

# Lack of reliable clinical predictors to identify obstructive sleep apnea in patients with hypertrophic cardiomyopathy

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**OBJECTIVE:** Obstructive sleep apnea is common among patients with hypertrophic cardiomyopathy and may contribute to poor cardiovascular outcomes. However, obstructive sleep apnea is largely unrecognized in this population. We sought to identify the clinical predictors of obstructive sleep apnea among patients with hypertrophic cardiomyopathy.

**METHODS:** Consecutive patients with hypertrophic cardiomyopathy were recruited from a tertiary University Hospital and were evaluated using validated sleep questionnaires (Berlin and Epworth) and overnight portable monitoring. Ninety patients (males, 51%; age,  $46 \pm 15$  years; body mass index,  $26.6 \pm 4.9$  kg/m<sup>2</sup>) were included, and obstructive sleep apnea (respiratory disturbance index  $\geq 15$  events/h) was present in 37 patients (41%).

**RESULTS:** Compared with the patients without obstructive sleep apnea, patients with obstructive sleep apnea were older and had higher body mass index, larger waist circumference, larger neck circumference, and higher prevalence of atrial fibrillation. Excessive daytime sleepiness (Epworth scale) was low and similar in the patients with and without obstructive sleep apnea, respectively. The only predictors of obstructive sleep apnea (using a logistic regression analysis) were age  $\geq 45$  years (odds ratio [OR], 4.46; 95% confidence interval [CI 95%], 1.47–13.54;  $p = 0.008$ ) and the presence of atrial fibrillation [OR, 5.37; CI 95%, 1.43–20.12;  $p = 0.013$ ].

**CONCLUSION:** Consistent clinical predictors of obstructive sleep apnea are lacking for patients with hypertrophic cardiomyopathy, which suggests that objective sleep evaluations should be considered in this population, particularly among elderly patients with atrial fibrillation.

**KEYWORDS:** Hypertrophic Cardiomyopathy; Obstructive Sleep Apnea; Atrial Fibrillation.

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## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiac disease that is characterized by left ventricular (LV) hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease capable of producing this hypertrophy (1). HCM is a potentially devastating disease; it occurs in all age groups (1) and is a significant cause of disability, including heart failure, atrial fibrillation (AF), and sudden death (2). Despite all efforts, the sudden death

rate in HCM patients is approximately 1% per year, and this disease primarily affects patients older than 55 years (3–5).

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of either partial or complete upper airway obstruction during sleep, leading to fragmented sleep and intermittent hypoxia (6). Growing evidence shows that OSA triggers a cascade of deleterious effects to the cardiovascular system, including increased sympathetic activity, oxidative stress, systemic inflammation, insulin resistance, endothelial dysfunction, atherosclerosis, and heart remodeling (7,8). OSA is considered to be a risk factor for hypertension and is independently associated with poor cardiovascular outcomes in the general population (9,10). The typical features of OSA patients who are referred to sleep laboratories include male, obese, loud snoring, and symptoms of excessive daytime sleepiness.

Novel evidence shows that OSA is surprisingly common among patients with HCM, with prevalences ranging from

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32% to 71%, depending on the diagnostic criteria (11–15). Because HCM is commonly diagnosed at young ages, the presence of OSA among HCM patients has been largely ignored. Moreover, for reasons that are not completely understood, evidence indicates that the patients with HCM and OSA are typically less obese than the patients with OSA observed in sleep clinics (13,15). However, cross-sectional data suggest that similarly to what has been well established in other populations, the presence of OSA may contribute to poor cardiovascular outcomes in HCM patients (16). For instance, in HCM patients, OSA has been independently associated with left atrial enlargement and AF (13,14), which is a risk factor for sudden death in these patients.

We have previously reported a high prevalence of OSA among HCM patients (13). Though the previous study conveyed novel and important findings, the clinical characteristics and predictors of OSA were not described. Therefore, the objective of the present study was to identify the predictors of OSA that may help to increase the awareness and diagnosis of OSA in HCM patients.

