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High Prevalence of Abnormal Nocturnal Oximetry in Patients With Hypertrophic Cardiomyopathy

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Objectives We sought to determine the prevalence of nocturnal oxygen desaturation and obstructive sleep apnea (OSA) in a population of patients with hypertrophic cardiomyopathy (HCM).

Background The coexistence of sleep apnea and HCM, 2 common cardiovascular conditions, has been largely unrecognized in the treatment of patients with HCM. The nocturnal hypoxia-induced hyperadrenergic state in OSA is expected to worsen hemodynamics and outcomes in HCM.

Methods One hundred subjects with HCM between June 1, 2006, and July 14, 2008, were screened with nocturnal oximetry. Clinical variables were collected for statistical analysis. Oximetry was classified abnormal (suspicion of sleep-disordered breathing) in the presence of repetitive desaturation (≥5 events/h) followed by a rapid return to baseline oxygen saturation (SaO_2) level with a decrease of ≥4% and threshold of 90%.

Results Seventy-one (71%) patients with HCM had abnormal nocturnal oximetry (71 ± 9%, 95% confidence interval: 62% to 80%). Subjects with abnormal oximetry were older (age 59.5 ± 15.3 years) and more were hypertensive (n = 39 [55%]) than those with normal oximetry (age 45.8 ± 18.5 years, n = 9 [31%], $p < 0.001$, $p = 0.03$). Patients with HCM were more symptomatic in the presence of abnormal oximetry (New York Heart Association functional class II to III) (62% vs. 83%, $p = 0.023$). HCM patients had a higher prevalence of abnormal nocturnal oximetry (n = 71, 71%) compared with a control group of similar age and sex distribution (n = 49, 49%) ($p = 0.001$).

Conclusions Abnormal nocturnal oximetry is common in patients with HCM, suggesting that OSA is prevalent. OSA may impact hemodynamics and symptoms in HCM. Further studies are needed to determine the long-term benefit of OSA treatment on hemodynamics and disease progression in HCM. (J Am Coll Cardiol 2009;54:1805–9)

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiovascular disease with a prevalence that approaches 1 in 500 (1). One in 5 individuals in the general population (9% to 12% of women and 27% to 35% of men) suffer from obstructive sleep apnea (OSA), an acquired clinical condition that is currently recognized as an important reversible cause of left ventricular (LV) hypertrophy (2,3). Furthermore, both HCM and OSA are independently associated with an increased risk of sudden cardiac death (1,2). Whether the 2 diseases commonly coexist in patients has not been examined.

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Current guidelines acknowledge a fundamental treatment goal of HCM is alleviation of symptoms (1). Symptoms such as dyspnea, angina, and syncope can be difficult to control with pharmacologic therapy and are associated with higher mortality in HCM patients (4–6). Nonpharmacologic measures including surgical myectomy and alcohol septal ablation are often necessary for drug refractory symptomatic patients with LV outflow tract obstruction. Until recently, no studies have investigated if OSA may be an important contributor to drug refractory symptoms in HCM.

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Abbreviations and Acronyms

BMI = body mass index
CPAP = continuous positive airway pressure
HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
NYHA = New York Heart Association
OSA = obstructive sleep apnea
SaO_2 = oxygen saturation

Dynamic LV outflow tract obstruction, a hallmark of HCM, is aggravated and potentiated by sympathetic stimulation. The nocturnal hypoxia-induced hyperadrenergic state known to exist in OSA is expected to worsen the hemodynamics in HCM (7). This study was prompted by our recent observation that patients with symptomatic HCM and OSA show improvement in symptoms after successful treatment of OSA. We have recently reported cases of HCM patients who experienced reduction of symptoms and outflow tract obstruction after treatment of OSA with continuous positive airway pressure (CPAP) (8). Screening with nocturnal oximetry of the HCM population would be useful if sleep-disordered breathing is found to be an important comorbidity. We sought to determine the prevalence of abnormal nocturnal oximetry in the HCM population.

Methods

Patients with HCM diagnosed by echocardiography between June 1, 2006, and July 14, 2008 were screened for undiagnosed sleep-disordered breathing with nocturnal oximetry. The majority of patients were enrolled from tertiary referral specialty clinics at Mayo Clinic in Arizona and Minnesota dedicated to the management of HCM. Screening with oximetry was performed as a routine, regardless of suspicion for underlying sleep-disordered breathing. Demographic, laboratory, echocardiographic, oximetry, and other clinical variables were collected into an electronic database for statistical analysis. New York Heart Association (NYHA) functional class was obtained through review of clinical information. A subset of HCM patients also had formal polysomnography, which was completed for clinically indicated purposes per the treating physician.

