CHEST

Original Research

SLEEP MEDICINE

Obstructive Sleep Apnea Is Common and Independently Associated With Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy

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Background: **Hypertrophic cardiomyopathy (HCM) is associated with arrhythmias and cardiovascular death. Left atrial enlargement and atrial fibrillation (AF) are considered markers for death due to heart failure in patients with HCM. Obstructive sleep apnea (OSA) is independently associated with heart remodeling and arrhythmias in other populations. We hypothesized that OSA is common and is associated with heart remodeling and AF in patients with HCM.**

Methods: **We evaluated 80 consecutive stable patients with a confirmed diagnosis of HCM by sleep questionnaire, blood tests, echocardiography, and sleep study (overnight respiratory monitoring).**

Results: **OSA (apnea-hypopnea index [AHI] > 15 events/h) was present in 32 patients (40%). Patients with OSA were significantly older (56 [41-64] vs 38.5 [30-53] years, $P < .001$) and presented higher BMI (28.2 ± 3.5 vs 25.2 ± 5.2 kg/m^2, $P < .01$) and increased left atrial diameter (45 [42-52.8] vs 41 [39-47] mm, $P = .01$) and aorta diameter (34 [30-37] vs 29 [28-32] mm, $P < .001$), compared with patients without OSA. Stepwise multiple linear regression showed that the AHI ($P = .05$) and BMI ($P = .06$) were associated with left atrial diameter. The AHI was the only variable associated with aorta diameter ($P = .01$). AF was present in 31% vs 6% of patients with and without OSA, respectively ($P < .01$). OSA ($P = .03$) and left atrial diameter ($P = .03$) were the only factors independently associated with AF.**

Conclusions: **OSA is highly prevalent in patients with HCM and it is associated with left atrial and aortic enlargement. OSA is independently associated with AF, a risk factor for cardiovascular death in this population.** ***CHEST 2010; 137(5):1078–1084***

Abbreviations: AF = atrial fibrillation; AHI = apnea-hypopnea index; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association; OSA = obstructive sleep apnea

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease, with an estimated prevalence of 0.2% in the general population.[1] HCM is a leading cause of disability and death in patients of all ages. 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%.[2-4] Atrial fibrillation (AF) is the most common sustained arrhythmia in individuals with HCM. AF is an independent determinant of HCM-related morbidity and mortality due to heart failure and stroke.[5-7] Recently, increased left atrial diameter has also been associated with increased risk for heart failure-related death in patients with HCM.[8,9]

Obstructive sleep apnea (OSA) 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.[10] OSA is now recognized as a major public health problem, with an estimated prevalence of 4% to 9% in the adult population.[11] The prevalence of OSA is much higher in patients with established cardiovascular disease.[12] For instance, in patients with AF, 50% have OSA.[13] In addition, untreated OSA has been associated with a two- to threefold increased risk of recurrence of AF after cardioversion compared with risk in patients treated for OSA.[14] OSA has also been associated with

atrial remodeling,[15,16] which, in turn, plays an important role in AF development.[17]

Because OSA is a widely prevalent disease, it would be expected that OSA would be common among patients with HCM and that OSA would represent an additional burden to the heart. One recent study found that nocturnal oxygen desaturation is common in patients with HCM.[18] In the present study, we investigated the prevalence of OSA using a validated portable monitoring device[19] in a large series of consecutive patients with HCM. In addition, we tested the hypothesis that OSA is independently associated with heart remodeling and cardiac arrhythmias among patients with HCM.

Materials and Methods

Patients

Consecutive patients with echocardiographic-established diagnosis of HCM were evaluated at the Cardiomyopathy Clinical Unit (Clinical Unit of Cardiomyopathies) Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil, from March 2008 to March 2009. The Heart Institute is a 420-bed tertiary referral center for research and treatment of cardiopulmonary diseases. Included were all patients older than 18 years of age who agreed to participate in the study. Patients with prior cardiac surgery, presence of other cardiac disease, or clinical instability as defined by hospital admission, or who underwent changes in New York Heart Association (NYHA) functional class or medication over the last 30 days were excluded. All procedures were carried out in accordance with institutional guidelines, our institutional review committee approved the protocol, and patients gave informed consent. Patients underwent laboratory evaluation, including venous blood for measurement of glucose, cholesterol, triglycerides, hemoglobin, and creatinine levels; 12-lead electrocardiography; echocardiography; and sleep study; and they also filled out a questionnaire.

