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REVIEW

Consequences of obstructive sleep apnoea syndrome on left ventricular geometry and diastolic function



Conséquences du syndrome d'apnées du sommeil obstructif sur la géométrie et la fonction diastolique ventriculaire gauche

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KEYWORDS

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Summary Obstructive sleep apnoea syndrome (OSAS) is a frequent sleep disorder that is known to be an independent risk factor for arterial hypertension (AHT). Potential confounding factors associated with both OSAS and AHT, such as age, diabetes mellitus and obesity, have been explored extensively, and are considered as independent but additive factors. However, these factors are also contributors to left ventricular (LV) hypertrophy (LVH) and LV diastolic dysfunction, both of which are important causes of cardiovascular morbidity, and have been reported to be associated with OSAS for decades. In this review, we present an overview of how OSAS may promote changes in LV geometry and diastolic dysfunction through its best-known cardiovascular complication, arterial hypertension. We also summarize the epidemiological links

Abbreviations: AHI, apnoea hypopnoea index; AHT, arterial hypertension; BMI, body mass index; BP, blood pressure; BSA, body surface area; CPAP, continuous positive airway pressure; E/A ratio, ratio between early and late diastolic mitral peak flow velocities; E/e' ratio, ratio between early diastolic mitral peak flow velocity and annular velocity; IVRT, isovolumic relaxation time; LV, left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; nCPAP, nasal continuous positive airway pressure; OSAS, obstructive sleep apnoea syndrome.

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between OSAS and LVH, outline diastolic dysfunction in OSAS patients, and try to highlight the mechanisms responsible, focusing on the effect of confounding factors.

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Résumé Le syndrome d'apnées du sommeil obstructif (SASO) est un trouble du sommeil fréquent, et un important facteur de risque d'hypertension artérielle (HTA). Les potentiels facteurs confondants associés au SASO ainsi qu'à l'HTA, comme l'âge, le diabète, et l'obésité, ont été largement explorés et sont aujourd'hui considérés comme des facteurs indépendants mais additionnels. De plus, ces facteurs contribuent à la survenue d'hypertrophie ventriculaire gauche et de dysfonction diastolique, deux conditions associées à une forte morbi-mortalité cardiovasculaire et associées au SASO depuis des décennies. Cette revue présente une vue d'ensemble des effets du SASO sur la géométrie ventriculaire gauche et sa fonction diastolique par sa principale complication cardiovasculaire qu'est l'HTA. Nous résumons les liens épidémiologiques entre SASO et HVG, décrivons la fonction diastolique dans le SASO, et présentons les mécanismes physiopathologiques impliqués en tenant compte des facteurs confondants.

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Background

Obstructive sleep apnoea syndrome (OSAS) is characterized by repetitive episodes of partial or complete collapse of the upper airway during sleep; this usually terminates in arousal, leading to sleep fragmentation. These periods of obstructed breathing result in intermittent hypoxaemia with underlying sympathetic nerve activity and increases in heart rate and blood pressure (BP). Diagnosis and severity of OSAS are determined by the apnoea hypopnoea index (AHI). The American Academy of Sleep Medicine sets a threshold of five events per hour of sleep, predominantly obstructive, with symptoms such as daytime sleepiness, insomnia or snoring, for the diagnosis of OSAS [1].

OSAS is a frequent sleep disorder that affects 2% of middle-aged women and 4% of men [2]. Prevalence has reached 20% in some studies [3], increasing with age [4] and the growing rate of obesity [3]. However, more than 80% of OSAS patients stay undiagnosed, especially women and those with a lower body mass index (BMI) [5]. OSAS is a well-known independent risk factor for arterial hypertension (AHT) [6–8], the prevalence of which reaches 50% in this population [9]. Reciprocally, the reported prevalence of OSAS among hypertensive populations ranges from 20% to 40% [10–12], and up to 70% [13]. AHT in OSAS patients is more likely to affect diastolic BP in young people than systolic BP in the elderly [14]; typically, it has a non-dipper or a riser (higher sleep BP than awake BP) pattern [15–18] that leads to a higher frequency of masked hypertension (around 30% of cases) [19,20], and both of these conditions are known to be associated with even worse outcomes [21]. OSAS is also a recognized cause of resistant AHT [22,23], where the prevalence of OSAS exceeds 80% [24]. Potential confounding factors associated with both OSAS and AHT, such as age, diabetes mellitus and obesity, have been explored extensively, and are considered as independent but additive

factors [4,7,8,14,25,26]. However, those factors are also contributors to left ventricular (LV) hypertrophy (LVH) and LV diastolic dysfunction, both of which are important causes of cardiovascular morbidity [27,28], and have been reported to be associated with OSAS for decades [29,30].

