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CLINICAL REVIEW

Obstructive sleep apnea and hypertrophic cardiomyopathy: A common and potential harmful combination

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SUMMARY

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease and is characterized by large and asymmetric septal and left ventricle hypertrophy. HCM is a cause of disability, including heart failure, atrial fibrillation, and sudden death, with an annual mortality varying from 1% to 6%. Obstructive sleep apnea (OSA) is extremely common among patients with established cardiovascular disease, including hypertension and atrial fibrillation and when present may contribute to worse cardiovascular outcome. Although patients with HCM do not necessarily have typical characteristics of patients with OSA, such as obesity and increasing age, there is recent evidence that OSA is extremely common among patients with HCM, with a prevalence ranging from 32% to 71%. The presence of OSA among patients with HCM is independently associated with worse structural and functional impairment of the heart, including atrial and aorta enlargement, worse New York Heart Association functional class, and worse quality of life. The prevalence of atria fibrillation, an independent marker of mortality among patients with HCM, is significantly higher (~four times) in the presence of OSA. Therefore, the recognition of OSA is a new area of research that may impact the management of patients with HCM.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease and is an important cause of disability, including heart failure, atrial fibrillation (AF), and sudden death in patients of all ages.[1] Patients with HCM frequently have sustained supraventricular and ventricular arrhythmia. AF is an independent determinant of HCM-related morbidity and mortality due to heart failure and stroke.[2–4] Despite the recent advances in the pathophysiology of HCM, little is known about the potential role of co-morbidities that may contribute to increase of cardiovascular risk.

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of either partial or complete upper airway obstruction during sleep, leading to episodes of interruption of respiration associated with fragmented sleep and intermittent hypoxia.[5] OSA is recognized as a major public health problem, with an estimated prevalence ranging from 4 to 32.9% in the adult population, depending on the diagnostic criteria.[6–8] The prevalence of OSA is extremely high among patients with established metabolic[9,10] and cardiovascular disease.[11,12] For instance, the estimated prevalence of OSA among patients with hypertension,[13,14] resistant hypertension,[15] AF,[16] and metabolic syndrome[10] ranges from 30% to 90%. This high prevalence of OSA among patients with established cardiovascular disease is in part explained by the fact that both share several common risk factors, such as increasing age, obesity, sedentary life, and male sex. However, there is mounting evidence that OSA is not only a frequent condition associated with cardiovascular disease due to an overlap of risk factors, but when present may causally participate in the development or aggravation of the underlying cardiovascular disease.

HCM is a genetic disease, some of these patients are diagnosed at young ages and do not necessarily possess the typical traits of patients with established metabolic and cardiovascular disease. For instance, several reports found that body mass index (BMI) in

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CPAP, continuous positive airway pressure; HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; OSA, obstructive sleep apnea; PM, portable monitor; PSG, polysomnography.

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patients with HCM ranged from 23.3 to 24.8 kg/m^2.[17–21] Therefore, the search for OSA among patients with HCM has been largely ignored. One recent comprehensive report on research priorities in HCM did not include OSA as a potential area of research.[22] However, at least five recent studies that investigated a total of 349 patients with HCM consistently found a high prevalence of OSA, ranging from 32% to 71%, depending on the methodology and diagnostic criteria.[23–27] There is also evidence that the presence of OSA is independently associated with worse structural and functional impairment of the heart, including over dilation of the left atrium and aorta, higher prevalence of AF, worse New York Heart Association (NYHA) functional class, as well as quality of life.[23–28] The presence of OSA among patients with HCM is therefore a new area of research that may impact the management of patients with HCM and therefore justifies this review.