A control group of patients with similar age and sex without HCM was used for comparison with HCM patients. All individuals in the control group had no prior diagnosis of sleep-disordered breathing or significant pulmonary disease and were screened with nocturnal oximetry by their treating physicians for underlying sleep apnea at our institution between January 1, 2007, and February 28, 2007.

HCM. The diagnosis of HCM was based on the echocardiographic criteria of LV hypertrophy with LV wall thickness >15 mm in a nondilated, hyperdynamic LV in which the degree of hypertrophy is not explained by another cardiac or systemic disease, such as longstanding hypertension (1).

Oximetry. Patients were provided with a pulse oximeter (Nonin 2500 PalmSAT [Nonin, Plymouth, Minnesota], sampling rate 4 s) and instructed in its use. Oximetry data were downloaded and displayed with Profox software (Profox, Escondido, California). Nocturnal oximetry was interpreted by board-certified pulmonologists and classified as abnormal (suspicion of sleep-disordered breathing) if the number of desaturation episodes was greater than 5 events/h of recording time followed by a rapid return to the baseline oxygen saturation (SaO_2) level. A desaturation event was defined as a decrease in SaO_2 level of at least 4%, with a threshold of 90% (9).

Statistical analysis. Clinical data were reported as mean ± SD or n (%). For proportion of subjects with abnormal oximetry, a 95% confidence interval was calculated. For independent groups (both control vs. HCM and abnormal vs. normal oximetry groups) the chi-square test was used to compare categorical variables, while the Student *t* test was used for continuous variables. A box plot diagram was used to depict the relationship of nocturnal hypoxia with NYHA functional class.

Results

Of 100 patients with HCM, 71 (71%) had abnormal nocturnal oximetry (presence of episodes of transient desaturation followed by a rapid return to the baseline SaO_2 level) (95% confidence interval: 71 ± 9%, range 62% to 80%). The abnormal oximetry group (group A) contained 42 (59%) men, average age 59.5 ± 15.3 years, body mass index (BMI) 31.1 ± 6.5 kg/m^2, 39 (55%) with hypertension, 38 (53%) with hyperlipidemia, 5 (7%) with diabetes mellitus, 59 (83%) with NYHA functional class II to III, and 52 (73%) with obstructive variant and mean resting LV outflow tract peak gradient 42.6 ± 29.9 mm Hg (Table 1). A total of 24 subjects from group A also had formal polysomnography, which confirmed the diagnosis of OSA in 23 (96%). Control group characteristics compared with HCM patients are summarized in Table 2. Risk factors for OSA including age, sex, hypertension, BMI, and smoking history were not significantly different between the 2 groups. The HCM group had a higher prevalence of abnormal nocturnal oximetry (n = 71, 71%) compared with the control group (n = 49, 49%) (p = 0.001).

Of 29 subjects (29%) with normal nocturnal oximetry (group B), 13 (45%) were men, average age 45.8 ± 18.5 years, BMI 28.9 ± 7.3 kg/m^2, 9 (31%) had hypertension, 12 (41%) had hyperlipidemia, 1 (3%) had diabetes mellitus, 18 (62%) had NYHA functional class II to III, and 18 (62%) had obstructive variant and mean resting LV outflow tract peak gradient 35.3 ± 35.2 mm Hg.

HCM subjects with abnormal oximetry were older and more likely to be hypertensive than those with normal oximetry ($p < 0.001$ and $p = 0.03$, respectively). A significantly higher number of subjects with abnormal oximetry also had an abnormal NYHA functional class (II to III) ($p = 0.023$) (Table 1). Resting LV outflow tract gradient also correlated with degree of symptoms ($p = 0.005$) (Fig. 1).

Table 1 HCM Subjects (n = 100)

Characteristics	Abnormal Oximetry (n = 71, 71%)*	Normal Oximetry (n = 29, 29%)	p Value
Age	59.5 ± 15.3	45.8 ± 18.5	<0.001
BMI (kg/m^2)	31.1 ± 6.5	28.9 ± 7.3	0.159
Men	42 (59%)	13 (45%)	0.191
Hypertension	39 (55%)	9 (31%)	0.030
Diabetes mellitus	5 (7%)	1 (3%)	0.823
Active smoking	6 (8%)	5 (17%)	0.356
Former smoking	23 (32%)	7 (24%)	0.4779
NYHA functional class II to III	59 (83%)	18 (62%)	0.023
IVS (mm)	19.0 ± 5.9	20.7 ± 6.0	0.184
EF (%)	68 ± 7.6	69 ± 5.8	0.518
Obstructive HCM	52 (73%)	18 (62%)	0.269
LVOT resting peak gradient (obstructive patients; n = 70)	42.6 ± 29.9	35.3 ± 35.2	0.433
Left atrial volume index (cc/m^2)	46.7 ± 19.4	42.5 ± 12.0	0.239
E/A ratio	1.19 ± 0.67	1.35 ± 0.75	0.199
Right ventricular systolic pressure (mm Hg)	34.0 ± 8.3	33.7 ± 12.0	0.510

*24 subjects also had a formal polysomnogram, which confirmed the diagnosis of obstructive sleep apnea in 23 (96%).

