The Role of Obstructive Sleep Apnea in Hypercapnic Respiratory Failure Identified in Critical Care, Emergency, Inpatient, and Outpatient Settings

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KEYWORDS

• Hypercapnia • Hypercapnic respiratory failure • Hypoventilation • Respiratory insufficiency • Sleep apnea • Non-invasive ventilation • Positive airway pressure

KEY POINTS

- The diagnostic evaluation of patients with hypercapnic respiratory failure has typically focused on finding a single cause for the hypercapnia, but many patients have multiple contributing conditions.
- The prevalence of obstructive sleep apnea (OSA) in patients with hypercapnic respiratory failure is poorly recognized. Over two-thirds of patients with hypercapnia in acute settings have underlying OSA if tested, but only 10% to 25% are diagnosed in routine clinical care.
- While the importance of OSA in obesity hypoventilation syndrome is well-established, its role in contributing to hypercapnia in general is under-investigated. Addressing this knowledge gap is crucial because sleep apnea is treatable, and hypercapnic respiratory failure is common and associated with substantial morbidity and mortality.
- Epidemiologic research on hypercapnic respiratory failure faces several challenges, including inaccuracy of health record-based comorbidity assessment, substantial follow-up loss between inpatient and outpatient settings, and oversimplified attribution of the cause of respiratory failure.

CASE PRESENTATION

A 67-year-old female with no previously obtained spirometry or sleep testing presented with confusion. She was admitted to the intensive care unit (ICU) for non-invasive ventilation after a venous blood gas obtained in the emergency room showed a pH of 7.25 and a $Paco_2$ of 72 mm Hg. She is a current smoker and has a body mass index (BMI) of 36 kg/m^2. A chest computed tomography (CT) scan was negative for pulmonary embolism but showed mild centrilobular emphysema. An echocardiogram showed right ventricle enlargement, elevated left-ventricular diastolic filling pressures, and a normal ejection fraction. The patient improved with non-invasive ventilation, diuresis, steroids, and antibiotics. She was discharged on 1 L/min of supplemental oxygen. The sleep clinic is contacted to facilitate a sleep study. How important is it to diagnose co-morbid obstructive sleep apnea

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(OSA), and how urgently should a sleep study be performed?

INTRODUCTION

The health impact of hypercapnic respiratory failure (an increase in arterial blood carbon dioxide resulting from insufficient alveolar ventilation to match the metabolic production of carbon dioxide) is under-appreciated, irrespective of clinical circumstance. An emerging body of evidence suggests that hypercapnic respiratory failure is common[1] and associated with significant morbidity[2] and mortality risk.[3] One in four hospitalized patients who receive a diagnostic code for hypercapnic respiratory failure are readmitted within 30 days.[4] Even amongst inpatients whose arterial blood gas is consistent with compensated hypercapnia (normalization of blood pH), roughly 1 in 3 die within 1 year.[5]

Changes in the physiology of breathing during sleep usually lead to the appearance of hypercapnia first at night. An increasing body of research highlights the role of sleep-disordered breathing (SDB), particularly OSA, in developing hypercapnia. In this article, the authors review the pertinent physiologic principles governing the occurrence of hypercapnia. They then review the existing literature to answer the common clinical scenario outlined in the case presented earlier—when a patient is identified as having hypercapnic respiratory failure, what is the likely contribution of sleep apnea in the development of their condition? They also discuss challenges encountered in research assessing the impact of OSA on hypercapnic respiratory failure risk, which limit the strength of the current evidence on the role of OSA in hypercapnia seen in hospitalized settings.

BACKGROUND

Hypercapnic (synonymously, hypercarbic[6]) respiratory failure occurs when the amount of inhaled air participating in gas exchange (alveolar ventilation, V_A) is insufficient to match carbon dioxide production (VCO_2) from cellular metabolism. The resulting rise in the partial pressure of CO_2 in arterial blood ($Paco_2$) to above 45 mm Hg (at sea level) operationally defines hypercapnic respiratory failure. Numerous disease states can contribute to the development of hypercapnic respiratory failure through differing physiologic mechanisms (**Fig. 1**)[7].

1. Increasing the rate of CO_2 production that must be exhaled (increased VCO_2).
2. Reducing the efficiency of ventilation (by increasing dead space or reducing desired arterial CO_2 tension).
3. Increasing the work required for a given amount of ventilation due to either increased resistance to airflow (such as obstructive airway disease) or increased elastic or inertial loads (such as stiff lungs or excess chest wall mass, respectively).
4. Decreasing the capacity of the respiratory apparatus to do work (neuro-muscular disease or mechanical disadvantage).
5. Disrupting the usual feedback loops that lead to increased ventilation in response to rising blood CO_2.

