Decreased Exercise Capacity and Sleep-Disordered Breathing in Patients With Hypertrophic Cardiomyopathy

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BACKGROUND: Mechanisms of decreased exercise capacity in patients with hypertrophic cardiomyopathy (HCM) are not well understood. Sleep-disordered breathing (SDB) is a highly prevalent but treatable disorder in patients with HCM. The role of comorbid SDB in the attenuated exercise capacity in HCM has not been studied previously.

METHODS: Overnight oximetry, cardiopulmonary exercise testing, and echocardiographic studies were performed in consecutive patients with HCM seen at the Mayo Clinic. SDB was considered present if the oxygen desaturation index (number of $\geq 4\%$ desaturations/h) was ≥ 10 . Peak oxygen consumption ($\dot{V}O_{2\text{peak}}$) (the most reproducible and prognostic measure of cardiovascular fitness) was then correlated with the presence and severity of SDB.

RESULTS: A total of 198 patients with HCM were studied (age, 53 ± 16 years; 122 men), of whom 32% met the criteria for the SDB diagnosis. Patients with SDB had decreased $\dot{V}O_{2\text{peak}}$ compared with those without SDB (16 mL O_2 /kg/min vs 21 mL O_2 /kg/min, $P < .001$). SDB remained significantly associated with $\dot{V}O_{2\text{peak}}$ after accounting for confounding clinical variables ($P < .001$) including age, sex, BMI, atrial fibrillation, and coronary artery disease.

CONCLUSIONS: In patients with HCM, the presence of SDB is associated with decreased $\dot{V}O_{2\text{peak}}$. SDB may represent an important and potentially modifiable contributor to impaired exercise tolerance in this unique population.

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ABBREVIATIONS: HCM = hypertrophic cardiomyopathy; HR = heart rate; MET = metabolic equivalent; NYHA = New York Heart Association; ODI = oxygen desaturation index; SDB = sleep-disordered breathing; $\dot{V}O_2$ = oxygen consumption; $\dot{V}O_{2\text{peak}}$ = peak oxygen consumption

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Hypertrophic cardiomyopathy (HCM) constitutes the most common inherited cardiomyopathy, affecting one in 500 adults through mutations affecting the myocardial sarcomeric protein.¹ Many patients with HCM experience limitations in their functional capacity over their lifetime,^{2,3} and alleviation of these symptoms is acknowledged in the current guidelines as a fundamental treatment goal.^{4,5} Sleep-disordered breathing (SDB), and particularly its most common form, OSA, is highly prevalent and is often underdiagnosed among patients with cardiovascular diseases, including

patients with HCM.^{6,7} In patients who do not have HCM, SDB has been identified as a potentially reversible contributor to decreased functional capacity,⁸⁻¹⁰ but whether such an association exists in patients with HCM remains unknown. Cardiopulmonary exercise testing provides the most accurate assessment of functional capacity in patients with HCM.^{11,12} We, therefore, tested the hypothesis that the presence and severity of SDB was accompanied by lower peak oxygen consumption ($\dot{V}O_{2peak}$) measured during cardiopulmonary exercise testing.

Materials and Methods

This study was approved by the institutional review board of the Mayo Clinic, Rochester, Minnesota (No. 10-002142).

Patient Population

We studied consecutive adult patients with HCM evaluated at the Mayo Clinic (Rochester, Minnesota) between January 2008 and December 2009. The diagnosis of HCM was based on clinical, ECG, and echocardiographic features of ventricular myocardial hypertrophy, not explained by any other significant cardiac or systemic disease.^{13,14} Patients underwent diagnostic evaluation including transthoracic echocardiogram, 12-lead ECG, cardiopulmonary exercise stress testing, and overnight oximetry. Those patients who could not or chose not to undergo either exercise testing or overnight oximetry were excluded. Demographic, clinical, and test variables were prospectively entered into a dedicated database and were reviewed retrospectively.