Echocardiography

Two-dimensional echocardiography with M-mode recording was obtained according to American Society of Echocardiography guidelines.[20] The resting systolic gradients were measured with color-guided, continuous-wave Doppler across the left ventricular cavity and outflow tract, orienting the transducer medially and anteriorly and away from the mitral regurgitant jet, when present. Patients maintained nonforced breathing, and the maximal peak velocity and gradient were obtained and registered. Mitral valve inflow was recorded with the sample volume placed at the leaflet tips. Left ventricular ejection fraction was calculated using the Teichholz formula or biplane method of disks (modified Simpson rule) for patients with wall motion abnormalities. The examinations were performed using a commercially available Acuson Sequoia (Siemens; Mountain View, CA) instrument with 2.5- and 3.5-MHz transducers by one experienced observer who was blinded to the presence or absence of OSA. Left ventricle internal end-diastolic diameter, end-systolic diameter, left ventricle diastolic posterior wall thickness, interventricular septum thickness, and left atrial diameter were recorded. Diastolic filling patterns were categorized based on previously published criteria.[21] All patients fulfilled the criteria for HCM as defined by a maximal left ventricular wall thickness ≥ 15 mm in any left ventricular segment in the absence of known causes of left ventricular hypertrophy.[1]

Sleep Study

All subjects underwent a validated, in-home, unattended overnight study with a standard four-channel recording device (Stardust II; Respironics, Inc.; Murrysville, PA). This device records nasal pressure, thoracic excursion (as measured by a piezoelectric crystal), body position, pulse oximetry, and heart rate, and has been validated against full polysomnography.[19] The data were scored by an experienced scorer. Hypopnea was defined as a 50% or discernible decrement in airflow lasting ≥ 10 s with oxygen desaturation of 3%. Apnea was defined when cessation of airflow lasted ≥ 10 s (whether central, obstructive, or mixed). Obstructive apneas were classified on the basis of presence of thoracic efforts. The total recording time was used in the denominator to calculate the apnea-hypopnea index (AHI).[19,22] OSA was defined as an AHI ≥ 15 events/h. Severe OSA was considered when AHI was ≥ 30 events/h. The Epworth Sleepiness Scale was used to evaluate subjective excessive daytime sleepiness. Briefly, the patient rated the probability of dozing (0 to 3) in eight different conditions and a score > 10 points was considered as the presence of excessive daytime sleepiness.[23]

Statistical Analysis

Results were expressed as mean ± SD or median (interquartile range) when appropriate. Student t or Mann-Whitney U test for independent samples or χ^2 test were used to compare variables among patients without and with OSA when appropriate. Stepwise multiple linear regressions were used to evaluate independent variables associated with left atrial and aorta diameters. Independent variables were age, hypertension, BMI, and AHI. Left ventricle outflow gradient > 30 mm Hg and ejection fraction were also included as independent variables associated with atrial diameter. Logistic regression was used to determine factors associated with AF. Variables included in the univariate analysis were age, NYHA functional class, hypertension, BMI, AHI, minimum O_2 saturation, syncope history, and echocardiographic variables. Variables with $P < .1$ on univariate analysis were entered into a multivariate analysis. The level of significance was set at $P < .05$. Computations were performed using Minitab Statistical Software, release 15 (State College, PA).

Results

We prospectively evaluated 92 patients with HCM. Twelve patients were excluded because of one or

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more exclusion criteria, and, therefore, 80 patients were studied (Fig 1). OSA was present in 32 patients (40%); 17 patients (21%) had severe OSA. Baseline characteristics of the entire population, as well as patients divided according to the absence or presence of OSA, are described in Table 1. Patients without and with OSA were similar regarding sex, race, arterial BP, heart rate, glucose, cholesterol, hemoglobin, creatinine levels, and daytime somnolence. In contrast, patients with OSA were older and had a higher BMI, larger waist and neck circumference, and higher triglyceride levels (Table 1).

