

## A STUDY OF THE PREVALENCE OF SLEEP DISORDERED BREATHING IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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### Abstract

**Background:** The aim of this study was to gain epidemiologic data on prevalence and type of SDB in patients with HCM and to investigate correlations between sleep apnea and other clinical and echocardiographic parameters. **Materials and Methods:** A cohort of roughly 1000 clinically characterized HCM patients were enrolled in department of medicine, Patna Medical College and Hospital, in which 57 patients with HCM. All patients were admitted to the hospital for a routine check-up, which included a screening for SDB. The diagnosis of HCM was based on typical clinical, electrocardiographic, and echocardiographic features, with global or segmental ventricular myocardial hypertrophy occurring in the absence of any other cardiac or systemic disease that could have been responsible (eg, aortic stenosis, Fabry disease, or storage disorders). All patients had preserved LVEF (ejection fraction [EF]  $\geq 55\%$ ). We excluded all patients with concomitant pulmonary disease, particularly all patients with forced expiratory volume in 1 second  $< 50\%$ . From the 57 HCM patients, 10 (19%) were considered nonobstructive under all conditions. In the 47 patients with HOCM (81%), septal alcohol ablation had been performed in 37 (65%), myectomy in 3 (4%), and pacemaker implant in 12 (21%) to reduce left ventricular outflow gradient. **Result:** In our cohort, 57 patients (81.8%) demonstrated SDB, with a mean AHI of  $21.0 \pm 18.7/h$  ( $\mu = 13.0/h$ ; interquartile range [IQR] =  $20.0/h$ ). Sleep apnea was diagnosed in 26 patients in the control group (74.0%;  $P =$  not significant [ns]). **Conclusion:** The severity of sleep apnea correlates with clinical symptoms and the echocardiographic parameters, left atrial size, and LVEDD. Thus, screening for and effective treatment of SDB are desirable in patients with HCM.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a hereditary cardiac condition,<sup>[1-3]</sup> characterized by wall thickening and ventricular filling abnormalities and, in about two thirds of cases, by left ventricular outflow tract obstruction (HOCM). Patients often experience exercise intolerance, dyspnea and/or chest pain, palpitations, and occasionally syncope. Within the HCM disease spectrum, the mortality rate is calculated to be about 1% per year. Main causes of death in elderly HCM patients are progressive heart failure and stroke,<sup>[4]</sup> whereas sudden cardiac death (SCD) seems to be more prevalent in younger and frequently asymptomatic people.<sup>[5]</sup>

The prevalence of sleep-disordered breathing (SDB) in the general adult population is reported to be between 1% and 4%.<sup>[6]</sup> Obstructive sleep apnea (OSA) seems to be more prevalent, with figures up to 24%.<sup>[7]</sup> Chronic heart failure (New York Heart Association [NYHA class  $\geq$  II) and impaired left

ventricular function (left ventricular ejection fraction [LVEF]  $\leq 40\%$ ) are associated with central sleep apnea (CSA), with Cheyne-Stokes respiration being present in 40% of cases.<sup>[8]</sup> Sleep apnea leads to oxygen desaturation with consecutive arousals from sleep,<sup>[9]</sup> activation of the sympathetic nervous system,<sup>[10]</sup> synthesis of acute phase proteins,<sup>[11,12]</sup> and endothelial dysfunction.<sup>[13,14]</sup> Several studies have demonstrated that sleep apnea unfavourably influences the prognosis of heart failure patients.<sup>[15,16]</sup> There are yet only few data on the prevalence of SDB in patients with HCM.<sup>[17,18]</sup> Furthermore, whether SDB may aggravate the natural course of patients with HCM is still unclear. The aim of this study was to gain epidemiologic data on prevalence and type of SDB in patients with HCM and to investigate correlations between sleep apnea and other clinical and echocardiographic parameters.