Overnight Oximetry

Overnight oximetry was performed by the Special Pulmonary Evaluation Laboratory of the Mayo Clinic. Recorded variables included the duration of oximetry recorded time, the frequency of desaturations (defined as $\geq 4\%$ drop in peripheral oxygen saturation from floating baseline), the nadir arterial oxygen saturation, and the percentage of oximetry recorded time with arterial oxygen saturation $< 90\%$ and $< 85\%$. The oxygen desaturation index (ODI) was defined as the total number of desaturations divided by the recorded time in hours. Clinically significant SDB was defined as $ODI \geq 10$.^{15,16} In an additional analysis, we divided patients by other previously published values of SDB severity and classified them as “no SDB” for $ODI \leq 5$, “mild to moderate SDB” for ODI of 5 to 15, and “severe SDB” for $ODI > 15$.^{17,18} Polysomnographic studies were not performed routinely as part of this study. However, previous reports show significant correlations between ODI and apnea hypopnea index.¹⁹

Cardiopulmonary Stress Testing

Symptom-limited graded exercise testing was performed using a motor-driven treadmill (Quinton) with continuous ECG monitoring (Marquette Electronics) and breath-to-breath metabolic measurement (Medical Graphics Corporation). An accelerated Naughton protocol, which consisted of 2-min duration stages beginning at approximately 2.5 metabolic equivalents (METs) and increasing by 2 METs per stage, was used. $\dot{V}O_{2peak}$ was computed using a Medical Graphics CPX/D metabolic cart after collecting expired gases. Calibration used gravimetric quality gases before each test, and physiologic calibration was performed for weekly quality control. $\dot{V}O_{2peak}$ was the highest averaged 30-s oxygen consumption ($\dot{V}O_2$) during exercise and was expressed as absolute peak $\dot{V}O_2$ or normalized peak $\dot{V}O_2$ (percentage of age, sex, and weight predicted).²⁰ The timing of the cardiopulmonary exercise testing and the overnight oximetry depended on each patient's schedule preferences and on the laboratory availability; the goal was to perform both tests within a 30-day period.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD, and categorical variables as number (percentage). Intragroup comparisons were conducted using the Student *t* test for continuous variables and χ^2 or Fisher exact test when appropriate for nominal variables. Univariate and multivariate logistic and linear regression analyses were used to explore correlations between SDB and $\dot{V}O_{2peak}$ (including assessments of potential confounding, colinearity, and effect modification). The measurements included in our multivariate analysis were selected because of their potential confounding effect on $\dot{V}O_{2peak}$ ²¹; these variables were prespecified prior to the data retrieval and included the following: age, sex, BMI, β -blocker use, calcium channel antagonist use, nonsinus rhythm during exercise testing, coronary artery disease, COPD, and diabetes mellitus. When the ODI was analyzed as a continuous variable, it was transformed using natural logarithms to achieve a normal distribution. *P* values $< .05$ were considered significant. All analyses were performed using JMP, version 9.0 (SAS Institute Inc).

Results

Patient Characteristics

Between January 2008 and December 2009, a total of 198 patients (mean age, 53 ± 16 years; 62% men), representing 44% of all patients with HCM seen at the Mayo Clinic during this time period, underwent an overnight oximetry and a cardiopulmonary exercise test as part of their outpatient evaluation. The patients in this study had a similar age, BMI, and sex distribution when compared with all the patients with HCM who

were seen during this time period but who did not meet all the inclusion criteria for this study (the patients with HCM seen [$n = 453$] had a mean age of 55 years and a BMI of 30.4 kg/m^2 , and 42% were women). Of the included patients, 64 (32%) were found to have SDB ($ODI \geq 10$) on overnight oximetry. Clinical, echocardiographic, and oximetry parameters stratified according to the presence of SDB are shown in Table 1. Patients with SDB were older than those without SDB and had a higher BMI. The prevalence of known coronary artery disease, COPD, and diabetes

