CHEST

Acute Effects of Nasal CPAP in Patients With Hypertrophic Cardiomyopathy

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BACKGROUND: Hypertrophic cardiomyopathy (HCM) is a common genetic disease that may cause left ventricular outflow tract (LVOT) obstruction, heart failure, and sudden death. Recent studies have shown a high prevalence of OSA among patients with HCM. Because the hemodynamics in patients with LVOT obstruction are unstable and depend on the loading conditions of the heart, we evaluated the acute effects of CPAP on hemodynamics and cardiac performance in patients with HCM.

METHODS: We studied 26 stable patients with HCM divided into nonobstructive HCM (n = 12) and obstructive HCM (n = 14) groups (LVOT gradient pressure lower or higher than 30 mm Hg, respectively). Patients in the supine position while awake were continuously monitored with beat-to-beat BP measurements and electrocardiography. Two-dimensional echocardiography was performed at rest (baseline) and after 20 min of nasal CPAP at 1.5 cm H_2O and 10 cm H_2O, which was applied in a random order interposed by 10 min without CPAP.

RESULTS: BP, cardiac output, stroke volume, heart rate, left ventricular ejection fraction, and LVOT gradient did not change during the study period in either group. CPAP at 10 cm H_2O decreased right atrial size and right ventricular relaxation in all patients. It also decreased left atrial volume significantly and decreased right ventricular outflow acceleration time, suggesting an increase in pulmonary artery pressure in patients with obstructive HCM.

CONCLUSIONS: The acute application of CPAP is apparently safe in patients with HCM, because CPAP does not lead to hemodynamic compromise. Long-term studies in patients with HCM and sleep apnea and nocturnal CPAP are warranted.

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ABBREVIATIONS: 10-CPAP = CPAP at 10 cm H_2O; ASV = adaptative Servo-ventilation; BNP = brain natriuretic peptide; CHF = congestive heart failure; HCM = hypertrophic cardiomyopathy; HR = heart rate; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MRF = mitral regurgitant fraction; RV = right ventricular; RVOT = right ventricular outflow tract; sham-CPAP = CPAP at 1.5 cm H_2O

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Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease.[1] HCM is characterized by large and asymmetrical septal and left ventricular (LV) hypertrophy and is a significant cause of disability, including heart failure, atrial fibrillation, and sudden death.[2-4] Patients with HCM may have a thickened septum (> 15 mm) that causes obstruction to blood ejection through the left ventricular outflow tract (LVOT). The dynamic nature of LVOT obstruction results from a series of changes in ventricular loading conditions and myocardial contractility that are sensitive to fluctuations in volume status, autonomic nervous activity, and medications. The severity of LVOT is a predictor of poor prognosis and sudden death.[5]

Recent evidence shows that OSA is extremely common among patients with HCM, with a prevalence ranging from 32% to 71%.[6-10] CPAP is the gold standard treatment for OSA and has proved beneficial in reducing cardiovascular morbidity and mortality in patients with cardiovascular disease and no HCM.[11] The acute application of CPAP is also widely used to treat decompensated cardiac diseases and therefore could be used in patients with decompensated HCM. However, acute application of CPAP reduces LV preload and afterload[12,13] and therefore affects cardiac loading and function.[14] These effects have been interpreted as beneficial in patients with congestive heart failure (CHF) without HCM.[15-18] However, reductions in both LV preload and afterload in patients with HCM and LVOT obstruction may worsen outflow obstruction.[5,19] Thus the aim of this study was to investigate the acute effects of CPAP on hemodynamics and cardiac performance in patients with HCM with LVOT obstruction and those with HCM without LVOT obstruction.

Methods

Patients

We recruited patients from the outpatient cardiomyopathy medical unit at the Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil between December 2010 and April 2013. All patients had an established diagnosis of HCM based on the presence of septal hypertrophy (thickness ≥ 15 mm) in the absence of other known causes of LV hypertrophy, such as hypertension and aortic stenosis.[20] We included patients of both sexes who were older than 18 years of age and clinically stable, as defined by the absence of a recent hospital admission and changes in medications over the preceding 6 months. We excluded patients with atrial fibrillation, the presence of associated cardiac disease, previous cardiac surgery, or previous cardiac arrest, as well as patients with pacemakers or implantable cardioverter defibrillators. All patients provided written informed consent, and the local ethics committee approved the protocol (No. 0213/09).