Hypertrophic cardiomyopathy (HCM)

HCM is the most common genetic cardiac disease[1] with an estimated prevalence of 1:500 habitants, in the general population[29] and is caused by mutations in myofilaments, calcium handling and Z-disc genes. So far, 19 genes were related with HCM, and over 900 mutations were described in those genes[30] (Supplementary Table S1). HCM is characterized by pronounced and asymmetric myocardial hypertrophy, predominantly in the interventricular septum.[31,32] Cardiac hypertrophy increases the intrinsic rigidity of the left ventricle (LV) wall, with impairment in relaxation and ventricular filling, resulting in diastolic dysfunction.[32] The diagnosis of HCM is established using two-dimensional echocardiography, by imaging a non dilated but hypertrophied LV chamber (left ventricular wall thickness $\geq$15 mm or $\geq$13 mm in patients with a first degree relative with HCM), in the absence of other diseases capable of causing hypertrophy (i.e., aortic stenosis and hypertension).[29,33] In approximately 25% of HCM patients, the septum becomes so thickened that it causes obstruction to blood ejection, through the left ventricular outflow tract (LVOT).[32] The outflow obstruction is also manifested in about 70% of nonobstructive patients during exercise,[1] causing the generation of a dynamic LVOT gradient. The dynamic nature of LVOT results from a series of changes in ventricular loading conditions and myocardial contractility that are sensitive to fluctuations in volume status, autonomic nervous activity and pharmacotherapy.[31] The severity of LVOT obstruction is clinically relevant because it is a major cause of symptoms, such as dizziness, dyspnea on exertion,[34] pre-syncope, syncope, as well as a predictor of poor prognosis and sudden death.[31] The highest outflow gradients have been linked to severe heart failure.[1] The left atrium is frequently dilated and hypertrophied, reflecting the high resistance to LV filling.

HCM is an important cause of disability, including heart failure, AF, and death in patients of all ages.[1] Sudden and unexpected death in young people is the most devastating component of its natural history, with an annual mortality varying from 1% to 6%.[35–37] AF is also an independent determinant of HCM-related morbidity and mortality due to heart failure and stroke.[2–4] High left atrial diameter has also been found to be associated with increased risk for heart failure-related death in patients with HCM.[38,39]

OSA and cardiovascular burden

The mechanisms of cardiovascular burden by which OSA can contribute to cardiovascular and metabolic disease are multiple and have been extensively investigated in patients with OSA without HCM. Acutely, the recurrent episodes of airway collapse during sleep are associated with vigorous inspiratory effort, negative swings in intrathoracic pressure, and asphyxia. These episodes of asphyxia are recurrent and typically terminate with arousals from sleep (see Fig. 1).[40,41] The consequences of the repetitive obstructive events during sleep are not restricted to nighttime but may extend throughout the day. OSA triggers a large list of neuro-hormonal and inflammatory responses that are potentially deleterious to the cardiovascular system, and include increased levels of sympathetic activity, products of oxidative stress, plasma C-reactive protein, fibrinogen, cytokines, leptin, as well as insulin resistance and endothelial dysfunction.[42–46] These studies suggest that OSA contributes to the development of atherosclerosis, and this hypothesis is strengthened by the demonstration that patients with OSA, compared with appropriate controls, have increased markers of atherosclerosis, including increased arterial stiffness and increased intima-media thickness of the carotid artery.[47,48] The treatment of moderate to severe OSA with continuous positive airway pressure (CPAP) is able to abolish OSA and has been used in observational and randomized trials to investigate the effects of OSA on several cardiovascular and metabolic outcomes. There is mounting evidence that the treatment of OSA with CPAP improves several harmful pathways, including sympathetic activity, C-reactive protein, insulin resistance, and endothelial function and ameliorates early signs of atherosclerosis.[43,46,49,50]