TABLE 1 Patient Characteristics According to the Presence or Absence of SDB

Variable	No SDB (n = 134)	SDB (n = 64)	P Value
Age, y	50 ± 17	59 ± 14	< .001
Sex, female	57 (43)	19 (30)	.090
BMI, kg/m ²	29 ± 6	32 ± 5	< .001
Skinfold composite, ^a mm	62 ± 23	74 ± 24	.0006
Diabetes mellitus	10 (7)	4 (6)	.97
Coronary artery disease	12 (9)	19 (14)	.33
COPD	8 (6)	5 (8)	.76
Anemia, men < 13 g/dL; women < 12 g/dL	6 (4)	6 (9)	.21
Atrial fibrillation, history of presence	26 (19)	21 (31)	.054
β-Blocker use	98 (73)	53 (83)	.16
Calcium channel antagonist use	36 (27)	24 (38)	.14
New York Heart Association class			.0017
I	41 (38)	16 (16)	
II	30 (28)	41 (42)	
III	36 (34)	40 (41)	
IV	0 (0)	0 (0)	
Left ventricular ejection fraction, %	69 ± 7	68 ± 8	.42
Basal ventricular septal thickness, mm	19 ± 5	20 ± 5	.34
Left ventricular outflow tract pressure gradient at rest, mm Hg	32 ± 36	35 ± 37	.58
Peak left ventricular outflow tract pressure gradient with provocation, mm Hg	54 ± 41	55 ± 45	.95
Systolic anterior motion of mitral valve	36 (28)	21 (33)	.50
Left ventricular stroke volume index, mL/m ²	54 ± 14	58 ± 19	.34
E/e'	17 ± 8	21 ± 11	.009
Left atrial volume index	44 ± 15	52 ± 16	< .001
Estimated right ventricular systolic pressure, mm Hg	34 ± 10	36 ± 11	.20
ODI, desaturation events/h of recording	1.8 ± 1.4	16 ± 12	< .001
Duration of oximetry recording, h	8.2 ± 1.3	8.0 ± 1.6	.59
Mean oximetry oxygen saturation	94 ± 2	92 ± 2	< .001
Minimum oximetry oxygen saturation	87 ± 5	79 ± 7	< .001
Time during oximetry with oxygen saturation < 90%, % of recorded time	6 ± 13	17 ± 20	< .001
Resting BP			
Systolic	116 ± 18	124 ± 21	.007
Diastolic	73 ± 11	77 ± 10	.006

Data are presented as mean ± SD or No (%). SDB was defined as ODI ≥ 10 as measured by overnight oximetry. ODI = oxygen desaturation index; SDB = sleep-disordered breathing.

^aSum of three skinfold measurements in the axillary, supriliac, and triceps regions.

mellitus was similar in both groups, but atrial fibrillation history was more commonly observed among patients with SDB. Both groups had comparable left ventricular ejection fractions and left ventricular outflow tract pressure gradients. On average, the groups with SDB and without SDB recorded oximetry tracings for a similar length of time.

Cardiopulmonary Exercise Testing

The results of cardiopulmonary exercise testing are shown in Table 2. In 91% of the patients, the exercise test was separated from the oximetry by < 30 days. Patients with SDB, compared with those without SDB, were found to have decreased $\dot{V}O_{2peak}$ (16.3 ± 5.4 vs 21.2 ± 7.2 , $P < .001$) (Fig 1A), which translated into reduced metabolic

TABLE 2] Results of Cardiopulmonary Exercise Testing According to the Presence or Absence of SDB