Transthoracic Echocardiography

Comprehensive echocardiographic studies were performed using an ultrasound machine (Sequoia 512, Acuson) with a 2.5-MHz harmonic imaging transducer. The peak instantaneous flow velocity was assessed using continuous-wave Doppler with the cursor positioned along the LV outflow tract for LVOT gradient determination. The gradient was obtained by using the modified equation of Bernoulli (gradient = $4V^2$). Patients were classified as having nonobstructive HCM and obstructive HCM according to their LVOT gradient pressure being lower or higher than 30 mm Hg, respectively.[4] Aortic root and left atrial (LA) diameters and septal and posterior wall diastolic thicknesses were measured. Left ventricular end-diastolic and end-systolic diameters were obtained from the parasternal short-axis view at the papillary muscle level, and fractional shortening was calculated as follows: LV diastolic diameter – LV systolic diameter/LV diastolic diameter × 100. LV diameters in both end-diastole and end-systole were used to calculate LV end-diastolic and systolic volumes and left ventricular ejection fraction (LVEF) by the Teichholz method, as volume = $7/(2.4 + \text{LV diameter}) + \text{LV diameter}^3$.[21] This formula was used because the patients did not have segmental wall-motion abnormalities. LV mass was calculated by M-mode echocardiography on the short-axis view, according to Devereux et al.[22] The right atrial area was calculated after tracing the right atrium from the plane of the tricuspid annulus and along the interatrial septum and the superior and anterolateral walls of the atrium. The presence of systolic anterior motion of the mitral valve was assessed using two-dimensional and M-mode echocardiography during ventricular systole. The myocardial performance index was calculated as previously described.[23] For evaluation of the right ventricle, pulmonary acceleration time of the right ventricular (RV) outflow, longitudinal and transverse length of the right ventricle, and fractional area change (100 × end-diastolic area – end-systolic area/end-diastolic area) were obtained. Diastolic function was assessed from pulsed-wave Doppler of the mitral inflow velocities: early (E, m/s) and late (A, m/s) diastolic peak velocities, and deacceleration time of the E wave (DT, ms).[24] Isovolumetric relaxation time (ms) was obtained using continuous-wave Doppler with the cursor positioned between the mitral valve and the LVOT. Systolic and diastolic myocardial velocities were evaluated by tissue Doppler imaging as previously described.[22] E' (septal + lateral), A', E/E', and S' of the septum and lateral mitral annulus (septal + lateral) as well as lateral tricuspid annulus peak velocities were studied. Mitral regurgitation was quantified by the planimetry of the color Doppler area of the regurgitant jet relative to the area of the left atrium and designated as the mitral regurgitant fraction (MRF). All reported measurements are the averages derived from three consecutive cardiac cycles.[25]

All echocardiographic images with ECG measurements were stored digitally for subsequent offline analysis by another experienced reader, who was blinded to the patient and the CPAP measurements. To determine echocardiographic intraobserver variability, a sample of 10% of the examinations was randomly chosen and submitted twice to the same reader 4 weeks later for analysis. For interobserver variability, a random sample of 70% of the examinations was chosen and submitted to a second reader for analysis.

Study Design

The study was performed at the Sleep Laboratory of the Heart Institute (InCor) during the morning period while the subjects were awake. The patients were asked to keep their eyes open during the study. All patients underwent a detailed history and physical examination,