In this review, we present an overview of how OSAS may promote changes in LV geometry and diastolic dysfunction through its best-known cardiovascular complication, arterial hypertension. We also summarize the epidemiological links between OSAS and LVH, outline diastolic dysfunction in OSAS patients and try to highlight the mechanisms responsible, focusing on the effect of confounding factors.

LV geometry and OSAS

Description of LVH and remodelling in OSAS

In 1990, Hedner et al. [30] conducted a case-control study comparing 61 OSAS and 61 control patients. The interventricular septum and LV posterior wall were thicker, and so the LV mass (LVM) and LVM index (LVMI) were significantly higher in OSAS patients. In 1995, Noda et al. [31] provided the first prevalence of LVH in OSAS patients, defined by LV wall thickness ≥ 12 mm. LVH was reported in 42% of the whole cohort ($n=51$), in 31% when the AHI was <20 and in 50% when the AHI was ≥ 20 . Using the same criteria for LVH, Cloward et al. [32] reported a prevalence of LVH of 88% among 25 obese and severe OSAS patients. A dose-response relationship was also observed between the severity of OSAS and the prevalence of LVH, using LVMI (normalized by height) for LVH assessment [33,34]. The largest cross-sectional study, including more than 2000 subjects (the Sleep Heart Health Study) [35], confirmed that LVMI (height) was significantly associated with both the AHI and the hypoxaemia index, even after adjustment for age, BMI, systolic BP and diabetes, with an

adjusted odds ratio for LVH of 1.78 (95% confidence interval 1.14–2.79) between patients with an AHI < 5 and those with an AHI $\geq$ 30. In this study, the prevalence of LVH reached 33% in severe OSAS patients.

The reported LVH is often eccentric; for example, Myslinski et al. [36] observed in 2007 that eccentric LVH was the predominant LV geometry in patients with newly diagnosed OSAS (without continuous positive airway pressure [CPAP] treatment). In this study [36] and in the Sleep Heart Health Study [35], the LV end-diastolic diameter in OSAS patients was significantly higher than in controls (or treated OSAS patients), and correlated positively with the AHI and the desaturation index. Eccentric LVH was also twice as frequent as concentric LVH among treated OSAS patients [37]. Conversely, Cioffi et al. reported that relative wall thickness was positively correlated with the AHI [38]; in this study, where BP was not different across the OSAS severity groups, LVM did not differ significantly, but LV concentric remodelling was independently associated with moderate-to-severe OSAS (odds ratio 7.6) and BMI (odds ratio 1.09). Likewise, Koga et al. [39] reported that concentric LVH was the most common LV geometry in 37 OSAS patients. Fig. 1 depicts the different types of LVH.