BMI = body mass index; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; IVS = interventricular septal thickness; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

Nocturnal oximetry recordings. The average number of desaturation events for HCM patients with abnormal oximetry (n = 71) was 11.6 ± 12.5 events/h. The average mean SaO_2 was 93 ± 2.0% and the average minimum SaO_2 was 82.3 ± 6.2%. Among subjects with abnormal oximetry, those with NYHA functional class III symptoms had a higher duration of nocturnal hypoxia (16.7 ± 23.7% of time spent at SaO_2 <90%) than those with no symptoms (3.2 ± 4.0% of time spent at SaO_2 <90%) (p = 0.006) (Fig. 2).

Discussion

Well-established risk factors for OSA include increasing age, obesity, male sex, and cigarette smoking (10,11). In fact, it is estimated that over 25% of the U.S. population is at risk for OSA (10). While it seems highly probable that some patients with HCM should also have OSA, there has been little research into this area. In our study, we found a high prevalence of abnormal oximetry in the HCM population, particularly in patients that were middle to older age, hypertensive, and symptomatic. Furthermore, patients with NYHA functional class III symptoms had more nocturnal hypoxia (longer percentage of time <90% SaO_2) than those without symptoms, suggesting an association between symptoms and severity of sleep-disordered breathing in HCM patients.

The high prevalence of hypertension in the abnormal oximetry group (55%) compared with the normal oximetry group (31%) is not surprising, given the independent asso-

Table 2 HCM and Control Patients

	HCM Group (n = 100)	Control Group (n = 100)	p Value
Age	55.5 ± 17.4	56.3 ± 7.7	0.68
BMI (kg/m^2)	30.4 ± 6.8	30.2 ± 5.5	0.77
Men	55 (55%)	55 (55%)	1.00
Hypertension	48 (48%)	39 (39%)	0.20
Diabetes mellitus	6 (6%)	5 (5%)	0.76
Active smoking	11 (11%)	14 (14%)	0.52
Former smoking	30 (30%)	39 (39%)	0.18
Abnormal oximetry	71 (71%)	49 (49%)	0.001
IVS (mm)	19.5 ± 6.0	11.2 ± 2.2	<0.001
EF (%)	69 ± 7.1	61 ± 8.3	<0.001
Left atrial volume index (cc/m^2)	35 ± 11	28 ± 7.4	<0.001
E/A ratio	1.25 ± 0.67	1.24 ± 0.52	0.85
Right ventricular systolic pressure (mm Hg)	35 ± 11	29 ± 8.7	0.003

Abbreviations as in Table 1.

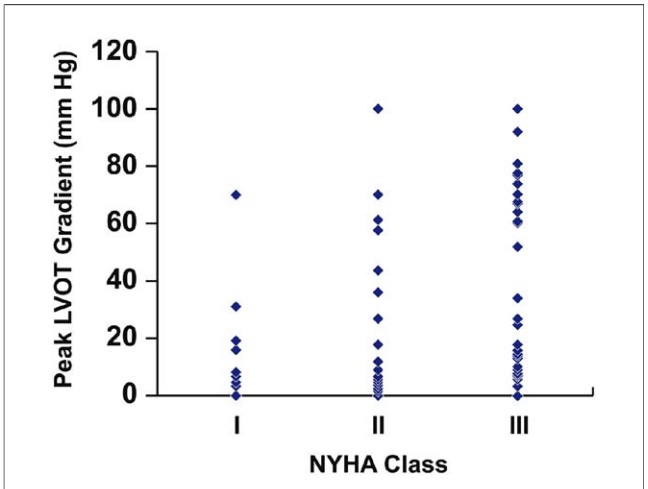

Figure 1 Resting Peak Gradient and NYHA Functional Class

Resting peak left ventricular outflow tract (LVOT) gradient in subjects with hypertrophic cardiomyopathy and relationship with symptom severity by New York Heart Association (NYHA) functional class (p = 0.005).

