarily obese nor suffer from daytime sleepiness. In general, patients with HFpEF tend to have less CSA in comparison with patients with HFrEF.[8]

ASSESSMENT OF SEVERITY OF OSA AND HYPOXIA IN HFPEF

The severity of OSA or CSA is often measured by the apnoea–hypopnoea index (AHI) derived from polysomnographic recordings. The ratio represents the average hourly frequency of apnoea (air flow absents for >10 s) plus hypopnoea (airflow diminution associated with a fall in arterial oxyhaemoglobin saturation of ≥3% or terminated by an electroencephalographic arousal) during sleep.

Using the AHI >5 measurement, studies in patients with HFpEF reported a prevalence rate of sleep disordered breathing of between 50% and 70% with the majority having OSA.[8–10] In the first study, by Chan *et al* in 1997, the prevalence of sleep apnoea (predominantly OSA) in a cohort of patients with what was called diastolic HF at that time (now HFpEF) was 55%. However, it was noted that a lower minimum percentage arterial oxygen saturation during sleep, not the AHI, was associated with more severe degree of diastolic dysfunction by echocardiography, including a lower ratio between the early peak transmitral flow velocity and the late peak atrial systolic velocity (the abnormal relaxation pattern (ARP)) and a prolonged isovolumic relaxation time.[9] This observation was one of the first to demonstrate that the percentage O_2 desaturation may be more important than AHI in determining the degree of diastolic dysfunction in patients with HFpEF and OSA.

OSA is associated with a poorer prognosis in HF patients.[11] Importantly, it has been demonstrated again that the duration of hypoxia (saturation <90%) is a stronger predictor of outcome than the number of apnoea episodes per night as measured by AHI.[12] Those with saturation levels in the lowest quartile had a 5-year survival of 50%. Watanabe *et al*[13] also demonstrated that a measure based on the proportion of time when oxygen saturation fell more than 4% from baseline was superior to AHI as a predictor of premature death. A more recent study has shown that an index of 'hypoxic burden' measured as the area under the desaturation curve associated with respiratory events was a predictor of incident HF, whereas AHI was not.[14] So it appears that the degree and duration of intermittent hypoxia (IH) is the main driver of OSA-related complications.

DIASTOLIC AND SYSTOLIC DYSFUNCTION IN OSA AND RELATIONSHIP WITH IH

A large number of echocardiographic studies have been done on this question. Bodez *et al*[15] have summarised the results, and they conclude 'LV diastolic dysfunction is often observed in OSA patients, even in the early stage of the disease, and regardless of the severity. However, in mild-to-moderate OSA, LV dysfunction seems to be linked primarily to extra -respiratory determining factors (age, BMI, AHT and LVH). An independent role for severity variables appears to be stronger in severe OSA'. However, this conclusion is based largely on poor correlation with AHI. However, as noted above, the degree and duration of oxygen saturation may be more important than the number of episodes. In an early study (2002), Fung *et al*[16] found that in a cohort of patients with severe OSA, 37% of the patients had an ARP of mitral inflow indicating diastolic dysfunction was present. Again, diastolic dysfunction with an ARP was found to be related only to the minimum pulse oxygen saturation (SpO_2). AHI and mean SpO_2 did not correlate with ARP diastolic dysfunction, and there was no significant difference between the two groups in other polysomnographic data. Many studies have confirmed now that in addition to diastolic dysfunction, systolic function is also impaired in OSA subjects despite a normal LV ejection fraction. This subclinical dysfunction can be detected using both tissue Doppler imaging of mitral annular velocities and speckle tracking imaging derived global longitudinal strain (GLS). In one recent study, Ma *et al*[17] found that in an echocardiographic study of 250 patients with a normal LVEF, GLS was significantly reduced in those with severe OSA and was associated with nocturnal lowest SpO_2, AHI and body mass index (BMI). Another recent study assessed LV systolic and diastolic function at rest and on exercise in patients with OSA and a normal LVEF and found that LV GLS was significantly reduced at rest (−13.4±3.8 vs −18.4±3.3 in controls, p<0.001) and at peak exercise.[18] This was associated with an impairment of functional diastolic reserve.