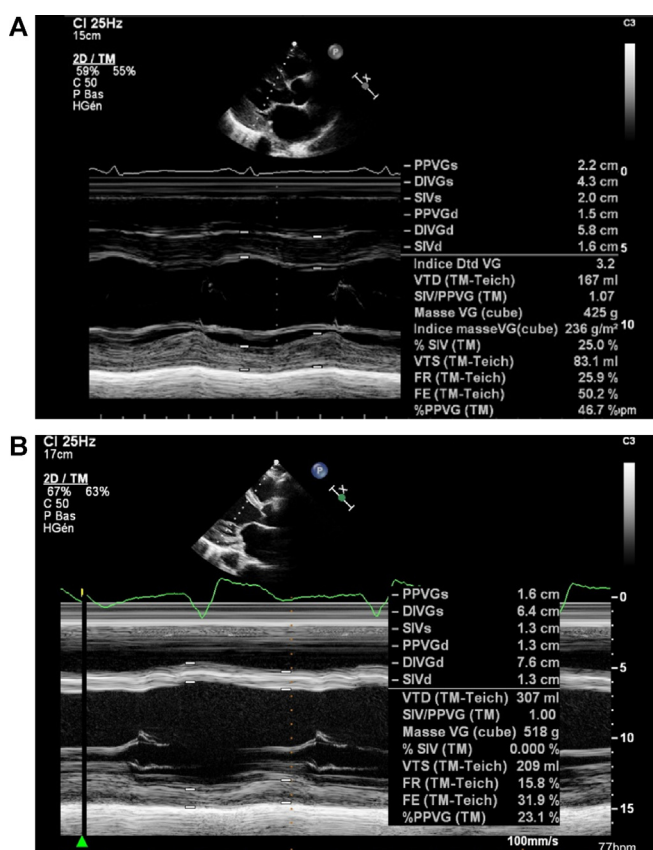


Figure 1. Different types of left ventricular hypertrophy (LVH). A. Concentric LVH. B. Eccentric LVH. DIVGd: LV internal diameter, diastole; DIVGs: LV internal diameter, systole; PPVGd: LV posterior wall thickness, diastole; PPVGs: LV posterior wall thickness, systole; SIVd: interventricular septum thickness, diastole; SIVs: interventricular septum thickness, systole.

LV remodelling in OSAS beyond AHT

Whether LVH in OSAS is a reality beyond AHT has been explored extensively and remains controversial. In the first case-control study showing LVH in OSAS patients [30], neither systolic nor diastolic BP correlated with the desaturation index, and LVMi was 15% higher in normotensive OSAS patients compared with normotensive controls, suggesting that OSAS affects LV geometry independent of AHT. Noda et al. [31] were the first to evaluate LV geometry and AHT based on ambulatory blood pressure monitoring. The prevalence of LVH, which was 50% in case of severe OSAS, reached 70% among patients with coexisting severe OSAS and AHT, defined as BP > 160/95 mmHg. All patients with LVH had AHT, whereas no patients without LVH had AHT. Moreover, LVMi (normalized by body surface area [BSA]) correlated significantly and strongly with 24-hour systolic and diastolic BP ($r=0.60$ and $r=0.48$, respectively), and markedly weakly with the obesity index ($r=0.05$), suggesting that AHT diagnosed via 24-hour ambulatory blood pressure monitoring is the most important determining factor for LVH in OSAS. These findings were supported by another cross-sectional study of 81 patients referred to a sleep laboratory [40], which reported that the AHI correlates with 24-hour BP and with LV thicknesses; however, this last correlation did not remain significant after adjustment for 24-hour BP and the use of antihypertensive drugs. In 2001, Niroumand et al. [41] conducted a large observational study among 533 patients, and concluded that LVMi (height) was correlated with age and AHT, but not with OSAS severity variables after multivariable analysis. Likewise, in a study conducted in non-hypertensive subjects, no differences were found in LV thicknesses, LVM or LVMi between controls, mild-to-moderate OSAS patients and severe OSAS patients [42], whereas a second study reported a higher interventricular septum thickness in patients with an AHI > 15, but these patients were also more obese [43]. However, among 130 newly diagnosed and untreated patients, Baguet et al. [1] found an independent correlation between LVMi (height) and mean nocturnal arterial oxygen saturation ($P=0.004$), in addition to a significant correlation with clinical BP ($P=0.01$). The low prevalence of LVH observed in this study (5–9.5%) may also be explained by less severe AHT (and obesity) compared with the previous study; this is consistent with a recent study reporting an LVH prevalence of 12% among well-controlled hypertensive patients [37]. In a recent study involving 155 resistant hypertensive patients, Dobrowolski et al. [44] also found an independent association between concentric geometry and both systolic BP and OSAS.

LV remodelling in OSAS beyond obesity

As the prevalence of LVH is very high in obese subjects [45], obesity can be a major confounding factor. In the first study reporting a higher LVMi in OSAS patients than in controls [30]. Yet, similar results were reported by Dursunoglu et al. [46], without differences in BMI across groups. Several studies have reported correlations between the AHI and LV thicknesses that did not remain significant after adjustment for BMI [40]. Besides, the very high prevalence of LVH (88%)

among 25 severe OSAS patients found by Cloward et al. [32] did not take into account the fact that all patients were obese (mean BMI 38 ± 11), because LV measurements were not related to obesity. However, when LV geometry was assessed by LVMI, results were not consistent, suggesting the importance of the method used. Indeed, some studies reported a significant correlation between LVMI and OSAS severity variables after multivariable analysis including BMI [39,47], whereas others did not [41]. Furthermore, several studies reported that, after multivariable analysis, LVMI was determined by metabolic syndrome, but not by BMI [48,49].