## MATERIALS AND METHODS

A cohort of roughly 1000 clinically characterized HCM patients were enrolled in department of medicine, Patna Medical College and Hospital, in which 57 patients with HCM. All patients were admitted to the hospital for a routine check-up, which included a screening for SDB. The diagnosis of HCM was based on typical clinical, electrocardiographic, and echocardiographic features, with global or segmental ventricular myocardial hypertrophy occurring in the absence of any other cardiac or systemic disease that could have been responsible (eg, aortic stenosis, Fabry disease, or storage disorders). All patients had preserved LVEF (ejection fraction [EF]  $\geq 55\%$ ). We excluded all patients with concomitant pulmonary disease, particularly all patients with forced expiratory volume in 1 second  $< 50\%$ .

From the 57 HCM patients, 10 (19%) were considered nonobstructive under all conditions. In the 47 patients with HOCM (81%), septal alcohol ablation had been performed in 37 (65%), myectomy in 3 (4%), and pacemaker implant in 12 (21%) to reduce left ventricular outflow gradient. Patient and echocardiographic data are given in [Table 1]. We investigated a control group of 50 patients, who had cardiac catheterization based on a pathologic stress test and individual risk stratification. Coronary artery disease was angiographically excluded in each of these patients. All individuals in the control group had preserved LVEF (EF  $> 55\%$ ) and no evidence of valve disease. The control group was matched for age and sex.

**Cardiorespiratory Polygraphy:** Sleep studies were performed by in-hospital unattended Cardiorespiratory Polygraphy as previously described.<sup>19</sup> With Embletta, nasal air flow, chest and abdominal efforts, pulse oximetry, and body position are continuously recorded. Data were analyzed using Somnologica for Embletta software. The automated analysis was reviewed and independently corrected by 3 SDB specialists not involved in the treatment of the patients. Patients with an apnea-hypopnea-index (AHI)  $\geq 5/h$  were considered to have SDB. According to the recommendations of the American Academy of Sleep Medicine,<sup>9</sup> patients with an AHI between 5/h and 14/h were considered to have mild sleep apnea. If the AHI was between 15/h and 29/h, sleep apnea was classified as moderate and  $\geq 30/h$  as severe. In case the AHI was  $\geq 15/h$ , patients were considered to need therapy of sleep apnea. If thoracic and abdominal inspiration efforts were documented, SDB was considered to be obstructive (OSA), otherwise CSA was diagnosed. If both CSA and OSA were observed, OSA or CSA was diagnosed according to the majority of events. Patients with mixed sleep apnea were excluded.

Echocardiography Echocardiographic evaluation was performed following European Association of Echocardiography (EAE) and American Society of

Echocardiography (ASE) recommendations.<sup>20</sup> The magnitude of hypertrophy and its maximum expression was assessed with M-mode and 2-dimensional transthoracic echocardiography using standard projections and off-axis views. The occurrence of a systolic anterior movement (SAM) of the mitral valve, correlating with presence and severity of HOCM, was recorded. The magnitude of the outflow gradient was assessed by continuous wave Doppler echocardiography at rest and during provocation, usually by a Valsalva maneuver. In select cases, dynamic stress echocardiography was used. The E/A ratio of the mitral inflow was measured as an indicator of diastolic LV function. Statistics Continuous data are expressed as mean standard deviation (SD). Statistical analyses were performed with PASW software (SPSS Inc, Chicago, IL). For continuous and normally distributed data, unpaired t tests, in case of non-normality of distribution Wilcoxon signed rank tests, were used. A 2-tailed P value  $< .05$  was considered significant. Continuous measurements were compared by Spearman correlation. For determining the strength of relationship between 2 variables we used  $\eta$  statistics.

## RESULTS

Patients and Controls Anthropometric and other baseline data demonstrated no significant differences between patients and controls [Table 2].

Sleep Apnea in Patients and Controls. In our cohort, 57 patients (81.8%) demonstrated SDB, with a mean AHI of  $21.0 \pm 18.7/h$  ( $\mu = 13.0/h$ ; interquartile range [IQR] =  $20.0/h$ ). Sleep apnea was diagnosed in 26 patients in the control group (74.0%;  $P = \text{not significant [ns]}$ ). The severity of sleep apnea was significantly lower in the control group, with a mean AHI of  $14.2 \pm 6.67/h$  ( $\mu = 11.5/h$ ; IOR =  $6.0/h$ ) ( $P = .003$ ). Furthermore, 21 patients (48.3%) had relevant sleep apnea qualifying for specific therapy (AHI  $\geq 14/h$ ); in the control group, there were only 6 (14%,  $P = .01$ ). Mean AHI in the cohort was  $38.4 \pm 17.6/h$  ( $\mu = 32.0/h$ ; IQR =  $24.0/h$ ) vs.  $28.2 \pm 9.8/h$  ( $\mu = 17.0/h$ ; IQR =  $7.0/h$ ) in the control group ( $P = .002$ ).