## ■ METHODS

### Study design

This cross-sectional observational study evaluated consecutive HCM patients who were previously diagnosed according to the standard criteria described below. All patients were recruited from the Cardiomyopathy Clinical Unit, (Clinical Unit of Cardiomyopathies) at the Heart Institute (InCor), University of São Paulo School of Medicine, São Paulo, Brazil, between March 2008 and October 2011. Each patient had been diagnosed with HCM with asymmetric septal hypertrophy, with septal thickness  $\geq 15$  mm in the absence of other known causes of left ventricular hypertrophy, such as hypertension and aortic stenosis (17). We included patients of both genders who were older than 18 years. Patients with another cardiac diseases and clinical instability, as defined by a recent hospital admission (the previous 6 months), were excluded.

### Clinical evaluation

All HCM patients underwent a detailed history and physical examination, including anthropometric and clinical data. We used two questionnaires, the Berlin questionnaire and the Epworth Sleepiness Scale, to evaluate the risk of having OSA and the level of excessive daytime sleepiness, respectively, as described below:

**Berlin Questionnaire** - This questionnaire classifies patients at low and high risk for OSA based on responses in three symptom categories regarding: 1) snoring, 2) tiredness, and 3) the presence of obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) or hypertension. Patients positive for at least two symptom categories were considered at high risk for OSA (18). Because none of the patients with HCM had hypertension, the third domain of the Berlin questionnaire was restricted to obesity.

**Epworth Sleepiness Scale (ESS)** - The ESS is used to evaluate subjective excessive daytime sleepiness. Briefly, the patient rates the probability of dozing (0 to 3) in eight different situations. A score above 10 is considered positive for the presence of excessive daytime sleepiness (19).

### Sleeps study

All participants underwent an overnight study with a standard 4-channel recording device (Stardust II, Respiromics Inc., Murrysville, Pennsylvania, USA). This device records nasal pressure, thoracic excursion (as measured using a piezoelectric crystal), body position, pulse oxymetry, and heart rate. The device is classified as a type 3 monitor in accordance with the AASM recommendations (20). The portable monitoring sleep study was unattended and performed at home. Hypopnea was defined as a  $\geq 50\%$  discernible decrement in airflow lasting  $\geq 10$  s with a 3% reduction in oxygen saturation. Apnea was defined when cessation of airflow lasted  $\geq 10$  s and was further classified as central, obstructive, or mixed based on the presence of respiratory effort (21). The total recording time was used as the denominator to calculate the respiratory-disordered index (RDI) (6). The RDI was calculated as the total number of respiratory events per hour of record. The classification of OSA severity was defined according to RDI as mild (5–14.9 events/h), moderate (15–29.9 events/h), or severe ( $\geq 30$  events/h) (6). In this study, we considered moderate to severe OSA ( $\geq 15$  events/h) as the cut-off for OSA.

### Statistical analysis

Quantitative variables are expressed as means  $\pm$  SD or medians (interquartile ranges [IQRs]) or in percentages, when appropriate. The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. The Students t-test for independent samples and the Mann-Whitney U-test were used to compare continuous variables when appropriate. The chi-squared test was used for categorical variables. A univariate binary logistic regression analysis was used to evaluate variables associated with the presence of OSA, considering an RDI  $\geq 15$  events/h. The tested variables were age ( $\geq 45$  years), BMI ( $\geq 27 \text{ kg/m}^2$ ), neck circumference ( $\geq 43$  cm and  $\geq 41$  cm for males and females, respectively) (22), waist circumference ( $\geq 102$  cm and  $\geq 88$  cm for males and females, respectively) (23), snoring, and a high risk for OSA, as assessed by the Berlin questionnaire. The cut-offs used for age and BMI were obtained using ROC curve analysis as the best values for sensitivity and specificity. Variables with a  $p$ -value  $< 0.1$  upon univariate analysis were entered into a multivariate binary logistic regression. Because snoring was one of the Berlin questionnaire domains, it was not included as an independent variable. In addition, sensitivity, specificity, and positive and negative predictive values of relevant variables were also calculated. Data were analyzed with SPSS 17.0 statistical software (SPSS Inc., Chicago, Illinois, USA). A  $p$ -value  $\leq 0.05$  was considered significant.