Effect of measurement method on LV geometry

Obtaining a reliable measurement of LVM in OSAS patients is difficult because this population is frequently overweight, which may significantly affect results. From one study to another, LVH may be defined as LV thicknesses (interventricular septum and/or posterior wall) ≥ 12 mm or may be based on LVM that can be normalized by BSA or height or not. Studies that assess LVH using LV measurements alone tend to report no association between LVH and OSAS or higher two-dimensional LV dimensions in OSAS patients that do not remain significant after adjustment for obesity [40,42,43,50,51]. Most recent studies show a persistent independent relationship between OSAS and LVMI (height) after adjustment for confounding factors or multivariable analysis [33,35,38,39,47,52]. However, few studies have reported no significant association between LVMI (BSA) [49,53] or LVMI (height) [41,48] and OSAS after taking into account confounding factors. Despite these discrepancies, we can reasonably think that OSAS is independently associated with LVMI, and that in addition to this, OSAS, BMI and AHT have significant interacting effects on LVMI [47].

Today, it is admitted that LVMI normalized by height and based on an obesity-independent measure of body size, is associated with a higher proportion of incident cardiovascular events than LVH detected by normalization for BSA, and is convenient for identification of individuals at high risk in populations with a high prevalence of obesity, such as OSAS populations. This method allows detection of poor prognosis and obesity-related LVH, which is not identified using BSA [54,55]. In a recent observational study among 188 treated and severe OSAS patients, the prevalence of LVH when assessed by LVMI normalized by height was two times higher than when normalized by BSA (12.4% vs. 6.5%) [37]. We should also mention that a small prospective study of 47 OSAS patients reported uniform results regarding the effects of CPAP on cardiac remodelling, assessed by echocardiography or cardiac magnetic resonance imaging [56].

Effects of OSAS treatment on LV geometry

Observational studies in obese and severe OSAS patients [32,57] reported regression of interventricular wall thickness after 6 months of nasal CPAP (nCPAP) (13 mm vs. 12.3 mm, $P < 0.02$ and 13 mm vs. 10 mm, $P < 0.001$, respectively), which was not observed for the LV posterior wall [32]. Subgroup analyses in this study [32] showed no effect of nCPAP in non-compliant patients. The findings also suggested a delayed effect of OSAS treatment, as LV dimensions were

not decreased after 1 month of treatment, just as in another study after 2–3 months of nCPAP or an oral appliance [58]. However, after 18 months of nCPAP, 41 obese patients did not show LVM improvement, except those with a decreased body weight, suggesting that CPAP treatment does not improve LV remodelling per se [48].

Physiopathology

Pathophysiological mechanisms involved in OSAS-related LV remodelling are summarized on Fig. 2. Because of repetitive respiratory disturbances leading to related hypoxia, hypercapnia, negative intrathoracic pressure and microarousals, OSAS patients experience permanent oscillations in their haemodynamic variables and sympathetic activation during sleep. This activation is observed more during sleep, but lasts through the day, leading to peripheral vascular remodelling, increased vascular resistance [59,60] and then increased afterload. In 2007, Drager et al. [53] compared pulse wave velocity (as a surrogate measure of arterial stiffness) and LV dimensions in non-hypertensive OSAS patients, hypertensive patients without OSAS and controls. OSAS and hypertension were both associated with increased arterial stiffness and LVH; the effects were of similar magnitude, but were also additive, suggesting that increased afterload may contribute to LV remodelling in OSAS patients. These observations were supported by Baguet et al. [33], who reported a significant correlation between carotid intima-media thickness and pulse wave velocity, and systolic and pulsed BP in OSAS patients. Moreover, repetitive episodes of hypoxaemia and reoxygenation may trigger oxidative stress mechanisms [61] and production of reactive oxygen species, leading to endothelial dysfunction [62,63], ischaemia-reperfusion injury and then ventricular remodelling. Besides, intermittent hypoxaemia also triggers activation of the renin-angiotensin-aldosterone system, as studies reported increased angiotensin II and aldosterone concentrations in OSAS patients [64,65]. This is another pathway that probably contributes to the development of LV remodelling.

Finally, circadian BP is involved in LV remodelling. In 1997, Verdecchia et al. [66] showed that LVMI (BSA) correlated more closely with nighttime BP than with daytime BP, and that LVMI was inversely correlated with the percentage of nocturnal BP fall. Yet, a reciprocal relationship between OSAS and nocturnal increase in BP is known. Moreover, Noda et al. [31] reported correlations between LVMI and BP on the one hand, and the duration of arterial oxygen saturation $< 90\%$ on the other. Desaturation time was also correlated with norepinephrine plasma concentration elevation, suggesting that LVH in OSAS results from hypoxia levels. These results are consistent with a recent observational study reporting that LV diameters significantly correlated with desaturation time, but not with the AHI [37].