Effects of intermittent hypoxia (IH) on myocardial tissue and inflammatory markers

Although the duration of hypoxic episodes may be short, the consequences accumulate as they happen many times a night often for years.[19] The effects include activation of the SNS, which persists after awakening. In addition, the periods of hypoxia induce an inflammatory response that involves a number of proinflammatory cytokines and growth factors that can affect the myocardium in a variety of ways.[2] Chen *et al* found in a rat model that after IH for 8 weeks, LV mass increased with eccentric hypertrophy with a significant increase in cardiac tissue of tumour necrosis factor-α, insulin-like growth factor, phosphorylated p38 mitogen-activated protein kinase, signal transducers and activators of transcription (STAT)-1 and STAT-3, interleukin-6, mitogen-activated protein kinase and extracellular signal-regulated kinase compared with the group without hypoxia.[20] Another pathway activated by IH is oxidative stress, which is considered to be an important underlying process in the development of vascular and myocardial diseases.[21] Oxidative stress may be a factor in the development of hypertension via increased sympathetic activation and increased angiotensin II,[22] which is a powerful stimulator of myocardial fibrosis via aldosterone[23] and also endothelial dysfunction. IH is considered to produce oxidative stress by decreasing the antioxidant mechanisms in periods of hypoxia and increasing reactive oxygen species (ROS) production during periods of reoxygenation leading to a kind of ischaemia–reperfusion injury. Monocytes and granulocytes from OSA patients have increased levels of ROS production when compared with control subjects.[24] In addition, endothelial cells taken from forearm veins of OSA patients show signs of increased inflammation and oxidative stress, which correlated with impaired endothelial function.[25] A new method to analyse breath samples from OSA patients has found that a family of compounds that are linked to oxidative stress are present.[26] It has been shown that oxidative stress may change the composition of the ECM of heart tissue.[27 28]

IH appears to have a direct effect on myocardial ECM. In a mouse model, Farré *et al*[29] studied macroscale mechanics in LV myocardium ECM strips by uniaxial tensile testing and found that macroscopic stiffness of the LV myocardium ECM is increased by episodes of IH similar to those induced by OSA. A recent systematic review of the role of matrix metalloproteinases (MMPs), which are known to modulate the extracellular matrix, concluded, despite the limited number of studies, that MMPs are important in the pathology associated with OSA. The evidence for this is animal studies that suggest the involvement of MMP in models of IH, increased MMP levels (MMP-9 in particular) and the association between blood level of MMP-9 and OSA severity in adults.[30]

All these mechanisms caused by IH are likely to have a profound effect on diastolic and systolic function owing to their effect on myocardial ECM and fibrosis.

Pathophysiology of HFpEF and the importance of the ECM

HFpEF is characterised by increased vascular and cardiac stiffness that affects both systolic contraction and diastolic filling of the LV.[7 31 32] Many studies have now confirmed the initial findings of reduced ventricular long axis function with reduced AV