Variable	No SDB (n = 134)	SDB (n = 64)	P Value
$\dot{V}O_{2peak}$, mL O ₂ /kg/min	21.2 ± 7.2	16.3 ± 5.4	< .001
			< .001 ^a
Calculated METs	6.1 ± 2.1	4.8 ± 1.6	< .001
$\dot{V}O_{2peak}$ not adjusted for patient's weight, mL O ₂ /min	1,868 ± 785	1,615 ± 632	.017
			< .001 ^a
$\dot{V}O_{2peak}$ % predicted by age and sex	68 ± 20	58 ± 18	.001
			< .001 ^a
$\dot{V}O_{2peak}/peak$ heart rate, mL O ₂ /beat	0.15 ± 0.04	0.14 ± 0.04	.004
Resting peripheral oxygen saturation, %	98 ± 3	98 ± 4	.74
Nadir peripheral oxygen saturation, %	98 ± 2	98 ± 2	.72
Respiratory exchange ratio at peak exercise	1.2 ± 0.1	1.2 ± 0.1	.13
Nadir $\dot{V}E/\dot{V}CO_2$	38 ± 5	38 ± 5	.91
Resting heart rate, beats/min	70 ± 12	70 ± 12	.89
Peak heart rate, beats/min	140 ± 28	121 ± 28	< .001
Rhythm during exercise testing			
Sinus	121 (90)	53 (83)	.16
Paced	11 (8)	8 (13)	.44
Atrial fibrillation/flutter	3 (1)	5 (5)	.33

Data are presented as mean ± SD or No (%). SDB was defined as ODI ≥ 10 as measured by overnight oximetry. MET = metabolic equivalent; $\dot{V}CO_2$ = minute volume of CO₂ uptake in the lung; $\dot{V}E$ = minute ventilation; $\dot{V}O_{2peak}$ = peak oxygen consumption during exercise. See Table 1 legend for expansion of other abbreviations.

^aAdjusted for age, sex, BMI, β -blocker use, calcium channel antagonist use, rhythm during exercise testing, and history of coronary artery disease, COPD, diabetes mellitus.

equivalents (4.8 ± 1.6 METs vs 6.1 ± 2.1 METs) (Fig 1B). In a multivariate analysis (adjusting for age, sex, BMI, β -blocker use, calcium channel antagonist use, nonsinus rhythm during exercise testing, coronary artery disease, COPD, and diabetes mellitus), we found that SDB remained an independent predictor of decreased $\dot{V}O_{2peak}$ (adjusted $P < .001$) with a β -coefficient of -3.0 (95% CI, -4.65 to -1.36), indicating that after adjusting for all other variables in the model, the presence of SDB predicted a decrease in $\dot{V}O_{2peak}$ by 3 mL O₂/kg/min (equivalent to 0.9 METs). Patients with SDB achieved a lower percentage of predicted $\dot{V}O_{2peak}$ (by age and sex) compared with those without SDB ($P = .001$, multivariate model adjusted $P < .001$) (Figs 1C, 1D). In further analysis, SDB was tested according to other previously published cutoffs of ODI, and a dose-dependent relationship between the severity of SDB and $\dot{V}O_{2peak}$ was identified (Fig 2A). An additional model using ODI as a continuous variable (transformed by a natural logarithm because of skewness) revealed a negative linear correlation between ODI and $\dot{V}O_{2peak}$ ($R = -0.37$, $P < .001$) (Fig 2B). The respiratory exchange ratio and the ventilatory equivalent for CO₂

did not differ between those with and without SDB. In a subanalysis that included only patients with a BMI ≤ 30 (n = 104), the negative correlation between ODI (continuous variable transformed by natural logarithm because of skewness) and $\dot{V}O_{2peak}$ remained unchanged ($R = -0.33$, $P < .001$).

Discussion

This study showed that SDB in patients with HCM is independently associated with decreased exercise tolerance as measured by $\dot{V}O_{2peak}$ during cardiopulmonary exercise testing. Patients with HCM and SDB manifested, on average, a 24% reduction in exercise capacity compared with patients with HCM without SDB (Fig 1B), and when assessing the percentage of predicted $\dot{V}O_{2peak}$, we noted that a striking 56% of patients with HCM and SDB achieved < 60% of their predicted $\dot{V}O_{2peak}$, compared with 34% of patients with HCM without SDB (Fig 1D). Other measures such as the respiratory exchange ratio and the ratio of the minute volume of ventilation to the minute volume of CO₂ uptake in the lung were not different in SDB, suggesting that the differences in $\dot{V}O_{2peak}$ were selective

Figure 1 – Patients with hypertrophic cardiomyopathy and SDB. A, Decreased $\dot{V}O_{2\text{peak}}$. B, Decreased calculated functional capacity in METs. C and D, Decreased percentage of predicted $\dot{V}O_{2\text{peak}}$. *Adjusted for age, sex, BMI, β -blocker use, calcium channel antagonist use, rhythm during exercise testing, and history of coronary artery disease, COPD, and diabetes mellitus. MET = metabolic equivalent; $\dot{V}O_{2\text{peak}}$ = peak oxygen consumption; SDB = sleep-disordered breathing; $\dot{V}O_2$ = oxygen consumption.

and not part of a general nonspecific effect of SDB or cardiopulmonary exercise testing.