Echocardiographic characteristics in patients without and with OSA were similar with respect to left ventricle ejection fraction (72.2% ± 11.4% vs 68.5% ± 8.5%, $P = .10$), interventricular septum thickness (21.5 [18.2-27.5] mm vs 20.5 [18.2-23.8] mm, $P = .23$), posterior wall thickness (12.5 [11-12.5] mm vs 11 [10-14] mm, $P = .41$), and left ventricle diastolic diameter (41 [38-46] mm vs 43 [40-47] mm, $P = .08$). The number of patients without and with OSA who presented left ventricle outflow obstruction (gradient > 30 mm Hg) was also similar (38% vs 31%, $P = .57$). Diastolic function was not evaluated in 21 patients because of the presence of AF (n = 13) or technical limitations (n = 8). Among the remaining 59 patients (40 without and 19 with OSA), the prevalence of diastolic dysfunction was similar in the two groups (40% vs 42%, $P = .87$). In contrast, compared with patients without OSA, patients with OSA had significantly enlarged left atrial and aorta diameters (41 [39-47] mm vs 45 [42-52.8] mm, $P = .01$ and 29 [28-32] mm vs 34 [30-37] mm, $P < .001$, respectively) (Fig 2). The only variables associated with left atrial diameter in stepwise multiple linear regression were AHI and BMI ($P = .05$ and $P = .06$, respectively; adjusted $R^2 = 11\%$). Stepwise multiple linear regression demonstrated that AHI was the only variable associated with aorta diameter ($P = .01$, adjusted $R^2 = 12.8\%$).

AF was significantly more common in patients with (31%) than without (6%) OSA (Fig 3). AHI in patients with, compared to those without, AF was 32.9 (17-55) vs 7.9 (3-21) events/h, respectively ($P < .001$). The variables associated with AF determined by logistic regression were age, NYHA functional class, AHI, left ventricle ejection fraction, and left atrial diameter (Table 2). Multivariate analysis demonstrated that only left atrial diameter and AHI were independent factors for AF (Table 3).

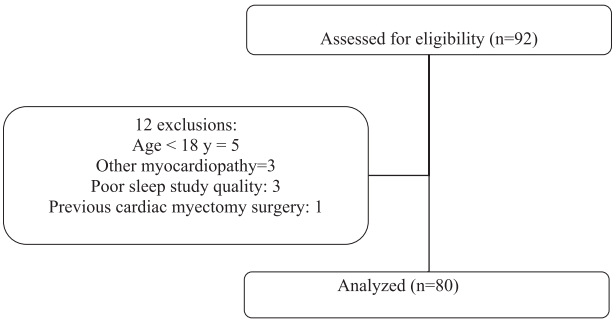

FIGURE 1. Patient flow diagram.

DISCUSSION

This study evaluated the presence of OSA in a large series of consecutive patients with HCM, and it conveys several new findings: First, 40% of patients with HCM had OSA. Second, patients with OSA had signs of heart remodeling characterized by increased left atrial diameter. Third, AF, a marker of cardiac mortality in patients with HCM,[7] was fivefold more common in patients with, than without, OSA. Finally, left atrial diameter and OSA severity were the only factors independently associated with AF in multivariate analysis.

The prevalence of OSA in the population of patients reported in this study is strikingly high and is at least twofold higher than in the general population.[11] This study therefore is in line with the recent observation of a high prevalence of overnight oxygen desaturation in patients with HCM.[18] Two characteristics of the patients studied are important. First, patients with HCM and OSA were relatively thin, with a BMI (~28 kg/m^2) lower than the BMI in typical patients with OSA drawn from the general population (~35 kg/m^2).[24] This pattern has been described previously in other specific populations, including patients with congestive heart failure[25] and those undergoing hemodialysis.[26] One possible explanation for such a high prevalence of OSA in relatively thin patients might be the fluid redistribution from edematous legs to peripharyngeal tissues when moving from the upright to the recumbent position impinging on the pharyngeal lumen and predisposing to collapse during sleep.[27,28] Another characteristic of these patients with OSA is the lack of excessive daytime somnolence, a hallmark of patients with OSA referred to sleep laboratories. The absence of sleep complaints has also been described in other populations of cardiovascular patients, including those with heart failure[25] and metabolic syndrome,[29,30] and in patients referred for long-term pacing.[31] The absence of typical body habitus and symptoms linked to OSA in this population may help explain the absence of previous systematic studies evaluating sleep in patients with HCM.