plane motion in systole and diastole by tissue Doppler imaging (reduced s′ and e′), strain (reduced GLS), and these abnormalities are more obvious on exercise.[31 33–35] Systolic dysfunction impairs early diastolic filling by reducing ventricular suction, which is the main driver of early filling. Ventricular suction is dependent on the stored force generated by the previous systole produced by twisting and compression of the ECM and which determines the degree and strength of the recoil that occurs after myocyte relaxation has occurred. As the heart untwists, the AV plane springs back around the incoming column of blood that is sucked into the ventricle. All this is done in a coordinated fashion with AV plane motion and untwisting occurring simultaneously in a flexible normal heart. This fundamental function depends effectively on the 'springs' in the myocardium, which are the collagen in the ECM and the titin molecule within the myocyte that release the stored energy from the previous systole.[23 36] Ventricular suction is particularly important for filling of the ventricles and especially so on exercise when diastasis is shortened and blood has to be rapidly sucked into the ventricle.[31 37] Thus, the state of the ECM and titin (which acts as a bidirectional spring) are fundamental in maintaining diastolic filling and thus cardiac output. Fibrosis is increased in HFpEF and more importantly the collagen type changes from collagen III to a stiffer collagen I.[38] Recently, it has been shown that myocardial extracellular volume (ECV) measured by cardiac magnetic resonance is the strongest imaging diagnostic marker for independently differentiating between hypertensive heart disease and HFpEF.[39] In addition, in this study, both GLS and ECV were strongly inversely correlated. Thus, an increase in ECV affects systolic function as much as diastolic. Dyssynchrony of contraction and relaxation will become apparent including torsional dyssynchrony, which will further impair suction and early diastolic filling.[31 40] Poor early filling leads to a compensatory increased active atrial contribution (booster pump), explaining the typical ARP, which is generally used as a marker of diastolic dysfunction. Increased left atrium (LA) size is indicative of a chronic raised LA pressure and typical of HFpEF and a useful diagnostic marker. Eventually, atrial failure will occur, at first on exercise[41] and later leading to AF perhaps due in part to increased atrial fibrosis. AF is a frequent accompaniment to HFpEF and adversely affects outcome.[42 43] OSA is associated independently with both hypertension and AF,[2 3 44] the former being a major precursor of HFpEF and AF being a major consequence of HFpEF. Thus, OSA is likely to aid the development HFpEF through hypertension and exacerbate its progression and symptoms by hastening the development of AF.(see figure 1).

Inflammation is also a feature of HFpEF. Studies have shown that the many comorbidities associated with HFpEF such as hypertension, obesity, type II diabetes, hyperlipidaemia and renal disease are associated with systemic inflammation and vascular endothelial dysfunction.[32 45] All of these, and now including OSA, can lead to increased myocardial fibrosis and adverse changes in the type of collagen (specifically the degree of cross-linking), which are well established as features of the HFpEF heart.[38 39] The interplay of these varied comorbidities will produce different phenotypes with differing degrees of damage to the heart and vasculature accounting for the fact that patients with HFpEF are not a homogenous group. However, the final common pathway to symptoms will be in the abnormal ventricular and atrial mechanics outlined above primarily through loss of ventricular suction, increased myocardial and arterial stiffness, with a general loss of 'springiness' of the heart and vasculature. It must be remembered that a sizeable proportion of patients with HFpEF will progress to HFrEF probably because of the changes in the ECM initiating the process of ventricular remodelling and dilatation.[41]

Thus, the consequences of OSA fit exactly into the framework suggested for the aetiology of HFpEF. It is yet another comorbidity-inducing systemic inflammation, endothelial dysfunction and increasing vascular and myocardial stiffness exacerbating and accelerating the 'normal' changes associated with ageing. OSA should be recognised therefore as a common