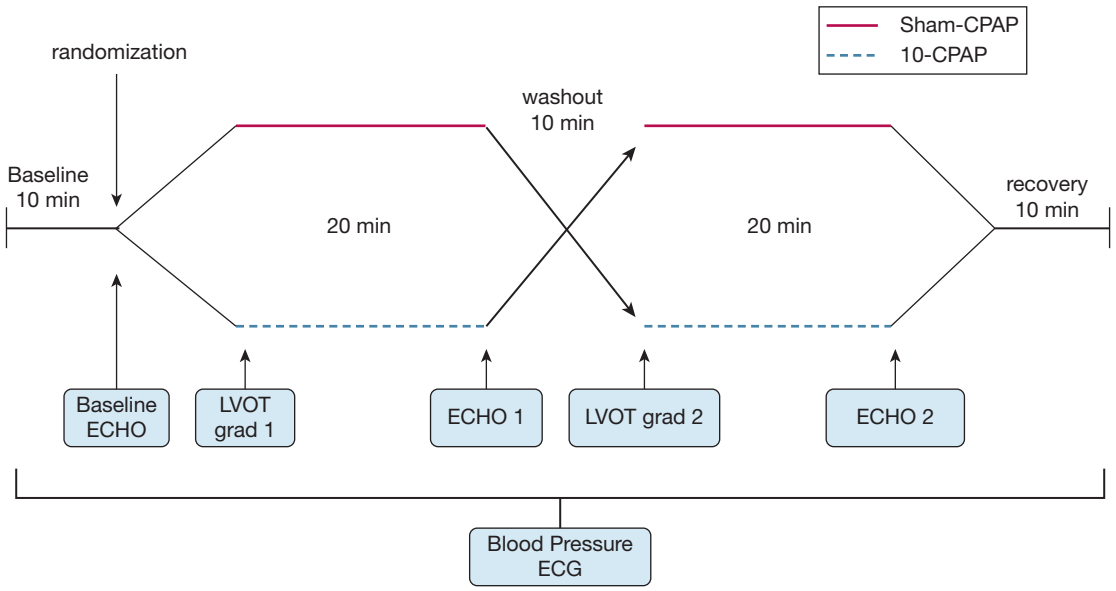

Figure 1 – *Study design. ECG = electrocardiography; ECHO = echocardiography; grad = LVOT gradient.*

including anthropometric and clinical data. BP while sitting was determined by the average results of two readings of systolic and diastolic BP obtained at 5-min intervals using a digital sphygmomanometer (Omron Healthcare HEM-742INT).[26] Blood samples were collected from venous blood after a 5-min resting period to evaluate brain natriuretic peptide (BNP) levels. Electrocardiography was performed continuously and beat-to-beat BP was measured continuously by an analog multichannel signal conditioning ECG device (amplified/filter AT/MCA-CODAS, DATAC Instruments Inc.) and by a noninvasive BP monitor (Portapres, TNO Biomedical Instrumentation). BP and ECG data were stored on a computer for offline analyses by dedicated software (Matlab, MathWorks) with a computational routine to calculate BP on a beat-to-beat basis.[27] The study design is summarized in Figure 1. BP and heart rate (HR) data were acquired 10 min after stabilization. The patients underwent 20 min of nasal CPAP at 10 cm H_2O (10-CPAP) and 20 min of CPAP at 1.5 cm H_2O (sham-CPAP) with 10 min of washout with no mask in between. The sequence of CPAP measurements was randomized and followed by 10 min of rest with no mask (recovery). Echocardiograms were obtained at baseline and during CPAP application after 20 min of stabilization at each pressure. The LVOT gradient pressure was measured during each echocardiogram and also immediately after the initiation of sham-CPAP and 10-CPAP (Fig 1). Beat-to-beat BP was averaged at min 1, 5, 10 of baseline, washout, and recovery and also after 20 min of CPAP application. If patients experienced a 25% drop in BP associated with symptoms of dizziness, the protocol would be interrupted.[28]

Statistical Analysis

Quantitative variables are expressed as mean ± SD, median (interquartile range), or percentage, as appropriate. The Kolmogorov-Smirnov test was used to assess normal distribution of continuous variables. The Student *t* test for independent samples and the Mann-Whitney *U* test were used to compare continuous variables as appropriate. The χ^2 test was used for categorical variables. Interobserver and intraobserver agreement was calculated using the intraclass correlation coefficient and the Bland-Altman plot.[29] A linear mixed model and multiple comparisons were performed to evaluate changes in BP and echocardiographic variables during the study period and between groups. We tested the carryover effect for the study design. Data were analyzed with SPSS, version 17.0 (SPSS Inc.) and R, version 2.15.1 (The R Project for Statistical Computing).[30] $P \leq .05$ was considered significant.