### Ethics

The institutional ethics committee approved this study (SDC 3252/09/003), which was performed in accordance with the Helsinki Declaration of 1975 (revised in 1983).

## ■ RESULTS

We evaluated 90 HCM patients who were consecutively recruited from the Cardiomyopathy Clinical Unit at a tertiary University Hospital. None of the patients were referred to the sleep laboratory because of sleep complaints or had a previous diagnosis of OSA. Table 1 summarizes the



**Table 1** – General and clinical characteristics of the entire population of patients with hypertrophic cardiomyopathy and the patients with and without obstructive sleep apnea.

	Total population (n=90)	No OSA (n=53)	OSA (n=37)	p-value
Age, years	46±15	41±14	53±13*	<0.001
Male, n (%)	46 (51)	26 (49)	21 (57)	0.742
Caucasians, n (%)	67 (74)	40 (75)	27 (72)	0.983
Body Mass Index, kg/m <sup>2</sup>	26.6±4.9	25.3±5.0	28.5±4.0*	0.003
Neck, cm	37.4±4.2	36.4±3.2	39.0±5.0*	0.002
Waist, cm	94.1±12.1	91.0±11.0	98.6±11.7*	0.003
NYHA 2 and 3, n (%)	44 (49)	23 (43)	20 (54)	0.434
Atrial fibrillation, n (%)	18 (20)	5 (9)	13 (35)*	0.003
Antihypertensive, n (%)				
Diuretics, n (%)	19 (23)	10 (20)	9 (27)	0.718
Beta-blockers, n (%)	61 (68)	34 (64)	26 (70)	0.705
Angiotensin-converting enzyme inhibitor, n (%)	4 (5)	1 (2)	3 (8)	0.302
Calcium channel blockers, n (%)	18 (22)	9 (17)	10 (27)	0.375
Angiotensin receptor blocker, n (%)	14 (17)	7 (13)	7 (19)	0.660
Hypnotics, n (%)	5 (6)	2 (4)	3 (8)	0.398
Antidepressants, n (%)	13 (16)	6 (11)	7 (29)	0.481

Values are presented as percentages, means±SD or medians (interquartile ranges) for the variables, as appropriate. OSA: obstructive sleep apnea. \*p≤0.05.

patient demographics and the medications of the entire population and divides the patients according to the absence or presence of OSA. The vast majority of patients were taking at least one cardiovascular medication (88%) (Table 1). Consistent with recent studies of HCM patients, moderate to severe OSA (Apnea-Hypopnea Index>15 events/h) was extremely common and was present in 41% of our population (13–15). The OSA patients were predominantly older males with higher BMIs, higher neck and waist circumferences, and higher prevalences of AF compared to the patients without OSA. However, in contrast to the typical patient with OSA referred to the sleep laboratory, the patients with HCM+OSA were not particularly obese (Table 1).

The sleep characteristics and sleep-related questionnaires of the entire population are summarized in Table 2 according to the presence or absence of OSA. A high OSA risk, as evaluated by the Berlin questionnaire, was more common among the patients with OSA than among the patients without OSA (Table 2). The frequencies of positive answers to the three categories of the Berlin questionnaire (snoring, tiredness, and obesity) are also shown in Table 2. Snoring and high BMI were more common in the OSA patients. In contrast, tiredness did not differ significantly

among the patients with and without OSA. Moreover, complaints of excessive daytime sleepiness, as assessed by the Epworth Sleepiness Scale, were relatively low in the entire population and were similar among patients with and without OSA (Table 2).

We performed a binary logistic regression to evaluate the predictors for OSA: the only variables that were independently associated with OSA were age ≥45 years and the presence of AF (Table 3). To translate our findings into clinically meaningful data, we determined the sensitivity, specificity, and positive and negative predictive values of the main traits, including demographics and OSA-associated complaints (Table 4). In general, all analyzed variables performed poorly in the analysis, which highlights the fact that several HCM patients are minimally symptomatic for OSA and do not have the typical features that helps to identify OSA.