Anthropometric Data and Sleep Apnea The patients with HCM and SDB had a mean age of  $57.9 \pm 14.3$  years (years), comparable with the mean age of the patients in the control group without SDB (mean age,  $61.2 \pm 4.8$  years; IQR =  $15.4$  years ( $\mu = 63.0$  = ns) in patients without sleep apnea. The same could be observed in the control group. The patients in the control group with SDB had a mean age of  $61.2 \pm 8.7$  years. = ns) ( $\mu = 65.2$  years; IQR =  $10.0$

We found no significant differences between severity of sleep apnea and sex. The men in the patient group had a mean AHI of  $21.3 \pm 18.9/h$  ( $\mu = 12/h$ ; IQR =  $25.8/h$ ) and the women had a mean AHI of  $11.3 \pm 14.1/h$  ( $\mu = 10/h$ ; IQR =  $13.1/h$ ) ( $P = \text{ns}$ ). The control group demonstrated comparable results (men

with a mean AHI of 5.9±6.0/h [ $\mu=6/h$ ; IQR=7.52/h] vs. women with a mean AHI of 6.9±5.7/h [ $\mu=6/h$ ; IQR=5.9/h]; P=ns).

Kg/m Patients with HCM and without SDB had a mean body mass index (BMI) of 24.6±2.32 kg/m( $\mu=22.52\text{kg/m}$ ; IQR=3.22kg/m). The patients with HCM and SDB demonstrated a comparable BMI of 24.0±7.22 kg/m ( $\mu=22.62\text{kg/m}$ ; IQR=1.22) (Pkg/m=ns). The same was observed in the control group (without SDB: mean BMI, 23.6±2.12 kg/m [ $\mu=28.52\text{kg/m}$ ; IQR=2.42kg/m] vs. with SDB: mean BMI, 23.9±4.72 kg/m[ $\mu=27.82\text{kg/m}$ ; IQR=6.72], P=ns).

Echocardiographic Parameters and Sleep Apnea We observed a correlation between the severity of SDB

and left ventricular end-diastolic diameter (LVEDD) ( $r=0.6$ ;  $P<.01$ ). Furthermore, left atrial diameter correlated with severity of sleep apnea ( $r=0.4$ ;  $P<.01$ ). No correlations were found between SDB and the other echocardiographic data. An overview is given in [Table 3].

Clinical Data and Sleep Apnea Mean NYHA class was 4.0±0.7. When analyzing the effect between NYHA class and severity of sleep apnea, a high strength of the relationship of  $\eta=0.8$  ( $\eta^2=0.610$ ) was found. Correlations between atrial fibrillation and the occurrence and severity of SDB in the patient or control group were not detectable.

**Table 1: Clinical and Echocardiographic Data of 57 Patients with Hypertrophic Cardiomyopathy Who Underwent Cardiorespiratory Polygraphy**

Parameter	(n=57)	37(65)
After percutaneous transluminal septal myocardial ablation		37(65)
After myectomy		3 (4)
Pacemaker		10 (19)
Atrial fibrillation		7 (13)
Implantable cardioverter-defibrillator		6(11)
Hypertension		18 (30.9)
Smoking		9 (15.7)
Diabetes mellitus		4(5.9)
Ejection fraction, %		60.0±9.5
Left ventricular end-diastolic diameter, mm		48.5±5.6
Diameter left atrium, mm		42.7±7.5
Thickness of diastolic interventricular septum, mm		18.6±2.4
Diastolic left ventricular posterior wall thickness, mm		11.3±8.3
E/A ratio		0.6±0.2
Resting left ventricular obstruction gradient, mm Hg		47.3±38.1
Provocation left ventricular obstruction gradient, mm Hg		95.1±48.4