Results

A total of 43 patients were invited to participate in this study. Seventeen were excluded (six refused and 11 were unable to participate mainly because they did not live in the urban area of São Paulo). Thus our sample comprised 26 patients with HCM, which was classified as nonobstructive HCM (n = 12) and obstructive HCM (n = 14) (Fig 2). Demographic and clinical characteristics, medications, and BNP levels for the entire population were divided into nonobstructive HCM and obstructive HCM and are summarized in Table 1. Patients from both groups were predominantly overweight white men. BNP levels were

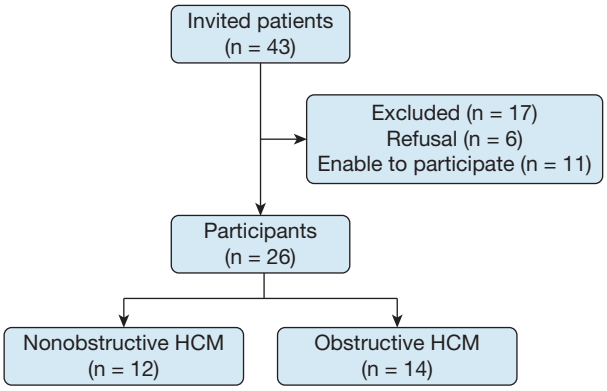

Figure 2 – *Flow diagram of patients included in the study. HCM = hypertrophic cardiomyopathy.*

TABLE 1] Baseline Demographic and Clinical Characteristics, Medications, and BNP Levels

Variable	Total (N = 26)	Nonobstructive HCM (n = 12)	Obstructive HCM (n = 14)	*P*
Age, y	46 ± 11	46 ± 12	45 ± 11	.833
Male sex, No. (%)	20 (77)	9 (75)	11 (79)	.829
White, No. (%)	15 (58)	6 (50)	9 (64)	.462
Body mass index, kg/m^2	28.0 ± 6.4	28.6 ± 5.5	29.1 ± 4.0	.766
Neck circumference, cm	39.8 ± 3.6	39.2 ± 3.9	40.3 ± 3.5	.461
Heart rate, bpm	63 ± 9	65 ± 11	61 ± 8	.319
Mean blood pressure, mm Hg	88 ± 16	89 ± 17	88 ± 16	.849
NYHA functional class III/IV, No. (%)	10 (38)	4 (33)	6 (43)	.619
Apnea-hypopnea index, events/h	24.4 ± 20.5	28.5 ± 23.8	21.8 ± 17.6	.351
Central sleep apnea, events/h	5.9 ± 10.1	7.1 ± 12.7	4.9 ± 7.7	.600
Obstructive sleep apnea, events/h	27.6 ± 51.1	33.9 ± 57.6	22.1 ± 46.2	.571
Obstructive sleep hypopnea, events/h	105.2 ± 86.8	101.7 ± 92.5	108.3 ± 85.2	.851
Lowest saturation, %	85 ± 5	85 ± 7	85 ± 4	.970
Medications				
Beta-blockers, No. (%)	21 (81)	9 (75)	12 (86)	.635
Angiotensin-converting enzyme inhibitor, No. (%)	1 (4)	1 (8)	0 (0)	.462
Calcium channel blockers, No. (%)	5 (19)	3 (25)	2 (14)	.635
Angiotensin receptor blocker, No. (%)	5 (19)	3 (25)	2 (14)	.635
Antiarrhythmics, No. (%)	4 (15)	3 (25)	1 (7)	.306
Diuretics, No. (%)	6 (23)	3 (25)	3 (21)	1.000
BNP, pg/mL	252 (149-488)	149 (113-284)	383 (237–538)	.005[a]

Values are presented as percentage, mean ± SD, or median (interquartile range) when appropriate. BNP = Brain natriuretic peptide. HCM = hypertrophic cardiomyopathy; NYHA = New York Association.
[a]$P \leq .05$.

significantly higher in patients with obstructive HCM compared with patients with nonobstructive HCM (Table 1). Baseline echocardiographic data are summarized in Table 2 and e-Table 1. Patients with obstructive HCM had higher values of LV mass index, LVOT gradient, LV filling pressures (E/E' septal, E/E' lateral, and E/E' septal + lateral), higher frequency of systolic anterior motion of the mitral valve, and higher LA volume and regurgitant jet, with no significant differences in MRF compared with patients with nonobstructive HCM. Interobserver agreement, calculated as the mean difference in the MRF between two independent readers, was 1.30% (95% limits of agreement from −10.1% to 12.7%; intraclass correlation coefficient, 0.80). The mean difference for intraobserver agreement was −0.92% (95% limits of agreement from −2.7% to 0.9%; intraclass correlation coefficient, 0.98). Bland-Altman plots are available in e-Figure 1.

