Patients with hypertrophic cardiomyopathy (HCM) represent a unique group of cardiovascular patients because common indicators of cardiomyopathy progression may be of limited utility in HCM (left ventricular ejection fraction), while other individualized measures have been identified to predict adverse outcomes (left atrial size, atrial and ventricular arrhythmias, septal thickness, peak oxygen consumption). The distinctive aspects of obstructive HCM pathophysiology can test the clinician’s skills during auscultation maneuvers as well as during unique management decisions (restrictions in the use of afterload reducing agents, adrenergic pres- sors). Septal reduction therapies (septal myectomy, septal ablation) have been the cornerstones of the effective treatments for patients with severe obstruction of the left ventricular outflow tract, along with the up-titration of adrenergic receptor blockers, and stratification for the prevention of sudden cardiac death.1

Sleep disordered breathing (SDB) has been suggested as an astonishingly frequent co-morbidity among HCM patients (prevalence of >50%).2 Several reports have documented improvement in symptoms of HCM patients after effective treatment of SDB, particularly its most common form — obstructive sleep apnea (OSA).3 In the past 10 years, the connection between SDB and HCM has been under increasing investigation, and this effort has identified association between untreated SDB and several adverse characteristics relevant to HCM: worse functional New York Heart Association class,4 worse peak exercise oxygen consumption,5 more frequent atrial fibrillation and enlarged left atrial size (potent predictors of survival in HCM),5,7 and increased mean heart rate (target of β-blocker therapy, the up-titration of which can be limited by side-effects in HCM).5,8

In this editorial we will attempt to coalesce the evolving framework of SDB-HCM interaction with the findings from the informative manuscript by Cui et al10 published in this issue of Mayo Clinic Proceedings.10 The esteemed authors of this novel study reviewed HCM patients who underwent clinically indicated septal myectomy at a specialized HCM center of excellence. Their analysis compared all-cause survival in patients with SDB versus without SDB as defined by premyectomy overnight oximetry. This study was possible thanks to a well-maintained database of surgical and medical variables, as well as due to the robust volume of myectomies performed at this center of HCM excellence (619 patients with myectomy and oximetry included in the study).

Sleep disordered breathing was reported to be very frequent in this studied cohort (55% of included patients had at least mild SDB) which was consistent with other HCM cohorts without myectomy.2 The supplemental analysis by Cui et al10 did not suggest that selection bias could explain such high prevalence. Also consistent with previous reports was the cross-sectional analysis at the time of myectomy which associated SDB with higher prevalence of adverse variables relevant to HCM: more atrial fibrillation, greater left atrial size, and increased estimated left ventricular filling pressures. The key novel finding was that SDB (as detected during premyectomy oximetry) was not associated with any worse all-cause survival after the myectomy compared with the
absence of SDB. The survival of both the SDB and non-SDB cohorts were in fact similar to an age- and sex-matched American population without HCM.

When contextualized with the previous studies on HCM and SDB, these findings validated SDB as one of the most common comorbidities of obstructive HCM patients. While this study identified all-cause survival after myectomy to be unaffected by SDB, future projects could clarify 3 important implications of these data: 1) Did more subtle indices (such as atrial fibrillation recurrence, worsening in left ventricular stiffness, exercise tolerance) differ between SDB and non-SDB cohorts in the long-term follow-up after myectomy? 2) Were there differences according to whether the SDB was treated versus not treated (and which modalities of treatment provided possible benefit)? and, finally, 3) Which SDB phenotypes were represented among the HCM patients undergoing myectomy (OSA vs central sleep apnea [CSA])? Particularly the distinction between OSA and CSA may be relevant to obstructive HCM pathophysiology because the acute hemodynamic changes brought on by OSA vs CSA are dramatically different, and so are their potential treatments. During OSA, the upper airway is obstructed, leading to a severe limitation of inspiratory air-flow, with the inspiratory muscles remaining highly active when trying to take a breath-in against the airway obstruction. Obstructive sleep apnea causes profound and repetitive changes in intrathoracic pressure. The effect of an OSA episode can be simulated in a conscious patient by the breathing maneuver called Mueller maneuver (inspiration attempted against closed glottis). The Mueller maneuver (and OSA) may interplay with obstructive HCM physiology similarly to a well-established maneuver which is commonly used to potentiate HCM obstruction — the Valsalva maneuver. The Valsalva maneuver also creates large intrathoracic pressure changes, and it is used during physical and echocardiographic examinations of HCM patients because the HCM-related left ventricular outflow tract obstruction is accentuated shortly after the Valsalva release phase when intrathoracic pressure suddenly drops. The sudden decrease in intrathoracic pressure at this phase in the Valsalva maneuver reduces both cardiac preload and afterload such that this effect heightens juxtaposition of the myocardial walls in HCM and, consequentially, increases outflow obstruction. When diagrammed on a time/pressure schematic (Figure), the Mueller and Valsalva maneuvers resemble mirror images, with similarly steep drops in the intrathoracic pressure occurring at the initiation of the Mueller and at the release of the Valsalva. Recent invasive hemodynamic measurements conducted in non-HCM patients suggested that the effect of the Mueller maneuver (and OSA) could even supersede the pressure changes induced by the Valsalva maneuver. This could be because at the initial phase of the Mueller maneuver the sudden decrease in intrathoracic pressure occurs within a negative pressure range, thereby heightening the sudden reduction in afterload, which in turn potentiates the outflow obstruction of HCM. The interest in whether OSA versus CSA were present in HCM patients with severe outflow tract obstruction stems from the fact that CSA entirely lacks the ability to change intra-thoracic pressures as it is caused by a paucity of neurologic inspiratory stimuli, compared with the above described large intrathoracic pressure changes during OSA. Additionally, it may have been the case that after myectomy, both OSA and CSA were not
particularly relevant to the well-being of a HCM patient, because the outflow tract obstruction has been resolved by the septal reduction.

The higher rates of atrial fibrillation and increased left ventricular filling pressure estimates among SDB patients prior to the myectomy suggested that SDB could have been a contributor to these adverse criteria. Whether the difference in these more subtle indices of HCM pathophysiology continues to diverge between SDB and non-SDB patients even after the myectomy remains to be answered. Similarly interesting would be to learn whether early detection and effective treatment of SDB (and particularly severe OSA) long before the progression to the stage when myectomy was needed could have had any clinical benefit in HCM (for example by reducing the atrial fibrillation prevalence, reducing heart rate in addition to the β-blocker use, or by improving exercise tolerance). Additionally, our ability to optimally detect and treat SDB is evolving, and remains far from optimal even among non-HCM patients with cardiac disease. Lastly, but definitely not least, would be to examine whether any of the emerging treatments for SDB could have a particular benefit in HCM patients prior to myectomy (use of hypoglossal stimulator vs continuous airway pressure versus mandibular device).

In summary, the authors are to be congratulated on a well-performed and well-presented study which confirms the high prevalence of SDB in HCM. Importantly, this study also points out the need for a more granular understanding of the individualized interactions between SDB and HCM in patients prior to and after myectomy, particularly as these pertain to the type of SDB; the development of HCM-specific morbidity with SDB; and novel modalities of effective SDB treatment.

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REFERENCES