Given the treatable nature of SDB together with previously documented cases of symptom improvement in patients with HCM after the initiation of SDB treatment,²² a diagnosis of SDB should be considered routinely in patients with HCM. Nevertheless, although treatment with CPAP has a relatively benign side effect profile, a randomized trial would be needed to provide a definitive answer as to whether effective treat-

ment of SDB improves short- and long-term outcomes in HCM.

Exercise Testing in Patients With HCM

Peak exercise capacity represents the strongest known independent predictor for the risk of death among normal subjects and also among patients with cardiovascular diseases.²³ In patients with HCM, exercise testing is considered safe, and greater exercise capacity predicts a lower incidence of serious cardiovascular morbidity and mortality.²⁴ The use of $\dot{V}O_{2\text{peak}}$ carries an advantage over the use of the New York Heart Association (NYHA) classification, which is derived from self-reported symptoms and by definition is subjective. Additionally, $\dot{V}O_{2\text{peak}}$ better identifies those patients with HCM who would be labeled as asymptomatic according to the NYHA classification, but in reality have decreased functional capacity (up to 70% of patients with NYHA class I with HCM have abnormal $\dot{V}O_{2\text{peak}}$).^{11,12}

Decreased $\dot{V}O_{2\text{peak}}$ and SDB: Potential Mechanisms in HCM

The ability to perform physical exercise is critically dependent upon the ability of the cardiovascular system to supply oxygen to the muscles.²⁵ The key factor limiting $\dot{V}O_{2\text{peak}}$ in HCM is the maximal cardiac output, which, in turn, is the product of heart rate (HR) $\times$ stroke volume at the time of peak exertion.

Heart Rate

Despite similar resting HRs of patients with HCM with and without SDB, those with SDB did not increase their HRs with exercise to the same extent as did those without SDB. (From Table 2, we defined ΔHR = peak HR – resting HR; $\Delta\text{HR}_{\text{SDB}}$ = +51 beats/min vs $\Delta\text{HR}_{\text{NoSDB}}$ = +70 beats/min.) Pathologically decreased ΔHR in patients with SDB was also identified in non-HCM cohorts,⁹ and one possible explanation could be altered autonomic balance: Patients with SDB suffer from chronically ramped up sympathetic output, which may limit their capacity for recruitment of additional sympathetic activation during exercise.²⁶

In our study, the higher prevalence of rate-control medication use (β -blockers and calcium antagonists) among patients with HCM and SDB may have also contributed to the lower ΔHR . Importantly, however, a subanalysis that stratified the study patients by both SDB and rate-control medication use revealed that patients with SDB achieved, on average, lower predicted $\dot{V}O_{2\text{peak}}$ regardless of their rate control medication status (Table 3).

Figure 2 – When dividing the patients with hypertrophic cardiomyopathy according to the presence and severity of SDB, we report a dose-dependent decrease in exercise tolerance as measured by $\dot{V}O_{2\text{peak}}$ on cardiopulmonary exercise testing. ODI = oxygen desaturation index. See Figure 1 legend for expansion of other abbreviations.

TABLE 3] Percent Predicted $\dot{V}O_{2peak}$ According to the Presence of SDB and Rate Control Medication Use (β -Blocking Agents or Calcium Channel Antagonists)

SDB Presence	On Rate Control Medications	No Rate Control Medications
SDB, %	58	65
No SDB, %	66	75

See Table 1 legend for expansion of abbreviations.