Effect on prognosis

It is now well recognized that LVH is associated with poor prognosis. In 1998, the Framingham Heart Study reported a twofold greater risk of sudden death in case of LVH (defined as LVMI [height] > 143 g/m in men and 102 g/m in women), with a 45% increased risk for each 50 g/m

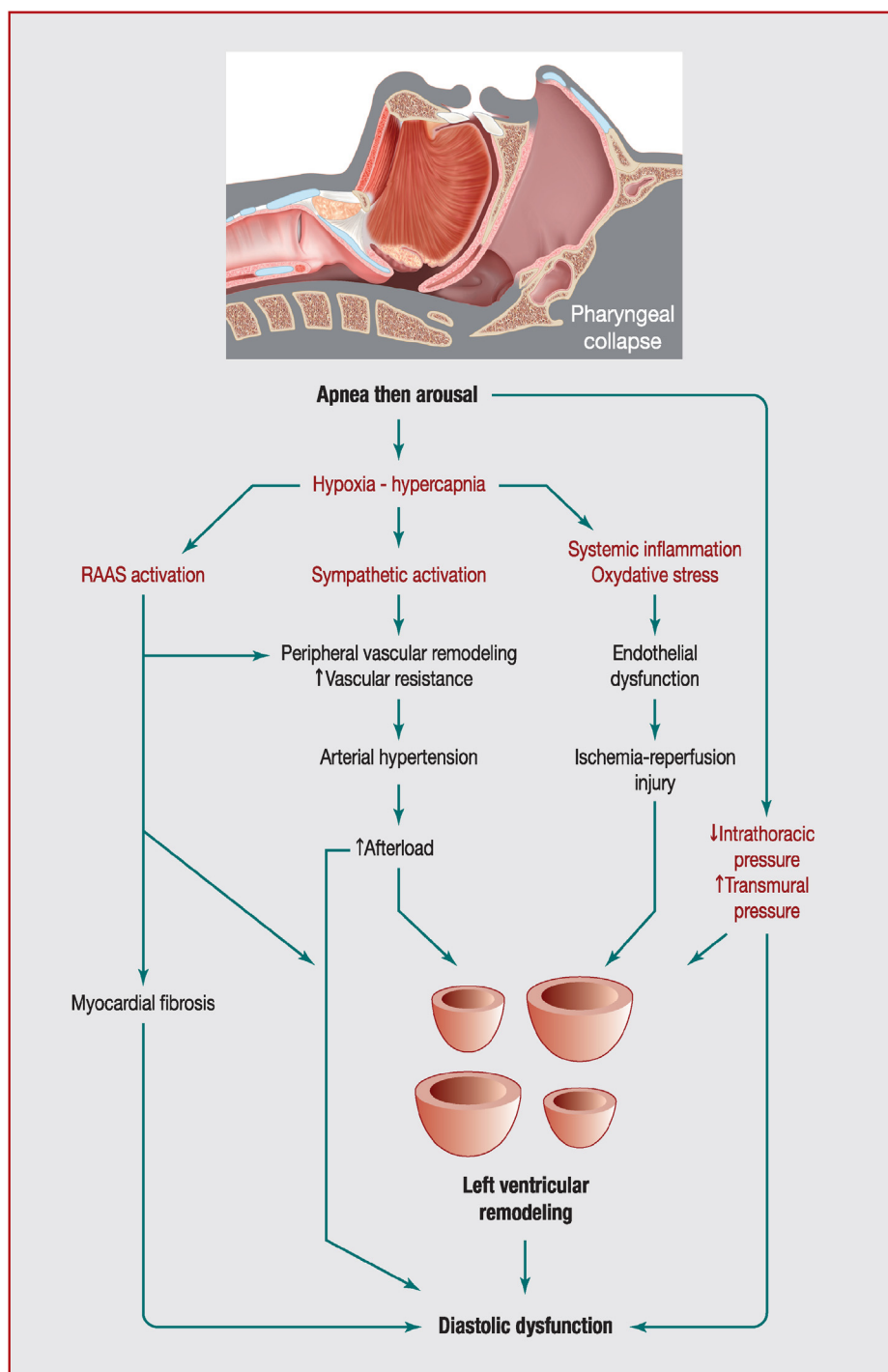


Figure 2. Pathophysiological mechanisms involved in obstructive sleep apnoea syndrome-related left ventricular remodelling and diastolic dysfunction. RAAS: renin-angiotensin-aldosterone system.