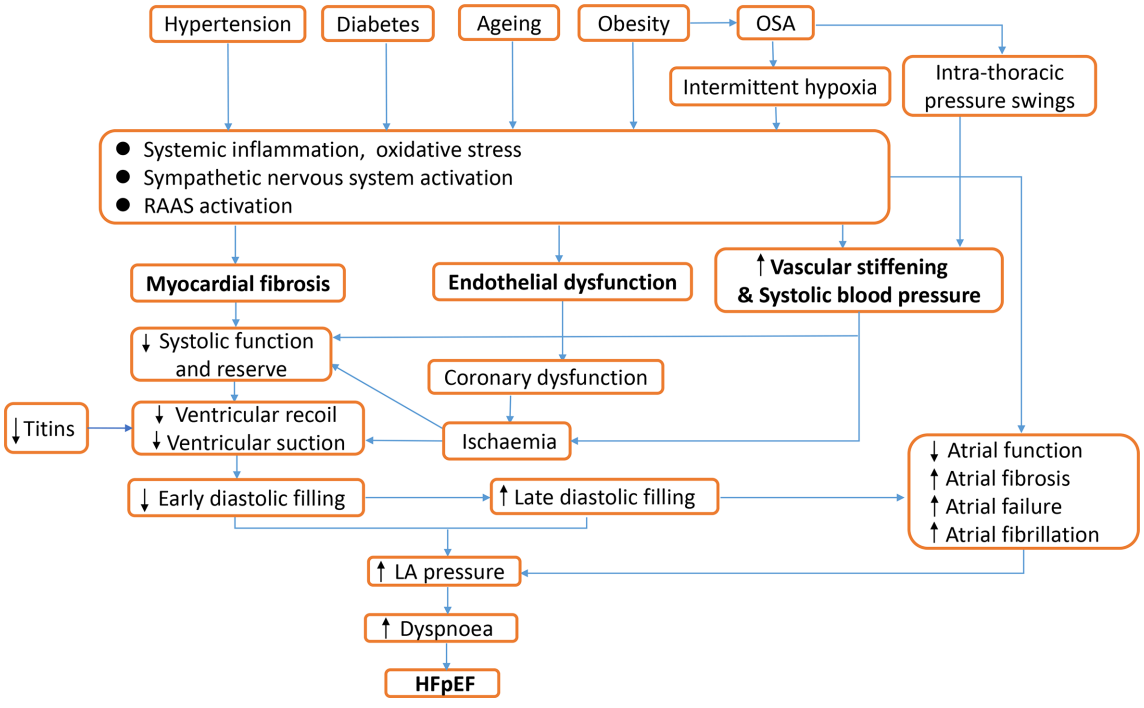

Figure 1 Schema outlining the overall pathophysiology of HFpEF and OSA and how the usual risk factors for HFpEF combine with OSA in a common pathway. HFpEF, heart failure with a preserved ejection fraction; OSA, obstructive sleep apnoea; RAAS, renin–angiotensin–aldosterone system.

cofactor in the development of HFpEF. Figure 1 provides a summary and schema of the pathophysiology of HFpEF and the potential role of OSA.

Does CPAP help systolic or diastolic dysfunction and HFpEF?

There have been several studies on the effect of CPAP on LV size, LVH, systolic and diastolic function in patients with OSA without HF. The results are mixed.[46] Butt *et al*[46] found that CPAP therapy resulted in reduction of the posterior wall thickness and improvement in LV ejection fraction, systolic s' velocity and diastolic LV impairment parameters. However, a recent randomised trial has shown that in patients with severe OSA (patients with LVEF <50% were excluded and none had overt HF), CPAP treatment for 3 months improved LV and RV function compared with sham treatment.[47] LV GLS improved compared with the sham treatment (–20.0%±2.1% vs –18.0%±2.5%; p=0.004), although there were no differences in LV dimension or ejection fraction. This improvement of systolic function was associated with better diastolic function (increase in e′) and interestingly LA function (increased LA GLS).

The role of CPAP, or adaptive servo ventilation (ASV), has been less studied in patients with clinical HFpEF. In a trial involving 36 patients with HF, LVEF >50% and an AHI >15 randomised to 6 months of ASV and then followed for a further year, symptom class, left atrial volume, BNP concentration, ventricular filling and event-free survival all improved in those so treated.[4 48] However, since there are few treatments for HFpEF other than treating comorbidities (and the possibility of mineralcorticoid receptor anatagonists in certain subtypes), there is a need for a large-scale randomised study of CPAP in a HFpEF population with OSA. Recently, Javaheri and colleagues have written on trial design for studies on OSA.[49] They emphasise the importance of including those with evidence of significant hypoxic burdern and excessive daytime sleepiness, which is correlated with an adverse cytokine profil (but paradoxically inversely correlated with SNS activity and survival in HF)[50].

CONCLUSIONS

There are many similarities between the pathophysiology of OSA and the other causes of HFpEF. All are associated with activation of a wide range of inflammatory, metabolic, neural and haemodynamic changes that can affect cardiac function. It appears that a common final pathway is probably via the development of myocardial fibrosis and collagen changes that cause stiffening leading to impaired systolic function, reduced ventricular suction and thus early diastolic filling particularly on exercise. Compensatory increased atrial function leads eventually to atrial failure and atrial fibrillation. Vasculature stiffening and hypertension will also exacerbate the situation in the myocardium by increasing afterload. The combination of OSA with other risk factors for HFpEF is a potent mixture that will amplify the deleterious effects on the myocardium and the vasculature. It is possible that treatment by CPAP may be beneficial at this early stage of HF.

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ORCID iD

John E Sanderson http://orcid.org/0000-0002-4407-0487

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