**Table 2: Anthropometric Data of Patients With Hypertrophic Cardiomyopathy and Controls**

	Patients	Control Group	P Value
No.	57	40	
Mean age, y	55.9±12.0 (32.0–81.0)	61.2±4.9 (37.0–78.0)	Not significant
Mean body mass index, kg/m <sup>2</sup>	29.6±2.8 (24.3–39.6)	25.4±6.4 (16.0–64.6)	Not significant

**Table 3: Comparison between Echocardiographic Parameter and Severity of Sleep Apnea Measured By AHI**

Correlation	P Value	r Value
LVEDD – AHI	<.01	0.7
LA diameter – AHI	<.01	0.6
Resting gradient – AHI	Not significant	
Provocation gradient – AHI	Not significant	
Occurrence of SAM – AHI	Not significant	
IVSd – AHI	Not significant	
LVPWd – AHI	Not significant	
E/A ratio – AHI	Not significant	
E <sub>max</sub> – AHI	Not significant	

## DISCUSSION

The reported prevalence of sleep apnea syndrome (including symptoms) in the general population is 1% to 4%.<sup>[6,7]</sup> Sleep apnea (with AHI  $\geq 5/h$  regardless of symptoms) in particular has been recognized as an important public health problem affecting 9% to 24% of the middle-aged population.<sup>[7]</sup> About 50% of patients with OSA have significant obesity.<sup>[21]</sup> In patients with cardiac disease, especially chronic heart failure, the prevalence of SDB is remarkably high.<sup>[8]</sup> SDB also has a high prevalence in hypertensive

patients<sup>8</sup> and an important prognostic impact in cardiac patients.<sup>[15,16]</sup> Patients with OSA have the highest rate of SCD during sleeping hours; otherwise, SCD is rare at that time.<sup>[4]</sup>

To date, however, there are limited data on SDB in HCM patients. In theory, due to recurrent oxygen desaturation, repetitive arousals,<sup>[9]</sup> activation of the sympathetic system,<sup>[10]</sup> and elevated catecholamine states, which in turn may worsen diastolic left ventricular function as well as outflow obstruction,<sup>[22]</sup> this problem may be an under-recognized contributor to symptoms, cardiac events, and death.<sup>[23]</sup> Our

results demonstrate that SDB is indeed also common in patients with HCM. About 81% of our patients presented with SDB, and 34% had relevant sleep apnea fulfilling accepted criteria for specific treatment. These results are comparable with recent data of Eleid and coworkers,<sup>[24]</sup> who found sleep apnea in about 71% of their patients. Both the cohort and the control patients predominantly had OSA. CSA seems not to be as relevant as OSA, particularly in patients with preserved LVEF, who are not at end-stage.<sup>[25,26]</sup>

Furthermore, we found significant correlations between severity of symptoms as expressed by NYHA functional class and severity of SDB. LVEDD and left atrial diameter also correlated with severity of sleep apnea. Both measures are markers for disease severity in HCM.<sup>[4,27]</sup> As described above, oxygen desaturation due to sleep apnea leads to recurrent activation of the sympathetic system with aggravation of the clinical symptoms (NYHA class) and worsening of general cardiac function.

A recent study showed that treatment with continuous positive airway pressure (CPAP) therapy can reduce elevated catecholamine states.<sup>[28]</sup> Furthermore, benefits of CPAP therapy have been reported in the treatment of hypertension and for the reduction of systemic inflammation.<sup>[29]</sup> The assumption that CPAP therapy may reduce the need for interventions aiming at outflow gradient reduction needs to be studied. Our data suggest that screening for and treatment of SDB might be worthwhile specifically in HCM patients with symptoms refractory to medical therapy and before making a decision for more invasive options such as myectomy or percutaneous septal ablation. Further long-term studies are required to evaluate the benefit of CPAP therapy in this population with respect to symptoms, hemodynamics, and ultimately with respect to hard end points such as cardiac death or end-stage heart failure.

## CONCLUSION

SDB is common in patients with HCM, with a predominance of OSA. The severity of sleep apnea correlates with clinical symptoms and the echocardiographic parameters, left atrial size, and LVEDD. Thus, screening for and effective treatment of SDB are desirable in patients with HCM.

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