increment in LVMI [67]. LVH is also a condition that is known to lead to heart failure, coronary heart disease, arrhythmia and stroke [68]. In the field of genetic hypertrophic cardiomyopathy, OSAS is known as a common co-factor for poor prognosis [69]. Nevertheless, to date, very few studies have analysed the prognostic value of LVH in the specific context of OSAS. There is indirect evidence of worsening prognosis in case of LVH associated with OSAS, with

elevation of B-type natriuretic peptide plasma concentrations [70]. Indeed, N-terminal pro-B-type natriuretic peptide is not associated with the presence of OSAS alone or with sleep-related indices, either in sleep laboratory populations [71] or in community-based populations [72]. Yet, it has been shown to be significantly associated with AHT and LVH [70], and to decrease significantly after nCPAP application in hypertensive OSAS patients. Thus, in the OSAS

population, N-terminal pro-B-type natriuretic peptide does not appear to be a marker for non-specific OSAS-related cardiovascular abnormalities, but rather a marker for cardiovascular co-morbidities and/or complications.

Diastolic function and OSAS

Prevalence of OSAS in diastolic heart failure

In 1997, Chan et al. [73] showed that 55% of 20 isolated diastolic dysfunction patients experienced sleep-disordered breathing, defined as an AHI > 10. In this small sample, 85% of patients were hypertensive, but BMI and prevalence of hypertension were similar in patients with or without sleep-disordered breathing. This high prevalence of sleep-disordered breathing among patients with heart failure with preserved ejection fraction was confirmed later in a larger cohort ($n=255$), in which sleep-disordered breathing was experienced by 69% of the population (among them, 40% had OSAS) [74].

Diastolic dysfunction in OSAS

The reported prevalence of diastolic dysfunction among OSAS patients varies from 23% to 56% [37,75–77], depending on the sample size and the method of diastolic dysfunction assessment. Furthermore, several studies have shown various impaired LV diastolic function markers in patients with OSAS compared with in controls: enlarged left atrial size [46,78–80], prolonged isovolumic relaxation time (IVRT) [46,57,78,81], altered E/A ratio [46,78,79,81–84], lower early diastolic mitral annular velocity (e') [79,82,83,85,86] and increased E/ e' ratio [43,78,87] (Fig. 3).

Studies have reported a dose-response relationship between severity of diastolic dysfunction and severity of OSAS [40,57,73]. However, they did not use the same variables to characterize diastolic function or the severity of OSAS. Two studies carried out on small populations [40,73] reported that lower minimum arterial oxygen saturation, but not AHI, was associated with the E/A ratio and a prolonged IVRT. Other studies reported a significant correlation between E/A and mean nocturnal oxygen saturation [79] or between e' and the AHI [82]. However, in numerous studies, LV diastolic dysfunction was observed in OSAS patients, together with older age [76], higher BP [46,81,87], higher BMI [81] or higher LVH [46,78,81,85]. In a recent review, Baguet et al. [29] focused on common OSAS co-morbidities, such as AHT and diabetes, which lead to OSAS-related cardiac disorders, such as coronary artery disease, LVH and atrial fibrillation, thus establishing a strong basis for a perfect continuum from diastolic dysfunction and heart failure with preserved ejection fraction to systolic heart failure.

For these reasons, several studies tried to demonstrate a role for OSAS as an independent risk factor for the development of LV diastolic dysfunction. In 2002, Fung et al. [77] reported that, after multivariable analysis among 27 OSAS patients, lower minimum pulse oximetric saturation, like age and hypertension, was independently associated with an abnormal relaxation pattern on the transmitral flow. A larger observational study, including 150 newly diagnosed (and mostly hypertensive) OSAS patients, older age and lower