During the study period, BP and HR remained stable and did not change significantly in either group (Fig 3, Table 2). The hemodynamic evaluation accessed by echocardiography represented by cardiac output, stroke volume, LVEF, and LVOT gradient also did not change during the study period (intragroup and intergroup comparisons can be seen in Table 2). In patients with nonobstructive HCM, 10-CPAP decreased RA area, with reductions in RV and LV relaxation (↓E' of RV and ↓E/A, respectively), with no changes in LA volume, regurgitant jet, and MRF. In patients with obstructive HCM, 10-CPAP produced the same effects in the right side of the heart as in patients with nonobstructive HCM. However, 10-CPAP also increased pulmonary artery pressure (↓RVOT acceleration time), reduced LA volume, and raised MRF (Fig 4, Table 2). There were no changes in intergroup or intragroup LVOT gradient measurements obtained during all the different phases of the study (Fig 5). No differences were found related to the sequence of CPAP pressures as evaluated by linear mixed model, indicating no significant carryover effect.

Discussion

Our study was designed to evaluate the acute effects of CPAP on hemodynamic and cardiac performance in

TABLE 2] Echocardiographic Parameters From Patients With Nonobstructive HCM and Patients With Obstructive HCM During the Study Period

Parameter	Nonobstructive HCM			Obstructive HCM		
	Baseline	Sham-CPAP	10-CPAP	Baseline	Sham-CPAP	10-CPAP
LVEDD, mm/m^2	23.1 (20.5-24.1)	22.9 (20.2-25.4)	21.5 (21.0-24.1)	24.6 (21.3-28.0)	23.8 (21.4-27.7)	23.1 (21.1-27.1)
LVESD, mm/m^2	13.3 (12.2-15.4)	13.4 (12.0-15.9)	12.8 (11.6-14.1)	14.4 (12.7-16.8)	15.2 (11.9-16.4)	13.7 (11.4-16.0)
LVEF, %	72 (68-76)	70 (68-73)	73 (68-77)	71 (68-74)	70 (66-74)	72 (67-77)
Heart rate, bpm	67 (62-71)	64 (60-68)	64 (59-69)	59 (56-62)	60 (56-64)	59 (53-64)
Stroke volume, mL/m^2	30.4 (26.7-36.6)	31.3 (25.4-40.4)	27.0 (23.7-37.9)	34.8 (30.4-41.0)	33.4 (28.1-46.0)	33.9 (27.3-45.5)
Cardiac output, L/m/m^2	2.1 (1.7-2.4)	2.0 (1.7-2.6)	1.9 (1.5-2.5)	2.1 (1.8-2.5)	1.9 (1.6-2.6)	2.0 (1.6-2.7)
E wave, cm/s	71.9 (58.0-85.8)	71.7 (57.4-86.0)	59.8 (46.3-73.3)[a,b]	85.4 (74.2-96.5)	81,1 (69.7-92.6)	83.6 (67.2-100.1)[c]
E/A	1.7 (1.1-2.4)	1.4 (1.0-1.8)[d]	1.1 (0.8-1.5)[a]	1.7 (1.2-2.2)	1.7 (1.2-2.2)	1.7 (1.2-2.3)
Isovolumetric relaxation time, MS	117 (91-143)	106 (89-123)	127 (102-152)	99 (89-111)	109 (84-134)	100 (85-116)
E wave deceleration time, MS	202 (171-233)	227 (184-269)	238 (195-280)	215 (183-247)	223 (184-262)	192 (172-213)
LVOT gradient, mm Hg	7.3 (5.5-9.0)	7.2 (5.1-9.2)	7.3 (5.4-9.2)	65.5 (51.7-79.3)	71.9 (57.0-86.9)	70.0 (58.5-81.4)
Left atrial volume, mL/m^2	22.2 (16.3-35.5)[c]	25.7 (20.2-30.8)[c]	29.6 (19.8-38.4)	47.8 (38.8-58.9)	46.1 (39.5-48.9)	42.2 (25.4-46.6)[e]
Regurgitant jet, mL	2.7 (0.0-5.3)[c]	2.2 (0.5-3.8)[c]	2.1 (0.8-3.4)[c]	11.1 (4.8-17.3)	17.2 (6.4-28.1)	18.1 (7.3-29.0)
Mitral regurgitant fraction, %	5,4 (0.4-10.3)	5.0 (1.2-8.9)[c]	3,5 (1.5-5.6)[c]	11.0 (5.6-16.4)	17.2 (6.4-28.1)	27.4 (13.5-41.3)[e]
RVOT acceleration time, ms	145 (100-190)	127 (92-163)	130 (83-177)	133 (105-161)	126 (92-160)	107 (83-131)[e]
E' right ventricle, cm/s	14.6 (12.6-16.6)	12.0 (10.6-13.4)[d]	11.7 (10.1-13.2)[c]	13.2 (11.3-15.1)	13.0 (10.9-15.1)	10.5 (8.9-12.1)[e,f]
Right atrial size, m^2	8.2 (7.8-8.9)	7.7 (6.5-8.4)[d]	6.4 (6.2-7.1)[a]	8.9 (7.4-9.6)	8.0 (7.1-9.1)	7.5 (6.6-8.2)[e]