## DISCUSSION

In this study, the prevalence of OSA among consecutive HCM patients was particularly high (41%), which aligned with data from previous studies (13–15). Our study was designed to determine the clinical characteristics that may help to identify OSA among HCM patients. The main

**Table 2** - Respiratory parameters derived from portable monitoring and sleep questionnaires for the entire population and for patients with and without obstructive sleep apnea.

	Total population (n=90)	No OSA (n=53)	OSA (n=37)	p-value
RDI, e/h	10.2 (4.5–24.8)	5 (2.7–8.1)	30.3 (21.2–39.3)*	<0.001
Lowest SpO <sub>2</sub> , %	84 (78–88)	87 (83–89.5)	80 (75.7–82.5)*	<0.001
Berlin high risk, n (%)	36 (40)	13 (25)	23 (66)*	<0.001
Snoring, n (%)	47 (52)	13 (35)	24 (65)	0.056
Tiredness, n (%)	35 (39)	18 (34)	19 (51)	0.152
BMI ≥30 kg/m <sup>2</sup> , n (%)	22 (24)	9 (16)	13 (35)	0.080
Epworth	7 (3–11)	7.5 (3.5–11)	7 (3–12.2)	0.924

Values are presented as percentages, means±SD or medians (interquartile ranges) for the variables with skewed distribution. OSA: obstructive sleep apnea. RDI: respiratory-disordered index; BMI: body mass index. \*p≤0.05.



**Table 3 - Binary logistic regression with the predictors of obstructive sleep apnea among patients with hypertrophic cardiomyopathy.**

	Univariate		Multivariate	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Age ≥45 years	3.76 (1.55–9.13)	0.003	4.46 (1.47–13.54)	0.008
BMI ≥27 kg/m <sup>2</sup>	2.62 (1.10–6.24)	0.029	0.842 (0.25–2.88)	0.843
Large neck	2.18 (0.83–5.71)	0.067	2.48 (0.64–9.49)	0.185
Large waist	2.07 (0.87–4.92)	0.097	2.07 (0.67–6.43)	0.207
Atrial fibrillation	5.20 (1.65–16.36)	0.005	5.37 (1.43–20.12)	0.013
Snoring	4.40 (1.59–12.18)	0.004		
Berlin high risk	3.39 (1.41–8.18)	0.007	2.46 (0.83–7.28)	0.103
Constant			0.086	0.000

OR: odds ratio; CI: confidence interval; BMI: body mass index.

findings were as follows: 1) the patients with HCM+OSA did not complain of excessive daytime sleepiness; 2) the patients with HCM+OSA were significantly older and had higher BMI and neck and waist circumferences, but on average, the patients with HCM+OSA were overweight and typically not obese; 3) the Berlin questionnaire, which has been previously validated to recognize patients with OSA in other populations (18,24,25), was not useful in recognizing

considered, only age and the presence of AF remained statistically significant. These findings are worrisome and indicate the necessity to test the hypothesis in future studies that OSA may contribute to the genesis of heart remodeling and AF among HCM patients. Despite this evidence, the clinical suspicion of OSA among HCM patients remains uncommon. There are several potential explanations for the lack of OSA recognition among these patients. First, cardiologists are not systematically trained in sleep medicine. Second, because HCM is a genetic disease, it is often diagnosed at young ages (when OSA is not frequent). Third, HCM patients frequently do not exhibit the typical features of OSA patients, such as obesity. Fourth, OSA has only recently been shown to be extremely common in this population. Finally, in contrast to the patient population referred to the sleep laboratory (30), patients with HCM+OSA frequently do not have typical clinical symptoms, such as tiredness and excessive daytime sleepiness. The lack of excessive daytime sleepiness in patients with OSA has also been observed in consecutive patients with established cardiovascular disease, including hypertension (24,25), metabolic syndrome (31), stroke (32), atrial fibrillation (33), and coronary artery disease (34). In our study, regarding the sensitivity and specificity to predict OSA, the Epworth Sleepiness Scale and Berlin questionnaire returned low values for all of the tested variables; therefore, these