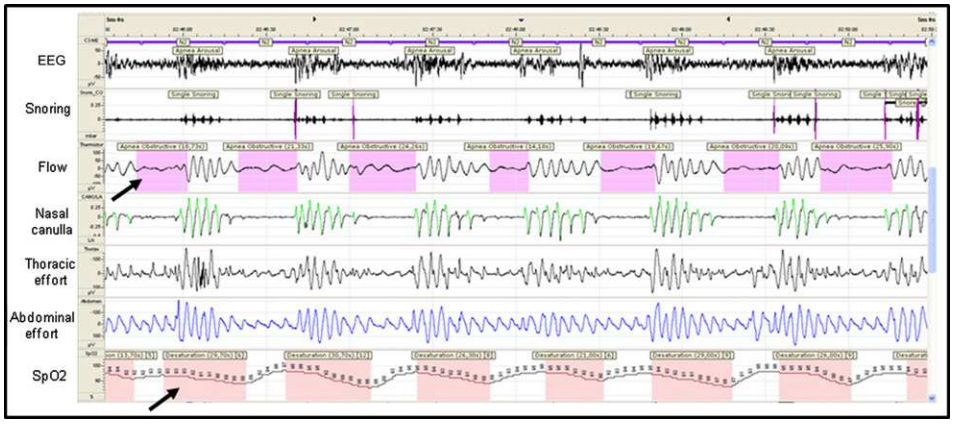

Fig. 1. Polysomnographic recording (5 min tracing) of a patient with hypertrophic cardiomyopathy presenting recurrent obstructive apneas during sleep.

The best documented relationship between OSA and cardiovascular disease is hypertension. OSA is a recognized cause of secondary hypertension and the treatment of OSA with CPAP is able to reduce blood pressure.[51,52] The overall reduction in blood pressure with CPAP treatment in two recent meta-analyses are relatively small (~2 mmHg).[53,54] However, most studies included a large number of normotensive and patients with controlled hypertension. It is also important to stress that even a small blood pressure reduction seems to be clinically relevant.[55] In addition, OSA has also been associated with cardiac structural and functional changes. Untreated OSA was associated with an increase in left atrial volume, suggesting that the treatment of OSA may prevent adverse left atrial remodeling.[56] OSA may promote right ventricular dilatation, right ventricle and interventricular septal hypertrophy,[57–59] OSA may also impair LV diastolic function velocity and increase left atrial volume.[60] The strong correlation between the carotid-femoral pulse wave velocity (estimate of the measure of arterial stiffness of the aorta) with the LV mass index in OSA patients suggests that increased afterload may contribute to heart remodeling.[48] Progression of heart remodeling may help to explain the strong association between OSA and AF. The prevalence of OSA among patients with AF is extremely high, ranging around 50%. More importantly, the treatment of OSA seems to reduce the risk of recurrent episodes of AF.[56] In addition, the presence of OSA has been associated with a two- to three-fold increased risk of recurrence of AF after cardioversion, compared with patients treated for OSA.[61] One observational study also showed that CPAP is associated with a reduction in fatal cardiovascular events among OSA patients.[62]

Review criteria

To review all studies available regarding the association between sleep disordered breathing and HCM, we conducted a search for articles published between January 1, 1980 and July 1, 2011 included in the MEDLINE and SciELO databases by using the key words hypertrophic cardiomyopathy or cardiomyopathies and the following key words: sleep, sleep-disordered breathing, obstructive sleep apnea and central sleep apnea. We found seven original articles and one case report.[23–28,63,64] We carefully examined all studies and reviewed the methodology used to recruit patients, diagnose sleep disordered breathing, and the association with cardiovascular outcome and quality of life.

Prevalence of OSA among HCM patients

Sleep-disordered breathing includes a number of disorders i.e., OSA, central sleep apnea syndrome, and central alveolar hypoventilation syndrome.[65] Central sleep apnea is rare in this population and we reported one patient with HCM and central sleep apnea associated with Cheyne-Stokes respiration.[63] One limitation of the majority of the studies in this area is that the method of detecting sleep disordered breathing was variable, and included overnight oximetry, the type III portable monitor (PM), and full polysomnography (PSG). Despite this limitation, in this review we used the term OSA, based on the high prevalence of OSA and the evidence observed in our laboratory that this is by far the most common sleep disordered breathing among patients with HCM. Therefore, for the sake of simplicity we adopted the term OSA, even when only oximetry data were presented.