Data are presented as mean (95% CI). 10-CPAP = CPAP at 10 cm H_2O; E/A = early to late; HCM = hypertrophic cardiomyopathy; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; sham-CPAP = CPAP at 1.5 cm H_2O. $P < .05$.

[a]Nonobstructive HCM baseline vs nonobstructive HCM 10-CPAP.

[b]Nonobstructive HCM sham-CPAP vs nonobstructive HCM 10-CPAP.

[c]Intergroup comparison.

[d]Nonobstructive HCM baseline vs nonobstructive HCM sham-CPAP.

[e]Obstructive HCM baseline vs obstructive HCM 10-CPAP.

[f]Obstructive HCM sham-CPAP vs obstructive HCM 10-CPAP.

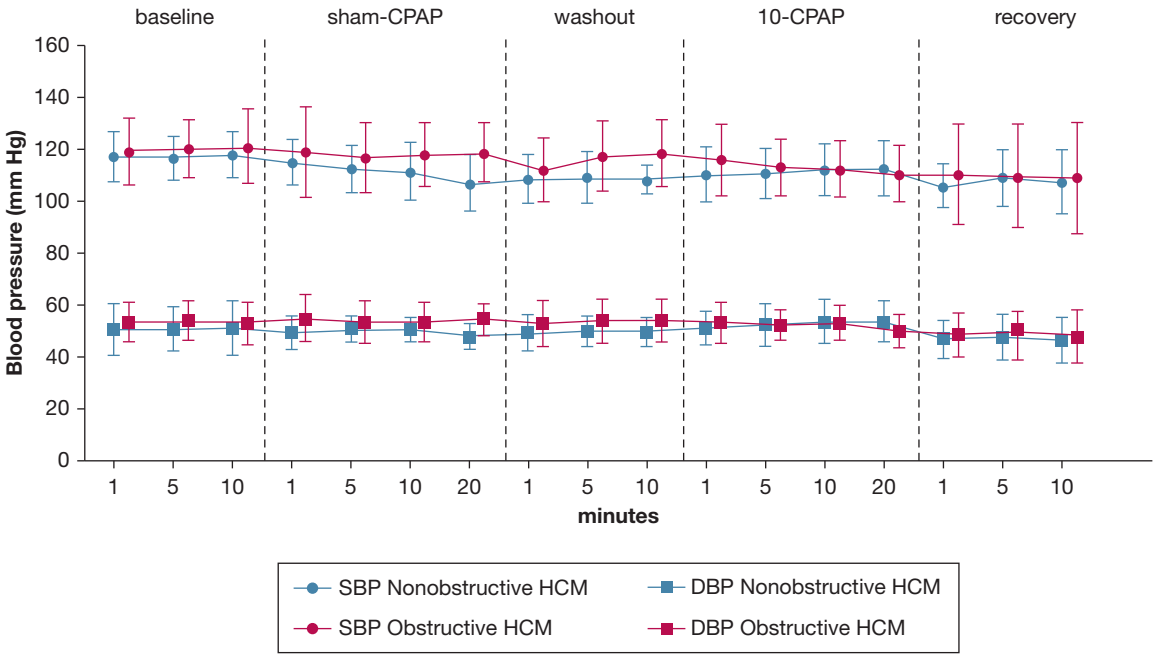

Figure 3 – *Systolic BP (SBP) and diastolic BP (DPB) during the study period for both groups.*