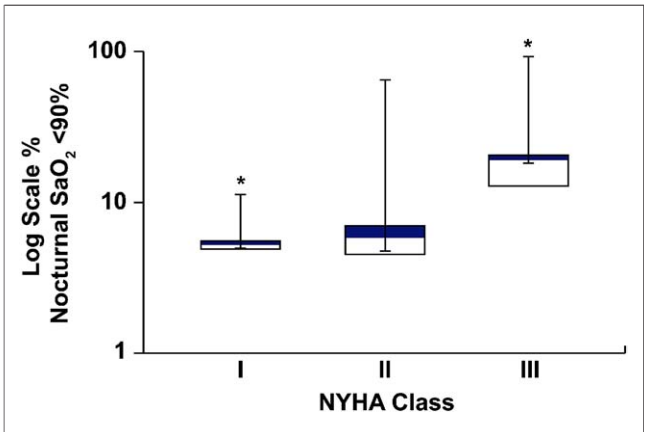

Figure 2 Nocturnal Hypoxia and NYHA Functional Class

Duration of nocturnal hypoxemia in subjects with hypertrophic cardiomyopathy and relationship with symptom severity by New York Heart Association (NYHA) functional class (p = 0.006). SaO_2 = oxygen saturation.

ciation between sleep-disordered breathing and hypertension (12). OSA results in sympathetic nervous system activation as well as nocturnal endothelin release, both of which contribute to elevated blood pressure throughout the day (7). Similar to individuals in our study with abnormal oximetry (both with and without HCM), the prevalence of hypertension in the general U.S. population age 60 or older is estimated to be 50% and 75% in non-Hispanic white men and women, respectively (13).

Diagnosis of OSA. OSA is caused by collapse of the pharyngeal airway during sleep, which results in recurrent interruption of ventilation (14). Collapse of the airway can result in either apnea (>10 s cessation of respiration with ongoing ventilatory effort) or hypopnea (a decrease [but not cessation] in respiratory effort with associated arousal or fall in oxygen saturation). The apnea hypopnea index, defined as the number of apneas and hypopneas during 1 h of sleep, is derived from formal polysomnography. An apnea hypopnea index >5 coupled with symptoms of excessive daytime sleepiness are considered diagnostic for OSA (14).

Possible physiologic interaction. Patients with OSA have elevated catecholamine levels, which have been shown to normalize after CPAP treatment (15). Elevated catecholamine states can worsen the obstruction and diastolic dysfunction in HCM, thus decreasing cardiac output, increasing LV filling pressures, and worsening dyspnea and dizziness (16). Furthermore, sympathetic activation from OSA is associated with subendocardial ischemia, which develops from impairment of the coronary microvascular flow due to shortened diastole, impaired diastolic function, and impaired coronary vasodilator capacity (17). Leptin, a peptide hormone known to cause cardiac myocyte hypertrophy, has elevated serum concentration in patients with OSA and may further contribute to disease and symptom progression (18,19).

Clinical implications. Occult OSA, an increasingly common condition in the developed world, may account for some of the symptom complex experienced by patients with HCM. Contrary to initial belief, symptoms of HCM have not been shown to correlate well with the degree of resting peak LV outflow tract gradient (20). Recently, we reported the first case series of HCM patients who experienced reduction in resting LV outflow tract gradient as well as symptom reduction after treatment of OSA (8). Many HCM patients who have drug refractory symptoms ultimately require invasive septal reduction procedures, which carry their own risk. It is postulated that timely therapy with CPAP in patients with OSA may reduce the need for surgical myectomy or alcohol septal ablation.

Given the potential adverse effects of nocturnal hypoxemia-induced sympathetic activation on HCM symptoms and outcomes coupled with the high prevalence of abnormal oximetry in this population, we recommend screening and appropriate management for OSA in patients with HCM. Subjects with abnormal oximetry in our study were significantly older and more likely to have symptoms of dyspnea, angina, syncope, or palpitations. Such HCM patient characteristics may be associated with an increased risk of sleep-disordered breathing. Treatment of OSA with CPAP is known to reduce blood pressure, sympathetic activity, and systemic inflammation (21). Potential benefits from identifying and treating this condition in HCM include symptom reduction, improved cardiac function, and decreased need for invasive septal reduction therapy. As previously described, some HCM patients with OSA have been observed to have resolution of resting LVOT obstruction after successful CPAP treatment.

Study limitations. The findings in our study represent an observational cohort and require prospective confirmation. While nocturnal oximetry is a beneficial screening test for OSA, it does not establish a diagnosis and requires confirmatory polysomnography. A subset of our patients did proceed on to polysomnography, which established the diagnosis of OSA. Our relatively small patient population may not reflect that of the general HCM population as they presented to a tertiary referral center for their care, and many were symptomatic.

Conclusions

Abnormal nocturnal oximetry is a common finding in the HCM population, suggesting that OSA is also highly prevalent in these patients. OSA with associated sympathetic activation has the strong potential to negatively impact HCM hemodynamics and outcomes. Based on these data, we recommend screening and appropriate management for OSA in the HCM population. Occult OSA may account for some of the cases of drug refractory symptoms experienced by patients with HCM. Further studies are needed to determine the true prevalence of OSA in HCM and the effect of treatment of OSA on symptoms, hemodynamics, and disease progression in HCM.

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