mean nocturnal oxygen saturation were identified as independent predictive factors for diastolic dysfunction assessed by the transmitral pattern [76]. Highlighting the importance of tissue Doppler imaging, Kim et al. [86] reported that e' was the only variable that was significantly decreased in severe OSAS patients (AHI > 30), and that its association with the AHI was independent of BMI, diabetes and AHT. Another study conducted among otherwise healthy obese patients, identified impaired diastolic function, assessed by left atrial size and tissue Doppler imaging on the mitral annulus, in patients with OSAS compared with in those without [88]. These results suggest an impaired LV function related to OSAS beyond obesity, but this needs to be confirmed by other data. Indeed, a study designed to assess LV diastolic dysfunction beyond obesity concluded that subjects with abdominal obesity had LV dysfunction (defined using E/A and e'/a' ratios) that was not associated with OSAS per se, but with metabolic syndrome [48]. The effect of metabolic syndrome was confirmed in other studies that identified both severe OSAS (AHI > 30) and metabolic syndrome as individual and synergistic determining factors for diastolic dysfunction [49,88].

Some other studies have failed to prove an independent relationship between OSAS and diastolic dysfunction. Niroumand et al. [41], in a cross-sectional study of 533 patients, reported a significant and independent association between age and diastolic dysfunction assessed by the E/A ratio, which was not observed with the AHI or nocturnal oxygen saturation. Likewise, among 188 OSAS patients undergoing LV diastolic function assessment by a global approach based on the most recent international guidelines [89], age was the only independent predictor of diastolic dysfunction [37].

To summarize, LV diastolic dysfunction is often observed in OSAS patients, even in the early stage of the disease [75,76,79,84], and regardless of the severity. However, in mild-to-moderate OSAS, LV dysfunction seems to be linked primarily to extrarespiratory determining factors (age, BMI, AHT, LVH). An independent role for severity variables appears to be stronger in severe OSAS.

Effects of OSAS treatment on diastolic dysfunction

Effects of nCPAP per se on diastolic function are not easy to comprehend, as studies on the subject did not report the same population characteristics, diastolic variables or methods of avoiding confounding factors. However, several reported improvements in left atrial size [78], IVRT [75,78,87], E/A ratio [75,78,82], e' [82] or E/ e' ratio [78], whereas Koga et al. [81] reported no difference in E/A ratio, E deceleration time and IVRT after 1 or 3 months of nCPAP. Some studies included only patients without AHT, in order to highlight OSAS treatment effects alone [75,87]. All effective reported treatments lasted at least 3 months. We have to mention that improvements in BP [78,87], body weight [48] or LVM [81,82], parallel to enhanced LV diastolic function, have been reported, which means that the independent effect of nCPAP is not well established. Finally, one study compared LV function variables between randomized OSAS

