The hemodynamic impact of acute nasal continuous positive airway pressure treatment in hypertrophic cardiomyopathy: is it safe?

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Provenance: This is an invited Editorial commissioned by the Section Editor Ning Ding (Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Nerbass FB, Salemi VM, Pedrosa RP, et al. Acute Effects of Nasal CPAP in Patients With Hypertrophic Cardiomyopathy. Chest 2016;150:1050-8.

Submitted Apr 08, 2017. Accepted for publication Apr 20, 2017. doi: 10.21037/jtd.2017.05.20 **View this article at:** http://dx.doi.org/10.21037/jtd.2017.05.20

Hypertrophic cardiomyopathy (HCM) is an important genetically inherited form of cardiomyopathy (1). In its obstructive form, dynamic left ventricular tract (LVOT) obstruction is a salient feature of the disease, and has been shown to be a strong independent predictor of progression to New York Heart Association functional III or IV heart failure, and increased mortality (2). Although dynamic LVOT obstruction in HCM has been conventionally associated with asymmetric septal hypertrophy, mitral valve and papillary muscle abnormalities in HCM may also predispose to significant LVOT obstruction in the absence of severe septal hypertrophy (3). Recognition and accurate diagnosis of the condition, and appropriate risk stratification including screening of first-degree relatives are important, because patients with HCM are at increased risk of sudden cardiac death (4,5).

It has been shown that the prevalence of obstructive sleep apnea (OSA) is high among patients with HCM spanning from approximately 30–70% (6,7). It is unclear whether established treatments for OSA, particularly continuous positive airway pressure (CPAP), may have any impact on the hemodynamics of patients with HCM. Theoretically, reductions in left ventricular (LV) preload caused by CPAP can translate into reduced left ventricular end systolic volume, worsening dynamic LVOT obstruction (8,9). A recent study published in *Chest* by Nerbass *et al.* attempted to address this question in part by assessing the acute effects of CPAP in 26 patients with HCM (10).

The authors conducted a randomized crossover design examining the impact of a twenty-minute period application of CPAP 10 cm water pressure to sham-CPAP (1.5 cm water pressure) on LVOT pressure gradients as well as other echocardiographic measures and beat-to-beat blood pressure measures in those with HCM defined as the presence of septal hypertrophy (≥15 mm), without an alternative explanation such as hypertension while in the supine position while awake. A 10-minute washout period (no mask) was incorporated to minimize carryover effect from intervention CPAP to sham CPAP. Fifty four percent of patients (14/26) had obstructive HCM (peak LVOT gradient ≥30 mmHg) and the remainder with non-obstructive HCM (peak LVOT gradient <30 mmHg). Participants were overall overweight, middle-aged Caucasian males with predominantly OSA physiology, with approximately one third with NYHA class III/IV heart failure. Those with obstructive HCM had higher BNP levels compared to those with non-obstructive HCM as well as higher LV mass index, LV filling pressures and left atrial (LA) volume.

In both the obstructive and non-obstructive HCM groups, there were no statistically significant differences in the LVOT gradient [and similarly no difference in cardiac output, stroke volume and left ventricular ejection fraction (LVEF)] with intervention versus sham-CPAP. Moreover, there were no significant differences in heart rate or blood pressure in either group in intervention versus sham CPAP. In those with obstructive HCM, there were greater reductions in LA volume (mL/m²), right ventricular outflow tract (RVOT) acceleration time (ms), E' right ventricle (cm/s) and right atrial size (cm²) and an increase of mitral regurgitant fraction (MRF) (%) compared to sham. Similarly, in those with non-obstructive HCM, there was a greater reduction in E' in the right ventricle and right atrial size suggesting similarities of CPAP-induced right sided cardiac alterations, however no difference in the other parameters outlined above in obstructive HCM. The authors concluded that CPAP did not exert detrimental influence in either obstructive or non-obstructive HCM from the standpoint of worsening LVOT or adverse systemic hemodynamic impact. Right atrial size reduction and increase in RV relaxation were observed in both obstructive and non-obstructive HCM. Unlike non-obstructive HCM, CPAP did have an effect on reduction of LA volume, increase in MRF and reduction of RVOT acceleration time, the latter suggesting increase in pulmonary arterial pressure in obstructive HCM.