The first evidence suggesting that OSA may be a prevalent disease among HCM patients was published in 2004 by Banno and colleagues.[23] The authors evaluated patients with different cardiomyopathies and reported that in a small sample of 15 patients with HCM, seven (47%) had OSA as diagnosed by full PSG. This initial observation was only fully investigated in the recent years (2009–2011), when three independent groups have reported the prevalence of OSA in a total of 334 patients with HCM.[24–27] Table 1 summarizes these recent studies, and it is clear that the prevalence of OSA is extremely high, ranging from 32% to 71%. The major limitations of these studies are three-fold. Firstly, the methodology used to diagnose OSA was different and varied from overnight oximetry to PM, and none of the recent studies used standard full PSG. However, there is growing evidence that PM is suitable for diagnosing OSA.[66] Moreover, in one study that used oximetry in 100 patients with HCM, the authors confirmed OSA in a subsample of 24 patients who underwent full PSG.[24] Secondly, the cut-off criteria for OSA diagnosis were variable among studies and are clearly shown in Table 1. Finally, it is possible to argue that the numbers of studies are relatively small and the impact of OSA recognition and treatment among HCM patients remains to be established. On the other hand, the sum of the studies published so far recruited over 300 patients and the main results are relatively consistent among different studies.

Characteristics of patients with OSA + HCM

The demographic characteristics of patients with and without OSA, as well as the association with cardiovascular outcomes, published are summarized in Table 2. Consistent with the general population, patients with OSA are in general predominantly male, significantly older, and more obese than patients without OSA (see Table 2). However, patients with HCM and OSA are less obese than the typical OSA patient referred to sleep laboratories, and the mean BMI among patients with HCM + OSA ranged from 27 to 31 kg/m^2. The observation that relatively lean patients may present OSA has also been reported in other specific populations, such as patients undergoing dialysis[67] and patients with congestive heart failure.[68] One interesting new unifying theory that may help to explain the propensity to OSA is provided by the observation that overnight rostral fluid shift to the neck could contribute to upper airway obstruction.[69] Rostral fluid shift is particularly relevant among patients with edematous states. Among patients with congestive heart failure fluid displacement from the legs to the neck and lungs can help to explain the genesis of both central and obstructive sleep apnea.[70] Among patients with end-stage renal disease, nocturnal rostral fluid shift was independently associated with the severity of OSA.[71] It also has been recently demonstrated that even in non-obese healthy subjects, the shift of fluid into the nuchal structures

Table 1
Characteristics of patients with hypertrophic cardiomyopathy included in studies.

Author	Eleid et al.[24] 2009	Pedrosa et al.[25] 2010	Konecny et al.[26] 2010	Prinz et al.[27] 2011
Patients, *n*	100	80	91	63
Age, y	55	47 (32–58)	52 (20–83)	59 (34–85)
Male, %	59	49	68	63
BMI, kg/m^2	35.3	26.4 (17–35.8)	31.6	26.9 (21.4–32.4)
Monitor	Overnight oximetry	Portable monitor	Overnight oximetry	Portable monitor
RDI/ODI, events/h	NA	9.2 (4.1–24.8)	8.6	34.8 (2.3–67.3)
Lowest SpO_2	NA	84 (78–88)	NA	NA
Cut-off, events/h	ODI > 5	RDI ≥ 15	ODI > 10	RDI ≥ 15
OSA, %	71	40	32	44

Values are mean (CI 95%). Variables with skewed distribution are presented as median (25–75% interquartile range) or percentage. Abbreviations: HCM: hypertrophic cardiomyopathy; BMI: body mass index; RDI: respiratory disorder index expressed in events/h; ODI: oxygen desaturation index expressed in events/h, OSA: obstructive sleep apnea; NA: no available data; SpO_2: lowest peripheral oxygenation.

Table 2
Characteristics of patients with hypertrophic cardiomyopathy, with and without obstructive sleep apnea.