Stroke Volume

Resting left ventricular stroke volume indexes of patients with HCM with and without SDB were comparable, and there were no significant differences in left ventricular ejection fraction, outflow tract gradient, or basal septal thickness. However, this study did not routinely image patients at peak exercise, and hence, differences in stroke volume during maximal exertion between those with and without SDB could not be assessed. The fact that resting echocardiograms of the patients with HCM and SDB revealed signs consistent with more pronounced impairment of the left ventricular diastolic function (left atrial volume index, E/e') suggests that some of the decreased $\dot{V}O_{2peak}$ could have resulted from an adverse effect of SDB on diastolic filling of an already stiffened left ventricle of HCM. Promising data from patients without HCM speak to the partial reversibility of this effect, because treatment with CPAP resulted in an improved diastolic function.²⁷ Whether a similar reversal could occur in patients with HCM and SDB remains to be seen.

Noncardiac Factors

Untreated SDB could theoretically lower exercise effort by promoting daytime drowsiness. In our study, the similar respiratory exchange ratios at peak exercise of the patients with and without SDB did not support any difference in exercise effort between the groups. An important potential confounder of SDB and exercise tolerance (ie, obesity) was adjusted for in our analysis (as the BMI in the multivariate analysis and also in the calculation of $\dot{V}O_{2peak}$, which reflects oxygen consumption per kilogram of body weight per minute), and SDB remained an independent predictor of low $\dot{V}O_{2peak}$. The subanalysis that focused on patients with HCM and a BMI ≤ 30 suggested that the inverse relationship between ODI and $\dot{V}O_{2peak}$ remains valid throughout the

BMI spectrum. Given the association between obesity and functional disability in HCM,²⁸ and the increase in the likelihood of SDB with increasing obesity,²⁶ it would be important for future studies to examine to what degree underdiagnosed SDB in overweight and obese patients with HCM may actually be contributing to the functional disability. Because evidence from non-HCM studies suggested that weight loss improved but did not fully normalize SDB,²⁹ and also because lifestyle modifications can often be difficult to implement and maintain, diagnosis and treatment of SDB may be recommended, in conjunction with safe rehabilitative exercise and a healthy diet, to overweight patients with HCM.

Limitations

This cross-sectional, observational study is subject to the attendant limitations, and as such, provides a hypothesis-generating foundation for future, more focused investigation. Nevertheless, it represents a large, single-center experience with a well-defined cohort of patients with HCM who underwent uniform evaluation at a state-of-the-art-facility. The use of oximetry poses a limitation: oximetry provides a more affordable and practical sleep assessment compared with polysomnography, but cannot reliably distinguish between OSA and central sleep apnea. Nevertheless, it has been shown to serve as a reliable measure of SDB, and its potential to underdiagnose SDB would be unlikely to alter the conclusions of this study.^{15,30} Significant limitations arise also from the fact that HCM is itself a heterogeneous disease, consisting of various forms (apical, basal, and so forth), as well as a variety of genotype mutations. How this diversity impacts the interactions between SDB and $\dot{V}O_{2peak}$, such as whether certain subtypes of HCM (genotypic or phenotypic) would manifest a higher prevalence of SDB and/or would receive greater benefit from the treatment of SDB, may be of great clinical relevance.

In conclusion, our data suggest that patients with HCM and SDB have a selective attenuation of exercise capacity as measured by $\dot{V}O_{2peak}$, with other measures during cardiopulmonary exercise testing remaining unchanged. Because SDB represents a potentially readily treatable diagnosis, an effective management of SDB in patients with HCM may offer an important strategy for improving exercise tolerance and reducing functional disability in this unique patient population.³¹