OSA has been associated previously with increased left ventricular septal thickness, left atrial diameter, and left ventricular mass in hypertensive patients[15] and with increased left ventricular mass and interventricular

Table 1—*Patients' Characteristics*

Characteristics	Total, N = 80	No OSA, n = 48	OSA, n = 32	*P* Value
Age, y	47 (32-58)	38.5 (30-53)	56 (41-64)	.0001
Male, %	49	46	53	.52
White, %	76	79	72	.45
Neck circumference, cm	37.3 ± 4.3	36.1 ± 3.1	39.1 ± 5.2	< .01
BMI, kg/m²	26.4 ± 4.8	25.2 ± 5.2	28.2 ± 3.5	< .01
Waist, cm	93.6 ± 12.1	90.5 ± 11.6	98.2 ± 11.5	< .01
Systolic BP, mm Hg	112 (106-127)	112 (109-124)	113 (101-132)	.72
Diastolic BP, mm Hg	70 (70-78)	70 (70-74)	72 (62-80)	.81
Heart rate, bpm	64 (60-70)	64 (60-70)	60 (56-71)	.24
Creatinine, mg/dL	0.98 (0.78-1.12)	0.92 (0.75-1.1)	1.0 (0.9-1.2)	.12
Fasting glucose, mg/dL	92 (86-101)	92 (86-98)	95 (89-105)	.16
Cholesterol, mg/dL	182 ± 47	185 ± 49	178 ± 45	.59
LDL, mg/dL	115 ± 37	116 ± 41	114 ± 33	.79
HDL, mg/dL	39 (33-46)	44 (38-51)	44 (31-44)	1.00
Hemoglobin, g/dL	14.1 (13.4-15.3)	14.1 (13.5-15.4)	14.1 (13-15.2)	.60
Triglycerides, mg/dL	103 (72-150)	79 (47-145)	131 (96-178)	< .01
NYHA I-II, %	74	81	63	.06
Smoking, %	9	4	16	.11
Medical therapy, %	88	83	94	.17
Diuretic, %	23	21	25	.66
β-Blocker, %	63	63	72	.38
ACE, %	4	2	6	.56
ARB, %	18	15	22	.40
Amiodarone, %	16	15	19	.62
Epworth sleepiness scale	7 (3-11)	7 (3-11)	7 (3-14)	.78
Time in bed, min	427 ± 82	417 ± 83	442 ± 78	.19
AHI, events/h	9.2 (4.1-24.8)	5 (2.3-7.9)	30 (21.5-40.8)	< .0001
Central apneas	0.3 (0-1.4)	0.2 (0-0.9)	1.3 (0.1-4.8)	< .01
Obstructive apneas	2.9 (0.7-9.8)	0.8 (0.3-1.5)	11.5 (7.3-21)	< .01
Mixed apneas	0 (0-0.2)	0 (0-0.1)	0.2 (0-0.6)	< .01
Hypopneas	4.5 (2.1-8.1)	2.9 (1.4-6.5)	8.3 (4.8-16.5)	< .01
Lowest oxygen saturation (%)	84 (78-88)	87 (83-89)	79 (75-82)	< .0001

Data are given as median (interquartile range), percentages, or mean ± SD. ACE = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin receptor blockers; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NYHA = New York Heart Association functional class; OSA = obstructive sleep apnea.

septal thickness in patients with congestive heart failure.[32] Obstructive apneas elicit a series of mechanical, hemodynamic, chemical, neural, and inflammatory responses with potential adverse consequences to the heart.[33] During obstructive apneas, patients generate negative intrathoracic pressure against an occluded upper airway, which increases left ventricle transmural pressure, an important determinant of left ventricular afterload. These mechanical responses to OSA may also be important to left atrial afterload, contributing to increased left atrial diameter.[16] In line with these previous studies, our study found an enlarged left atrial diameter in patients with HCM and OSA compared with patients with HCM but no OSA. In the present study, patients with OSA had a left atrial diameter that was, on average, 9% larger than that of patients without OSA, which is remarkably similar to a previous report on patients with OSA but no HCM (9%).[16] Another important finding of our study is the observation of an independent association between ascending aorta diameter and OSA, even after adjusting for confounding factors. This finding is in line with the study by Serizawa et al[34] in patients with OSA and no significant heart disease. Increased transmural pressure in the aortic wall due to negative intrathoracic pressure secondary to apneas may play a central role in aorta dilation. In contrast to what would be expected from previous studies in patients with OSA, our findings showed no significant difference in left ventricle diameters in patients without and with OSA among patients with HCM. The number of patients with left ventricle outflow obstruction (gradient > 30 mm Hg) in patients without and with OSA was also similar. We speculate that genetic determinants of left ventricle hypertrophy that characterize HCM overcome the influence of OSA on left ventricular remodeling.