	Eleid et al.[24] 2009			Pedrosa et al.[25] 2010			Konecny et al.[26] 2010			Prinz et al.[27] 2011		
	No OSA	OSA	*p*	No OSA	OSA	*p*	No OSA	OSA	*p*	No OSA	OSA	*p*
Patients, *n*	29	71	NA	48	32	NA	61	30	NA	11	52	NA
Age, y	46 (9–82)	59 (29–89)	<0.001	38 (30–53)	56 (41–64)	<0.001	48 (16–77)	64 (34–88)	<0.001	59 (36–81)	60 (34–86)	NS
Male, %	45	59	0.191	46	53	0.52	66	70	0.81	NA	NA	NA
BMI, kg/m^2	29 (15–43)	31 (18–44)	0.159	25 (15–35)	28.2 (21–35)	0.01	32 (16–48)	31 (21–41)	0.41	26 (20–33)	27 (22–33)	NS
RDI/ODI, events/hour	NA	12 (0–36)	NA	5 (2–8)	30 (21–41)	<0.001	3 (0–4)	20 (0–40)	<0.001	NA	23 (12–58)	NA
Atrial fibrillation, %	–	–	–	6	31	<0.001[a]	11	46	0.005	–	–	–
Left atrial enlargement	–	–	–	41 (39–47)	45 (42–53)	0.01[a]	NA	NA	Positive correlation[*]	NA	NA	Positive correlation[**]
Aortic enlargement	–	–	–	29 (28–32)	34 (30–37)	<0.001[a]	–	–	–	–	–	–

Values are mean (CI 95%). Variables with skewed distribution are presented as median (25–75% interquartile range) or percentage. Abbreviations: HCM: hypertrophic cardiomyopathy; BMI: body mass index; RDI: respiratory disorder index expressed in events/h; ODI: oxygen desaturation index expressed in events/h, OSA: obstructive sleep apnea; NA: notavailable, NS: notsignificant.

[*] Positive correlation between left atrial volume index and OSA severity expressed by the oxygen desaturation index (R=0.32; p= 0.002).

[**] Positive correlation between left atrial diameter and OSA severity expressed by apnea-hypopnea index (R=0.4; p<0.01).

[a] Remained significant in multivariate analysis.

may contribute to increase neck circumference and upper airway resistance.[72] Therefore overnight fluid shift could, at least in theory, play a role in the genesis of OSA among patients with HCM with no overt signs of leg edema.

OSA, HCM and poor outcome

It is remarkable that both OSA and HCM share common harmful pathways to the cardiovascular system as shown in Fig. 2. We acknowledge that most information derived from OSA was obtained from patients without HCM, and therefore the question whether OSA will be less, equally or more harmful in patients with and without HCM remains unclear. Firstly, patients with OSA experience overnight overstimulation of the sympathetic nervous system, which remains elevated during the day. On the other hand, patients with HCM may also have increased sympathetic activity that may not only be a marker of HCM severity,[73] but once present may participate in a vicious cycle that further contributes to poor outcome. Elevated catecholamine levels in OSA could influence the pathophysiology of HCM by increasing hypertrophy and left ventricular filling pressures, decreasing cardiac output, and initiating or worsening LVOT obstruction, dyspnea, and dizziness, and mitral regurgitation.[64] Moreover, patients with HCM experience a high incidence of ventricular tachyarrhythmia that is effectively treated with beta-blocking.[64] Therefore, it is possible to speculate that sympathetic overstimulation associated with OSA may be particularly harmful when present in patients with HCM. Secondly, OSA is independently associated with left atrium dilation reflecting heart remodeling.[25,27,48] In addition, septal hypertrophy typically found in patients with HCM has previously been shown to be independently associated with OSA severity in patients without HCM.[58,74] In patients with OSA without HCM, LV hypertrophy seems to be present even in the setting of normal blood pressure, suggesting that factors other than hemodynamic overload contribute to hypertrophy. Thirdly, both OSA and HCM are independently associated with AF that may be partially explained by the structural changes promoted by both conditions. Finally, OSA patients without HCM may have a higher risk for sudden death,[75] that in turn is a hallmark complication of HCM.[76,77]