patients with HCM. The main findings are the following: (1) 10-CPAP did not acutely affect BP, HR, cardiac output, stroke volume, LVEF, and LVOT gradient in either group; (2) 10-CPAP induced a reduction in RA size and in RV relaxation in all patients; (3) 10-CPAP promoted effects that were group specific as observed by reductions in LV relaxation only in patients with nonobstructive HCM. In contrast, 10-CPAP promoted a decrease in LA volume plus an increase in MRF and a decrease in RVOT acceleration time, suggesting an increase in pulmonary artery pressure only in patients with obstructive HCM.

The acute effects of the application of positive intrathoracic pressure with CPAP and devices with two levels of PAP such as adaptative servo ventilation (ASV)[31] have been studied in several clinical conditions using different methodologies and may help to explain why the results are variable.[12,17,32-36] The observation of an acute reduction in RA size in patients with and those without a LVOT gradient is consistent with the concept that 10-CPAP reduces venous return and is in line with several studies in the literature.[35,37,38] 10-CPAP promoted a significant increase in pulmonary artery pressure (evaluated indirectly by RVOT acceleration time) and a decrease in LA size only in patients with obstructive HCM. We speculate that patients with obstructive HCM were more vulnerable to the effects of extrinsic compression promoted by increased intrathoracic pressure from CPAP. At baseline, this group presented a twofold higher LA diameter, increased LV hypertrophy and LV filling pressure (e-Table 1). Thus we believe that they were more likely due to reductions in LA size and to an overload in pulmonary vasculature. The unique effects of positive pressure promoting a decrease in cardiac chambers and an increase in pulmonary artery pressure have been previously observed in pigs who were mechanically ventilated[37] and in healthy volunteers who underwent CPAP.[35]

In patients with CHF, the acute application of CPAP is, in general, beneficial. Increased intrathoracic pressure may compress the dilated left atrium and was associated with an increase in cardiac output,[38-41] a decrease in myocardial oxygen consumption,[16] an improvement in the LVEF, and a decrease in MRF.[15] To the best of our knowledge, this is the first study to evaluate the impact of CPAP in patients with HCM. The study showed that CPAP did not acutely change BP, HR, cardiac output, stroke volume, LVEF, or LVOT. The hemodynamic effects of positive intrathoracic pressure will depend on the interplay between several factors that regulate venous return and cardiac function.[17] The absence of major hemodynamic effects from CPAP are in line with several studies conducted under different conditions.[17,33,35,42,43] Patients with obstructive HCM were clinically more severe than those with nonobstructive HCM and also higher levels of BNP (Table 1). Therefore, patients with obstructive HCM