OSA is tightly linked to arrhythmias. Obesity and the magnitude of nocturnal oxygen desaturation associated with OSA are independent risk factors for incidental AF in individuals < 65 years of age. AF is fivefold more common in patients with OSA than in patients without OSA.[35] Our study also found a fivefold increased prevalence of AF in patients with HCM

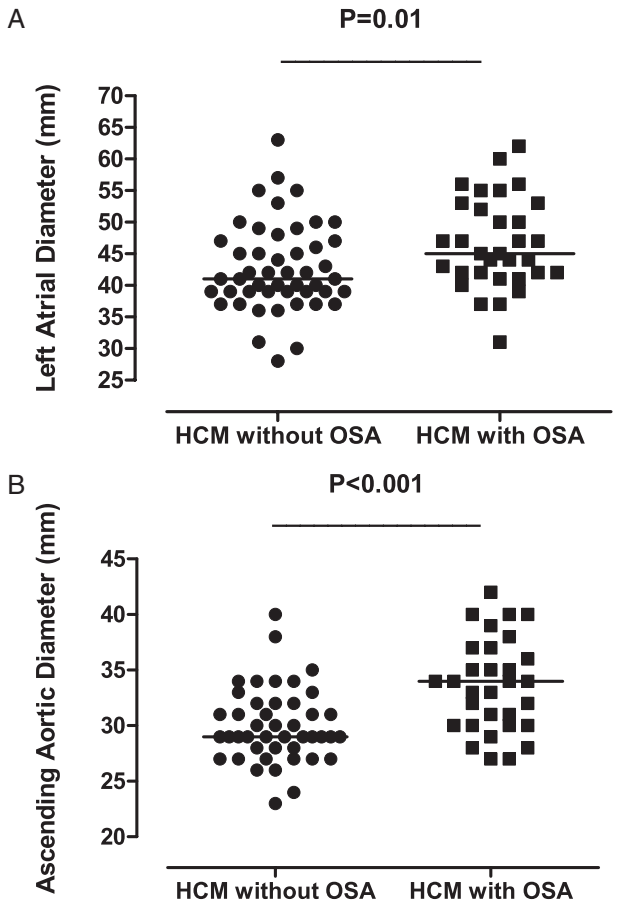

FIGURE 2. Left atrial diameter in patients with HCM without and with OSA (*A*). Ascending aortic diameter in patients with HCM without and with OSA (*B*). HCM = hypertrophic cardiomyopathy; OSA = obstructive sleep apnea.

and OSA compared with patients with HCM but without OSA. Despite the relatively small sample size, the power for detecting differences in the prevalence of AF among patients with and without OSA was 86%. The only independent factors associated with AF were left atrial diameter (in line with previous findings)[36] and OSA. In the general population, it has been shown that OSA managed with the standard treatment of continuous positive airway pressure decreases the

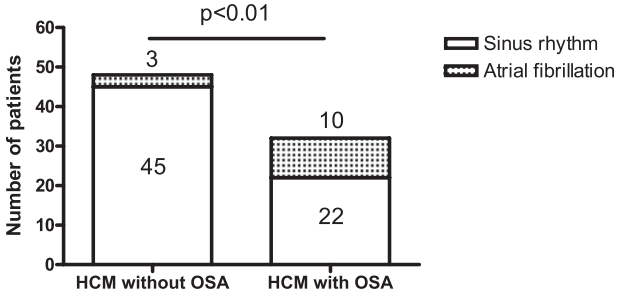

FIGURE 3. Presence of atrial fibrillation in patients with HCM without and with OSA. See Figure 2 legend for expansion of abbreviations.

