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 (SaO₂) 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.

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.
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 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/m², 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 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.

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 SaO₂ 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/m², 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).
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 assoc-

### Table 1: HCM Subjects (n = 100)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Abnormal Oximetry (n = 71, 71%)*</th>
<th>Normal Oximetry (n = 29, 29%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.5 ± 15.3</td>
<td>45.8 ± 18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>31.1 ± 6.5</td>
<td>28.9 ± 7.3</td>
<td>0.159</td>
</tr>
<tr>
<td>Men</td>
<td>42 (59%)</td>
<td>13 (45%)</td>
<td>0.191</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39 (55%)</td>
<td>9 (31%)</td>
<td>0.030</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (7%)</td>
<td>1 (3%)</td>
<td>0.823</td>
</tr>
<tr>
<td>Active smoking</td>
<td>6 (8%)</td>
<td>5 (17%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Former smoking</td>
<td>23 (32%)</td>
<td>7 (24%)</td>
<td>0.4779</td>
</tr>
<tr>
<td>NYHA functional class II to III</td>
<td>59 (83%)</td>
<td>18 (62%)</td>
<td>0.023</td>
</tr>
<tr>
<td>LVOT (mm)</td>
<td>19.0 ± 5.9</td>
<td>20.7 ± 6.0</td>
<td>0.184</td>
</tr>
<tr>
<td>EF (%)</td>
<td>68 ± 7.6</td>
<td>69 ± 5.8</td>
<td>0.518</td>
</tr>
<tr>
<td>Obstructive HCM</td>
<td>52 (73%)</td>
<td>18 (62%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Left atrial volume index (cc/m$^2$)</td>
<td>46.7 ± 19.4</td>
<td>42.5 ± 12.0</td>
<td>0.239</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.19 ± 0.67</td>
<td>1.35 ± 0.76</td>
<td>0.199</td>
</tr>
<tr>
<td>Right ventricular systolic pressure (mm Hg)</td>
<td>34.0 ± 8.3</td>
<td>33.7 ± 12.0</td>
<td>0.510</td>
</tr>
</tbody>
</table>

*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.

### Table 2: HCM and Control Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HCM Group (n = 100)</th>
<th>Control Group (n = 100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.5 ± 17.4</td>
<td>56.3 ± 7.7</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>30.4 ± 6.8</td>
<td>30.2 ± 5.5</td>
<td>0.77</td>
</tr>
<tr>
<td>Men</td>
<td>55 (55%)</td>
<td>55 (55%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (48%)</td>
<td>39 (39%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Active smoking</td>
<td>11 (11%)</td>
<td>14 (14%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Former smoking</td>
<td>30 (30%)</td>
<td>39 (39%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Abnormal oximetry</td>
<td>71 (71%)</td>
<td>49 (49%)</td>
<td>0.001</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>19.5 ± 6.0</td>
<td>11.2 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69 ± 7.1</td>
<td>61 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial volume index (cc/m$^2$)</td>
<td>35 ± 11</td>
<td>28 ± 7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.26 ± 0.67</td>
<td>1.24 ± 0.52</td>
<td>0.85</td>
</tr>
<tr>
<td>Right ventricular systolic pressure (mm Hg)</td>
<td>35 ± 11</td>
<td>29 ± 8.7</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
ciation between sleep-disordered breathing and hyperten-
sion (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 hypo-
pnea 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 catechol-
amine states can worsen the obstruction and diastolic 
dysfunction in HCM, thus decreasing cardiac output, in-
creasing 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 
deptide hormone known to cause cardiac myocyte hyper-
trophy, 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 com-
mon 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 ulti-
mately 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 symp-
toms 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 obstruc-
tion 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 confir-
matory 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 sympa-
thetic activation has the strong potential to negatively 
impact HCM hemodynamics and outcomes. Based on these 
data, we recommend screening and appropriate manage-
ment 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, hemo-
dynamics, and disease progression in HCM.

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