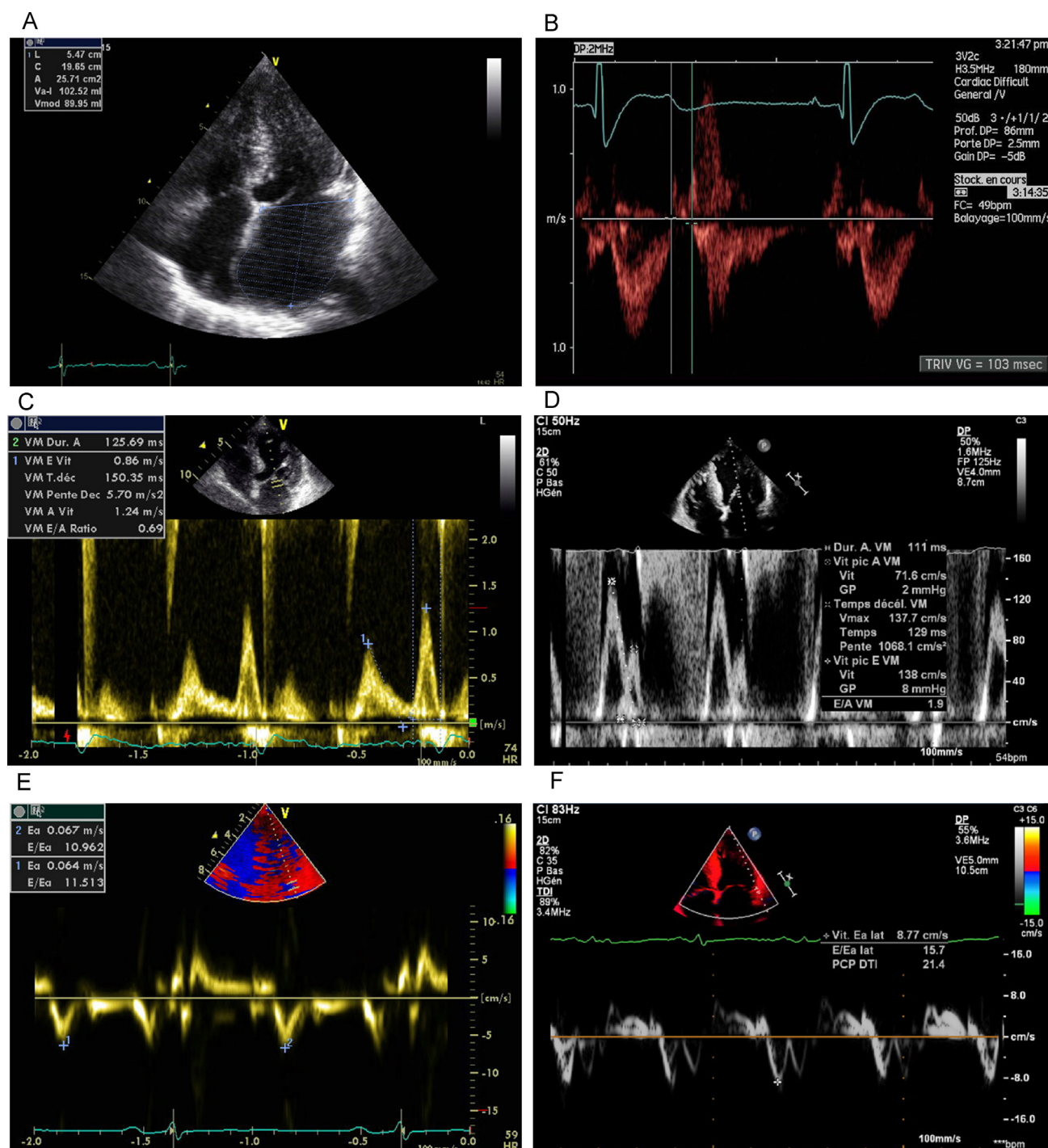


Figure 3. Diastolic dysfunction markers: A. Enlarged left atrium. B. Prolonged isovolumic relaxation time. C. Decreased E/A ratio. D. Restrictive mitral inflow pattern. E. Lower early diastolic mitral annular velocity (Ea in this figure). F. Increased E/e' ratio. TRIV: isovolumic relaxation time; VM E Vit: early diastolic mitral peak flow velocity; VM T déc: E deceleration time; VM A Vit: late diastolic mitral peak flow velocity; Ea: early diastolic mitral annular velocity (e').

groups with or without nCPAP [75]; other studies performed before and after nCPAP comparisons [48,78,81,82,87].

Physiopathology

Hypertension is the main cause of LVH [90] and diastolic dysfunction [91], and is also a major consequence of OSAS

(Fig. 2). Indeed, increased BP during apnoeic episodes leads to pressure overload in the left ventricle [92], as well as to LVH and myocardial fibrosis, which are both known causes of diastolic dysfunction. Moreover, LV pressure overload may result from sympathetic activation during sleep [93], from recurrent episodes of negative intrathoracic pressure [92] and from increased arterial stiffness [94], which

are well characterized in OSAS. Myocardial fibrosis can also be promoted by activation of the renin-angiotensin-aldosterone system, another consequence of OSAS, and therefore another plausible factor for diastolic dysfunction by myocardial remodelling [95]. We can also suppose that hypoxia-reoxygenation sequences are plausible contributing factors for LV remodelling, just as in ischaemic cardiomyopathy [96]. This concept is supported by the impairment of vascular endothelial function observed in OSAS-related diastolic dysfunction, and correlated to hypoxaemia markers [97].

Conclusions

OSAS is a very frequent disorder affecting mostly middle-aged or elderly, obese and hypertensive men. For these epidemiological reasons, LVH and LV diastolic dysfunction are largely associated with OSAS. Pathophysiological mechanisms are widely shared by these conditions: repetitive hypoxaemia reoxygenation sequences, bursts of sympathetic activity, hormonal and metabolic dysregulation, oxidative stress, systemic inflammation and mechanical haemodynamic disturbances. These all participate in the development of LVH and LV diastolic dysfunction, even if the role of each component considered separately is not yet well understood; in truth, there is probably a multifactorial effect. Most of these conditions seem to be improved by nCPAP therapy, although further large, controlled, randomized trials are needed to improve the management of OSAS patients.

Disclosure of interest

TD has received grant research support and is consultant for Res Med. All other authors declare that they have no competing interest.

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