The clear strengths of the study include the use of a crossover design which enhances efficiency in terms of allowing each patient to serve as his/her own control, thereby reducing the number of individuals needed to detect differences in outcomes, and allows comparisons between and within groups and ideally used when the effects of treatments are brief and reversible. A washout period was used which albeit is unclear in terms of the optimal duration, there was no evidence of carryover effect per statistical analyses. Other strengths include the care taken to blind the echocardiographer from the intervention type and performing intra- and inter-observer reliability assessments which thereby enhances study internal validity. Although study findings are not reflective of cardiac physiology as it occurs during sleep, patients were in the supine position thereby reflective of positional-related fluid shifts.

It would be helpful to know the extent of septal hypertrophy across the study patients and the mean septal wall thickness among non-obstructive versus obstructive patients. Timing of medication intake, particularly diuretics may impact cardiac physiology and therefore potentially affect interpretation of study findings. Although findings can be viewed as exploratory and the primary outcome of interest was LVOT obstruction, statistical consideration of multiple comparisons may be reasonable. Some methodologic aspects of the study bear mention. Although the Teichholz method was used to calculate LVEF for the study patients, the most commonly used method for assessment of left ventricular volumes and LVEF by 2-dimensional echocardiography is the biplane method of disks (modified Simpson's rule) as recommended by the current American Society of Echocardiography chamber quantification guidelines (11). Additionally, in this study, mitral regurgitation was assessed by calculating MRF, based on planimetry of the regurgitant jet on color Doppler, relative to the LA area. Conventional recommended methods of quantification of mitral regurgitation include the assessment of the vena contracta width and calculation of the mitral regurgitant volume and effective regurgitant orifice area by the proximal isovelocity surface method (PISA) method (12,13). Examination of other conventional estimates of pulmonary artery systolic pressure (including estimation of right ventricular systolic pressure, based on the peak velocity of the tricuspid regurgitant signal) would allow evaluation of internal consistency of findings (11).

The authors should be commended for this work as given the unanticipated findings of studies such as the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) randomized controlled trial in which adaptive servoventilation (ASV) was identified to increase cardiovascular mortality compared to controls in central predominant sleep apnea with reduced ejection fraction, many questions were left unanswered in terms of the underlying mechanism by which ASV and the possibility positive pressure may contribute adversely to cardiac hemodynamics and physiology. Carefully performed, rigorous studies such as the current one performed by Nerbass and colleagues are needed to help inform clinical trials in various pathophysiologic states such as HCM so that we have a clear understanding of how positive airway pressure impacts the cardiac physiologic substrate.

Results from this novel study suggest that there are no significant adverse hemodynamic effects (reflected by changes in heart rate, blood pressure or dynamic LVOT gradients) during a short duration of CPAP treatment. Generalizability of findings are not applicable to those with atrial fibrillation, associated cardiac conditions, prior cardiac surgery, prior cardiac arrest, as well as patients with pacemakers or implantable cardioverter defibrillators (ICDs), i.e., arguably those with a high risk of sudden cardiac death. It is also unclear whether sleep would introduce dynamic physiologic changes which could impact LVOT obstruction, therefore provocation testing may further elucidate these inter-relationships. These areas, therefore, represent an opportunity for further study. While the current study is a well-done step in the right direction, future longer-term and larger trials considering influence of variable CPAP pressures are needed to validate these

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findings incorporating contemporary echocardiographic standards with consideration of invasive cardiopulmonary hemodynamic monitoring to inform future interventional studies of CPAP treatment in patients with HCM and OSA.

Acknowledgements

Funding: Dr. R Mehra has received NIH funding for which she has served as Principal Investigator (NHLBI RO1 1 R01 HL 109493).

Footnote

Conflicts of Interest: Dr. Mehra serves as a standing member on an NIH study section for which she receives honorarium. She serves as the Associate Editor for the journal *Chest*. She has received royalties from Up to Date and honorarium from the American Academy of Sleep Medicine. Her institution has received positive airway pressure machines and equipment from Philips Respironics and Resmed for research purposes. Dr. Xu has no conflicts of interest to declare.

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Cite this article as: Xu B, Mehra R. The hemodynamic impact of acute nasal continuous positive airway pressure treatment in hypertrophic cardiomyopathy: is it safe? J Thorac Dis 2017;9(6):1409-1411. doi: 10.21037/jtd.2017.05.20 Resonance and Echocardiography. Circ Cardiovasc Imaging 2015;8:e003132.

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