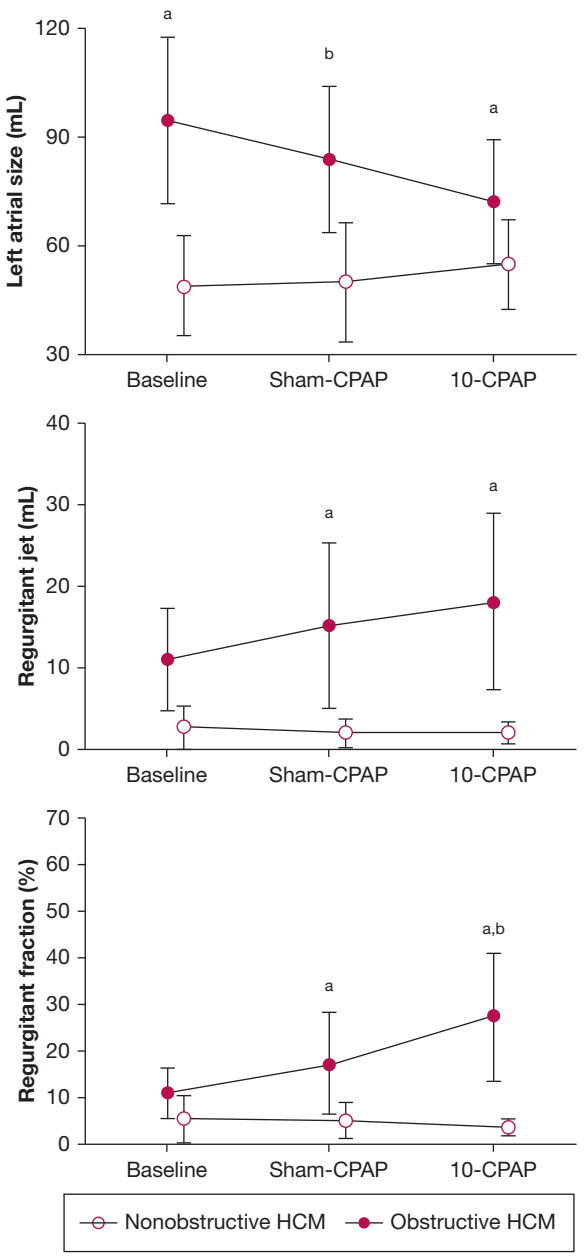

Figure 4 – *Echocardiographic measurements of mitral regurgitation-related variables in different CPAPs for both groups.*
[a]P< .05 *for intergroup comparison.*
[b]*Obstructive HCM baseline vs obstructive-HCM 10-CPAP.*

may benefit the most from the recognition of OSA and treatment with CPAP. However, this is also the population that may be more susceptible to the effects of CPAP, as evidenced by signs of increased pulmonary artery pressure. Conversely, the observation that CPAP did promote a hemodynamic impact and did not worsen LVOT obstruction in either group is reassuring.

Patients with HCM, as well as the general population of patients with CHF, frequently experience sleep-disordered breathing that may be treated with

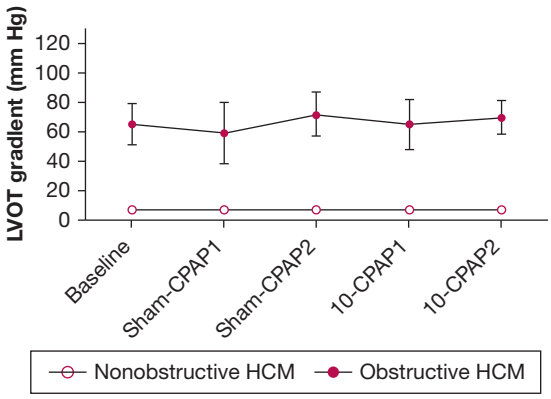

Figure 5 – *Left ventricular outflow tract (LVOT) gradients measured during the study period.*

noninvasive positive pressure during sleep. Two large randomized trials failed to show a decrease in long-term mortality in patients with CHF and central sleep apnea treated with CPAP and ASV.[44,45] Moreover, the last study raised concerns because it showed an unexpected increase in cardiovascular mortality among patients randomized to servo ventilation.[45] One possible explanation is that CPAP compromises hemodynamics in patients with CHF. Our study is relevant because it studied a population of patients with HCM who are potentially more sensitive to acute reductions in cardiac preload. The absence of major acute effects even in this population opens the possibility of studies evaluating the long-term effects of CPAP in patients with HCM and sleep-disordered breathing.

Our study has some strengths and limitations. Our randomized crossover design helped to guarantee that the echocardiographer was not aware of the CPAP level. We used transthoracic two-dimensional echocardiography, and two experienced investigators performed the offline analysis in a blinded fashion. Moreover, we used a beat-to-beat evaluation of BP, which is a very sensitive method to detect rapid and transient hemodynamic changes in BP. Because we focused on echocardiographic parameters, we excluded patients with atrial fibrillation, who are more susceptible to preload changes, and our results should therefore be extrapolated with caution to patients with HCM and atrial fibrillation.

Conclusions

Our study shows that CPAP does not lead to hemodynamic compromise, suggesting that with respect to hemodynamics, the therapy is safe in patients with HCM. However, long-term studies in patients with HCM with sleep apnea and nocturnal CPAP use are warranted.

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Additional information: The e-Figure and e-Table can be found in the Supplemental Materials section of the online article.

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