Is the association between sleep apnea and left ventricular hypertrophy obesity-independent?

Cesare Cuspidi MD1,2 | Marijana Tadic MD, PhD3 | Carla Sala MD4 | Guido Grassi MD1

1 Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy
2 Istituto Auxologico Italiano IRCCS, Milano, Italy
3 Department of Cardiology, University Hospital "Dr. Dragisa Misovic - Dedine", Belgrade, Serbia
4 Department of Clinical Sciences and Community Health, University of Milano and Fondazione Ospedale Maggiore IRCCS Policlinico di Milano, Milano, Italy

Correspondence: Cesare Cuspidi, MD, Clinical Research Unit, Istituto Auxologico Italiano IRCCS, Viale della Resistenza 23, 20036 Meda, Italy. Email: cesare.cuspidi@unimib.it

Left ventricular hypertrophy (LVH) is a powerful predictor of cardiovascular morbidity and mortality in different clinical settings, resulting from the exposure of LV to non-modifiable and modifiable unhealthy risk factors. In the general population, hypertension and obesity, and their increasingly frequent association, represent the major causes of LVH. As for systemic hypertension, a consistent body of evidence supports an interplay between blood pressure (BP) elevation with genetic, humoral, and hormonal factors as major determinant of LVH. As for obesity, several pathophysiologic mechanisms have been invoked to explain the link between and LVH independently of hypertension, including (a) expansion of the circulatory volume; (b) enhanced sympathetic nervous activity and over-expression of renin-angiotensin-aldosterone system; (c) abnormal release of myocardial growth substances from abdominal and cardiac adipose tissue; and (d) metabolic abnormalities resulting in increased arterial stiffness and peripheral vascular resistances. Last but not least, the growing prevalence of Obstructive sleep apnea (OSA) in the general population in parallel with epidemic obesity has been shown to play a key role in the pathogenesis of LVH.

OSA is a widely prevalent disorder affecting up to 50% of men and 25% of women in the middle-aged population; the real prevalence of this condition is probably underestimated due to absence of symptoms in a large fraction of patients.

The pathophysiologic mechanisms underlying OSA and cardiac/vascular complications include an interplay of systemic and local factors responsible for LV structural and functional alterations in OSA patients. In particular, a cascade of events starting from hypoxia and increased carbon dioxide concentrations triggers a marked stimulation of sympathetic nervous system, renin-angiotensin-aldosterone axis, endothelin, and inflammatory mediators resulting in high BP and increased prevalence of nocturnal hypertension associated with non-dipping and impaired large artery compliance.

Additional mechanisms encompass impaired production of nitric oxide, insulin resistance, and negative intra-thoracic pressure during apnea episodes that enhance venous return and cardiac volume overload.

Experimental and clinical studies suggest an independent association between OSA and LVH, and this topic, however, remains debated, as patients with OSA often present comorbidities or risk factors linked to LVH. As part of this debate, obesity has highlighted by some experts as a major confounder in the association between OSA and LVH and the possible driver of the high prevalence of this cardiac phenotype in the OSA setting.

Taking into account the clinical importance of this topic, we have examined the studies published from January 1, 2000, to August 31, 2019, addressing the association of OSA and LVH, as assessed by standard echocardiography, in order to provide a concise and critical view of this controversial issue. Main inclusion criteria of our literature search were as follows (a) English articles published since the 2000s in peer-reviewed journals; (b) studies comparing prevalence rates of LVH, defined by validated echocardiographic criteria, among adult OSA and controls, taking into account the confounding effect of body mass index (BMI); and (c) studies performed in OSA patients without major comorbidities impacting on LV structure and function, in particular chronic heart failure.

The first literature search identified a total of 3712 papers. After the initial screening of titles and abstracts, 3619 reports were excluded and 98 were reviewed; of these, 10 studies1-10 fulfilled the inclusion...
criteria. Overall, 4916 participants (2481 with OSA and 2425 controls) were included in the selected studies (sample size range 53-1835). OSA was defined according to apnoea/hypo-apnoea index (AHI) cutoff of ≥5 events/h in eight studies, ≥15 events/h in the remaining two studies.8,9 LVH was identified according to four different diagnostic criteria. LV mass indexes equal or exceeding 48 g/h².7 in men and 44 g/h².7 in women and 115 g/m² in men and 95 g/m² were the prevalent LVH diagnostic criteria. Eight out of 10 studies targeted echocardiographic LVH in patients with mild to severe OSA referred to outpatient or in-hospital sleep clinics for suspected or known sleep-disordered breathing. The remaining two studies investigated OSA prevalence and its association with cardiovascular risk factors including LVH at the community level.3,10 Of note, only one study was carried out in the obesity setting7 and average body mass index (BMI) in patients with OSA ranged from 27 ± 5 kg/m² to 44 ± 1 kg/m².7

The confounding effect of obesity was appropriately taken into account in all 10 studies. In three studies, for example, patients with OSA were compared to controls with similar body size and clinical characteristics. In the remaining seven studies, the potential impact of factors other than OSA on LV mass was assessed by adjusting the differences between cases and controls for several variables (ie, age, sex, ethnicity, BMI, hypertension, and diabetes) or testing the independent association of OSA and LVH by multivariate analysis. LVH prevalence rates in patients with OSA and in their non-OSA counterparts markedly varied among studies (22%-71% vs 9%-67%, respectively).

Five of the 10 studies, including about a third of the pooled OSA population (793 out of 2481) and 14% of the controls (336 out of 2425), showed similar prevalence rates of LVH in patients with OSA and non-OSA controls, after adjustment for major confounders.2,5,7,9 Two aspects of these studies should be underlined: First, they included a large number of patients with mild OSA (AHI ≥ 5 events/h); second, a separate analysis for subgroups with different OSA severity was not performed. On the contrary, the remaining five studies, which enrolled together the vast majority of the cases and controls (1688 and 2731, respectively), reported a significantly higher prevalence of LVH in patients with OSA, regardless of confounding factors, including obesity.1,3,4,6,10

A key contribution in interpreting these conflicting findings is provided by the two large population studies that analyzed the relationship between OSA and LVH, according to the severity of the syndrome.3,10 In the study by Chami et al,3 including a total of 1835 participants, a progressive increase in LVH prevalence was observed from controls (21%) through patients with mild (27%), moderate (32%), and severe OSA (44%). In fully adjusted models, a significant difference between OSA and controls was observed only for AHI > 15 events/h. Similar results have recently been reported by Bauters et al10 in 1809 subjects from the Asklepios cohort, as only in patients with moderate and severe OSA the frequency of LVH was significantly higher compared to non-OSA participants (25% and 28% vs 15%, P < .01).

In conclusion, the risk of LVH in patients with OSA progressively increases with the severity of sleep breathing disorder; moreover, the pathogenesis this cardiac phenotype in more advanced stages of the syndrome appears to be obesity-independent. This observation, however, is not intended to minimize the role of obesity in the pathogenesis of LVH in OSA, as there is a direct relationship between BMI and severity of the syndrome.

From a clinical perspective, early detection of OSA and timely implementation of measures (including the fight against obesity) aimed to slow down the progression of the disease may reduce the burden of LVH in the community. Finally, an echocardiographic examination is recommended in all patients with severe OSA regardless of their comorbidities, including obesity, in order to prevent cardiovascular complications of this dangerous association.

CONFLICT OF INTEREST
None.

ORCID
Cesare Cuspidi https://orcid.org/0000-0002-7689-478X
Marijana Tadic https://orcid.org/0000-0002-6235-5152
Guido Grassi https://orcid.org/0000-0003-1922-6547

REFERENCES

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