Table 2—*Logistic Regression Between Atrial Fibrillation With Anthropometric, Echocardiographic, Sleep Apnea Variables and Hypertension Diagnosis*

Characteristics	OR	95% CI	*P* Value
Age	1.05	1.01-1.10	.03
NYHA	2.93	1.37-6.24	< .01
Hypertension	2.52	0.74-8.55	.14
BMI	1.07	0.94-1.21	.29
AHI	1.08	1.04-1.13	< .001
Min oxygen sat	0.97	0.93-1.02	.25
Syncope	1.93	0.44-8.4	.38
IVSTh > 30 mm	0.38	0.05-3.23	.38
LVOTG > 30 mm Hg	0.29	0.06-1.4	.12
LVEF	0.95	0.9-1.01	.09
Moderate or severe MR	0.88	0.1-8.03	.90
Left atrial diameter	1.16	1.06-1.27	< .01
Aorta diameter	1.06	0.91-1.22	.48

IVSTh = interventricular septum thickness; LVEF = left ventricle ejection fraction; LVOTG = left ventricle outflow tract gradient; Min oxygen sat = minimum oxygen saturation during sleep; MR = mitral regurgitation; OR = odds ratio. See Table 1 for expansion of other abbreviations.

recurrence of AF, pointing to the importance of this relationship. In accordance with this hypothesis, Sengupta et al[37] recently reported four patients with OSA and obstructive HCM referred for open cardiac myectomy because of refractory heart failure symptoms, which improved dramatically with OSA treatment with continuous positive airway pressure such that surgery was avoided. This finding is particularly relevant because there is a clear relationship between AF and cardiovascular death among patients with HCM. AF occurs in 5% to 25% of patients with HCM, increases with age, and is linked to left atrial enlargement.[4,5,7,15,38-40] This study raises the possibility that early recognition and treatment of OSA in patients with HCM may reduce the cardiovascular burden.

One limitation of our study was the use of a four-channel recording device that does not measure sleep. Thus, our measurements of AHI were based on total recording time, rather than total sleep time, which can be reduced in some patients with symptoms of heart failure. On the other hand, this device has been validated recently against full polysomnography[19] and an in-home sleep study can better reproduce the pattern

Table 3—*Multiple Logistic Regression Between Atrial Fibrillation With Significant Variables From Univariate Analysis*

Characteristics	OR	95% CI	*P* Value
Age	1.02	0.94-1.11	.62
NYHA	1.88	0.67-5.24	.23
AHI	1.07	1.01-1.13	.03
LVEF	0.94	0.88-1.01	.10
Left atrial diameter	1.17	1.02-1.34	.03

See Tables 1 and 2 for expansion of abbreviations.

of sleep. Moreover, using a easier-to-perform test in populations with a high prevalence of OSA increases the feasibility of implementing our findings into clinical practice. Another limitation is that we could not distinguish between central and obstructive hypopneas because of the use of a piezoelectric crystal to measure thoracic excursions. On the other hand, obstructive apneas were much more common than central apneas in all patients (Table 1) and were probably also more common than hypopneas. Finally, because of the cross-sectional nature of the present study, it is not possible to conclude that OSA is independently associated with future cardiovascular complications in patients with HCM. Moreover, patients with and without OSA were different in several aspects (Table 1), and it is not possible to ensure that all confounding variables were fully adjusted in multivariate analysis. However, our study is in line with previous findings in other populations[24,41,42] and the independent association of OSA with AF points to its relevance in patients with HCM.

Conclusions

In conclusion, OSA is highly prevalent in patients with HCM and is associated with heart remodeling (left atrial and aorta enlargement). OSA is also independently associated with AF, a risk factor for cardiovascular death in this population. These results suggest that OSA should be screened for in patients with HCM. Further studies are needed to evaluate the safety and clinical outcomes of treating OSA in these subjects.

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Dr Drager: contributed to study design and manuscript draft.
Dr Genta: contributed to data analysis.
Ms Amaro: contributed to data collection.
Dr Antunes: contributed to data collection.
Dr Matsumoto: contributed to echocardiographic evaluation.
Dr Arteaga: contributed to data collection.
Dr Mady: contributed to data collection.
Dr Lorenzi-Filho: contributed to study design and manuscript draft.
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