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References

- Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation*. 1995;92(4):785-789.
- Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation*. 1968;37(5):759-788.
- Maron BJ, Bonow RO, Cannon RO III, Leon MB, Epstein SE. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (2). *N Engl J Med*. 1987;316(14):844-852.
- Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(24):e783-e831.
- Maron BJ, McKenna WJ, Danielson GK, et al; Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42(9):1687-1713.
- Eleid MF, Konecny T, Orban M, et al. High prevalence of abnormal nocturnal oximetry in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009;54(19):1805-1809.
- Konecny T, Kuniyoshi FH, Orban M, et al. Under-diagnosis of sleep apnea in patients after acute myocardial infarction. *J Am Coll Cardiol*. 2010;56(9):742-743.
- Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110(4):364-367.
- Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol*. 2012;60(8):705-715.
- Li S, Scherlag BJ, Yu L, et al. Low-level vagosympathetic stimulation: a paradox and potential new modality for the treatment of focal atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2009;2(6):645-651.
- Sharma S, Firooz S, McKenna WJ. Value of exercise testing in assessing clinical state and prognosis in hypertrophic cardiomyopathy. *Cardiol Rev*. 2001;9(2):70-76.
- Sharma S, Elliott P, Whyte G, et al. Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. *Am J Cardiol*. 2000;86(2):162-168.
- Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation*. 1996;93(5):841-842.
- Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. *Am J Cardiol*. 1979;43(6):1242-1244.
- Netzer N, Eliasson AH, Netzer C, Kristo DA. Overnight pulse oximetry for sleep-disordered breathing in adults: a review. *Chest*. 2001;120(2):625-633.
- Konecny T, Brady PA, Orban M, et al. Interactions between sleep disordered breathing and atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;105(11):1597-1602.
- Loube DI, Andrada TF. Comparison of respiratory polysomnographic parameters in matched cohorts of upper airway resistance and obstructive sleep apnea syndrome patients. *Chest*. 1999;115(6):1519-1524.
- Lévy P, Pépin JL, Deschaux-Blanc C, Paramelle B, Brambilla C. Accuracy of oximetry for detection of respiratory disturbances in sleep apnea syndrome. *Chest*. 1996;109(2):395-399.
- Oeverland B, Skatvedt O, Kvaerner KJ, Akre H. Pulseoximetry: sufficient to diagnose severe sleep apnea. *Sleep Med*. 2002;3(2):133-138.
- Ghias M, Scherlag BJ, Lu Z, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. *J Am Coll Cardiol*. 2009;54(22):2075-2083.
- Milani RV, Lavie CJ, Mehra MR, Ventura HO. Understanding the basics of cardiopulmonary exercise testing. *Mayo Clin Proc*. 2006;81(12):1603-1611.
- Sengupta PP, Sorajja D, Eleid MF, et al. Hypertrophic obstructive cardiomyopathy and sleep-disordered breathing: an unfavorable combination. *Nat Clin Pract Cardiovasc Med*. 2009;6(1):14-15.
- Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
- Bunch TJ, Chandrasekaran K, Ehsam JE, et al. Prognostic significance of exercise induced arrhythmias and echocardiographic variables in hypertrophic cardiomyopathy. *Am J Cardiol*. 2007;99(6):835-838.
- Zhang Y, Scherlag BJ, Lu Z, et al. Comparison of atrial fibrillation inducibility by electrical stimulation of either the extrinsic or the intrinsic autonomic nervous systems. *J Interv Card Electrophysiol*. 2009;24(1):5-10.
- Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol*. 2008;52(8):686-717.

27. Butt M, Dwivedi G, Shantsila A, Khair OA, Lip GY. Left ventricular systolic and diastolic function in obstructive sleep apnea: impact of continuous positive airway pressure therapy. *Circ Heart Fail*. 2012;5(2):226-233.
28. Olivetto I, Maron BJ, Tomberli B, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2013;62(5):449-457.
29. Dixon JB, Schachter LM, O'Brien PE, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;308(11):1142-1149.
30. Romem A, Romem A, Koldobskiy D, Scharf SM. Diagnosis of obstructive sleep apnea using pulse oximeter derived photoplethysmographic signals. *J Clin Sleep Med*. 2014;10(3):285-290.
31. Konecny T, Somers VK. Sleep-disordered breathing in hypertrophic cardiomyopathy: challenges and opportunities. *Chest*. 2014;146(1):228-234.