**Table 4 - Performance of clinical and sleep-related characteristics of the HCM patients.**

	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
Age ≥45 years	0.26 (0.15–0.42)	0.42 (0.28–0.57)	0.31 (0.18–0.49)	0.36 (0.23–0.51)
Gender	0.38 (0.24–0.54)	0.54 (0.39–0.69)	0.44 (0.28–0.61)	0.48 (0.34–0.62)
BMI ≥27 kg/m <sup>2</sup>	0.53 (0.38–0.67)	0.69 (0.53–0.82)	0.65 (0.48–0.79)	0.57 (0.43–0.71)
BMI ≥30 kg/m <sup>2</sup>	0.59 (0.36–0.78)	0.63 (0.50–0.74)	0.34 (0.20–0.51)	0.82 (0.69–0.91)
Large neck	0.56 (0.34–0.76)	0.62 (0.50–0.73)	0.34 (0.20–0.51)	0.80 (0.67–0.90)
Large waist	0.50 (0.35–0.64)	0.67 (0.50–0.81)	0.65 (0.48–0.79)	0.51 (0.37–0.65)
AF	0.72 (0.46–0.89)	0.66 (0.54–0.72)	0.36 (0.21–0.53)	0.90 (0.77–0.96)
Snoring	0.56 (0.41–0.70)	0.77 (0.58–0.89)	0.79 (0.61–0.90)	0.53 (0.38–0.68)
Berlin	0.40 (0.25–0.57)	0.30 (0.18–0.44)	0.28 (0.17–0.43)	0.42 (0.26–0.59)
Epworth >10	0.46 (0.28–0.65)	0.60 (0.46–0.72)	0.36 (0.22–0.54)	0.69 (0.54–0.80)

PPV: positive predictive value; NPV: negative predictive value; AF: atrial fibrillation.

OSA among HCM patients and 4) age ≥45 years and the presence of AF were the only variables that were independently associated with OSA. However, age ≥45 years had a low sensitivity and specificity to predict OSA. Conversely, the presence of AF presented a relatively high sensitivity (0.72, 95% confidence interval [CI 95%], 0.46–0.89). Altogether, our results suggest a lack of reliable clinical predictors to identify OSA among HCM patients.

OSA is common in the general population (26,27) and is independently associated with increased cardiovascular risk (9,10). In HCM patients, evidence also shows that the presence of OSA may be associated with worse structural and functional impairment of the heart, including atrial and aortic enlargement, worse New York Heart Association functional class, and worse quality of life (13–15,28). In HCM patients, AF is an independent marker of mortality (29), and its prevalence is significantly higher (~5 times) in the presence of OSA (13,14). Consistent with these previous observations, in the present study, AF was ~3 to 4 times more common among patients with HCM+OSA than in patients with HCM but not OSA. Moreover, in the multivariate analysis, when all possible clinical predictors were

tools are not useful in clinical practice (Table 4). All of these findings are important and emphasize that cardiologists should take the responsibility to actively search for OSA among patients with HCM.

Our study has some limitations that should be addressed. First, because of the specific nature of the underlying disease, the external validity of our data should be analyzed carefully. Second, our sleep study was performed using a portable monitor. However, portable monitors have also been confirmed as a useful alternative to overnight polysomnography for the diagnosis of sleep-disordered breathing in a series of patients with cardiovascular disease (34–36).

In conclusion, our study confirms that OSA is common in HCM patients. In this population, using clinical characteristics or validated questionnaires to identify OSA does not accurately identify the patients at high risk for OSA. Our results indicate the necessity for more accurate screening strategies for identifying OSA in HCM patients. Considering the high prevalence of OSA and its potential cardiovascular consequences, sleep studies should be widely considered for diagnosing OSA in patients with HCM, particularly among elderly patients with AF.



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## AUTHOR CONTRIBUTIONS

Nerbass FB participated in the study design, data collection, statistical analysis, and manuscript development. Pedrosa RP participated in the study design, data collection, and manuscript development. Genta PR performed the statistical analysis. Antunes MO participated in the data collection. Arteaga-Fernández E contributed to the manuscript development. Drager LF and Lorenzi-Filho G participated in the study design, statistical analysis, and manuscript development.

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