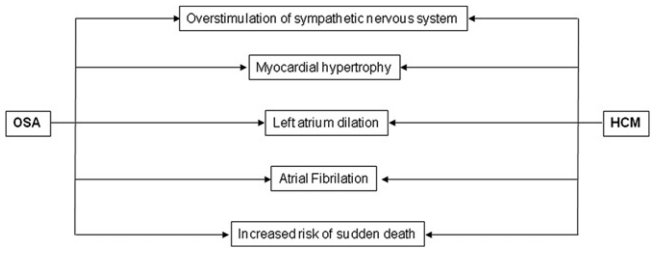

Fig. 2. Common but independent pathways in obstructive sleep apnea and hypertrophic cardiomyopathy.

The recent studies reported so far among patients with HCM + OSA are based on cross sectional data. The major limitation of any study that reports associations between OSA and poor cardiovascular outcome is that patients with OSA share traits that may independently contribute to cardiovascular dysfunction. Consistent with this observation, and as discussed above, patients with OSA and HCM are in general significantly older and more obese (see Table 2). Table 2 also shows a four fold higher prevalence of AF among patients with HCM and OSA than among patients with HCM but no OSA (see Table 2). It is unlikely that such differences are solely explained by the differences in the demographic characteristics. Similar to what has been shown in other populations, among patients with HCM multivariate analysis showed that the severity of OSA was independently associated with left atrial enlargement,[25–27] increased left ventricular end-diastolic diameter[27] and aortic enlargement.[25] Prinz and colleagues[27] also reported that OSA was strongly associated with clinical symptoms and worse NYHA functional class.

Perspectives

OSA is common among patients with cardiovascular disease and has many potential deleterious effects on the cardiovascular system. So, it is reasonable to speculate that even in a scenario of a genetically determined cardiac disease, such as HCM, OSA can increase sympathetic activities and contribute to cardiac remodeling, to the evolution and even to the prognosis of these patients. Further studies in this important research area should clarify the relative role of OSA in HCM prognosis. Based on the previous evidence in patients with OSA and without HCM, it is reasonable to

speculate, that the treatment of OSA with CPAP may positively impact several outcomes in the setting of HCM. This hypothesis was raised by one preliminary report of four patients with HCM and OSA that presented improvement in functional class evaluated by NYHA, reductions in left atrial volume, and reduction in LVOT after OSA treatment.[64] On the other hand, the safety of CPAP therapy in patients with HCM has not been investigated.

In conclusion, OSA is common among patients with HCM and independently associated with markers of worse cardiovascular outcome, including heart remodeling and AF. Future studies are necessary to clarify whether OSA is independently associated with increased cardiovascular risk in patients with HCM. Moreover, the impact of OSA treatment in randomized studies will clarify the role of OSA on HCM.

Practice points

1) Obstructive sleep apnea is common among patients with hypertrophic cardiomyopathy, with a prevalence ranging from 32% to 71%;
2) The presence of obstructive sleep apnea among patients with hypertrophic cardiomyopathy may be independently associated with worse structural and functional impairment of the heart including left atrial and aortic enlargement as well as worse NYHA functional class, worse quality of life.
3) The presence of obstructive sleep apnea among patients with hypertrophic cardiomyopathy is associated with a four times higher prevalence of atrial fibrillation. Atrial fibrillation is in turn an independent determinant of morbidity and mortality due to heart failure and stroke among patients with hypertrophic cardiomyopathy.

Research agenda

1) Full polysomnography studies comparing patients with HCM and patients with other cardiac disease, with appropriate control group.
2) Evaluation of the impact of the association of OSA + HCM on autonomic control variables.
3) Determination of the impact of treatment of obstructive sleep apnea in patients with hypertrophic cardiomyopathy on several outcomes, including quality of life, cardiovascular burden and mortality.

Conflict of interest

None declared.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.smrv.2012.06.006.

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