Hypercapnic respiratory failure is difficult to diagnose. Except for the use of capnography in some procedural and intensive care settings, arterial CO_2 levels are not monitored or estimated as part of routine care. Clinicians must actively look for hypercapnia and order appropriate diagnostic testing. Signs and symptoms of hypercapnic respiratory failure, such as confusion, lethargy, tachycardia, and shortness of breath (or its absence), are non-specific. Furthermore, empiric supportive respiratory care often temporarily stabilizes patients without properly understanding the cause(s) of hypercapnia. Thus, hypercapnic respiratory failure is frequently missed in clinical practice.[8–10]

Hypercapnic respiratory failure and sleep are intertwined.[11] Several physiologic changes to the respiratory system promote the development of hypercapnia during sleep.[12,13] First, the respiratory control system becomes less responsive to increases in blood CO_2, particularly during rapid eye movement (REM) sleep.[14] Mechanical changes to the respiratory system also occur.[15] Supine positioning reduces lung volumes, particularly in patients with excess abdominal adiposity,[16] which predisposes the upper airway to narrowing or collapse and thereby causes obstructive hypopneas or apneas.[17] Skeletal muscles, except the diaphragm, are hypotonic during REM. In healthy individuals, this contributes to a 13% decrease in the tidal volume and minute ventilation.[18] The metabolic production of CO_2 drops during sleep, but the minute ventilation drops even more, resulting in a rise in blood CO_2 levels.[19] In healthy individuals, the arterial CO_2 tension can increase up to 4 to 6 mm Hg during sleep.[20] However, individuals who rely more on accessory muscles, such as those with muscular dystrophies, phrenic nerve injuries, or hyperinflation, experience a greater decrease in ventilation during REM sleep. Pathologic nocturnal hypoventilation is defined by an increase in CO_2 to 55 mm Hg (or above 50 mm Hg and more than 10 mm Hg above awake, supine CO_2) sustained for 10 or more minutes measured using end-tidal or transcutaneous CO_2 monitoring.[21]

High Ventilatory Need
Low Desired Arterial CO2
• Metabolic acidosis • Hypoxia

High Ventilatory Need:
Increased CO2 Production

• Fever, Infection, or Inflammation
• Advanced malignancy
• Muscle activity
  • Seizures
  • Exercise
  • ↑↑ Work of breathing
• Toxic ingestion
• **Obesity**

$$Arterial\ CO2 \propto \frac{Production\ of\ CO2}{(Ventilation - Deadspace)}$$

Decreased Ventilation		
Decreased Drive to Breathe:	Muscle weakness or inefficiency	Increased respiratory system loads

• **Opiates and other sedatives**
• Brainstem lesions
• **Compensated hypercapnia**
• Submissive Hypercapnia
• Sleep
• Metabolic alkalosis
	• **Neuromuscular disease**
	• Lung Hyperinflation
	• Respiratory muscle hypoxia
		• Elevated airway resistance
		  • **COPD,** Asthma
		  • Mucus
		  • **Upper-airway obstruction**
		• Stiff Lungs
		  • Parenchymal lung disease
		  • Pulmonary edema
		• Stiff Chest Wall
		  • Pleural disease
		  • Excess or stiff chest wall tissue

High Ventilatory Need:
Increased Deadspace "Wasted Ventilation"

• Anatomic
  • shallow breathing
• Physiologic
  • Pulmonary embolism
  • Pulmonary hypertension
  • Congestive heart failure
  • **Parenchymal lung disease of any kind**

Fig. 1. Determinants of the arterial blood CO_2 tension. The efficiency of ventilation refers to the portion of ventilation (air moved by the respiratory system) that participates in gas exchange. Deadspace (Vd) is synonymous with "wasted ventilation" that does not participate in gas exchange. Therefore, the unwasted ventilation is 1 minus the deadspace fraction (Vd/Vt, Vt refers to the overall tidal volume). The production of CO_2 (VCO_2) depends on the overall metabolic rate, and the portion of that is aerobic versus anaerobic. Each condition can contribute to hypercapnia through multiple mechanisms (eg, COPD may result in elevated dead space, resistive respiratory system loads, and mechanical disadvantage from hyperinflation) and multiple diseases can contribute to each physiologic abnormality.

Nocturnal hypoventilation is often an initial manifestation of a disease state that will subsequently lead to daytime hypoventilation,[22,23] but SDB can also lead to hypercapnia on its own. Increases in blood CO_2 levels occur during obstructive apneas because ventilation halts while metabolic CO_2 production continues (**Fig. 2**). Ventilation must increase between apneic events to unload the accumulating CO_2. Otherwise, the blood CO_2 level will rise.[24] Hypercapnia develops when obstructive respiratory events are either frequent or prolonged enough or the inter-event increase in ventilation is limited.[12] Therefore, "pure" sleep hypoventilation and hypoventilation resulting from sleep apnea exist on a spectrum rather than as discrete categories, particularly in patients who do not appropriately increase their ventilation between apneas.[12] Obesity hypoventilation syndrome (OHS) epitomizes this spectrum. Patients with OHS and severe OSA resolve their hypercapnia following treatment of obstructive respiratory events by continuous positive airway pressure.[25] In contrast, patients with a more "pure hypoventilation" without significant OSA are recommended bilevel positive airway pressure.[26,27] A similar spectrum of resolution of hypercapnia in response to OSA treatment likely occurs in other "overlap syndromes," such as chronic obstructive pulmonary disease (COPD) and OSA,[28,29] though insufficient evidence exists for strong management recommendations.[30]

In summary, changes in the mechanics and regulation of breathing during sleep lead to the initial development of hypercapnia at night. Sleep apnea, mainly when severe or co-occurring with limited ability to increase inter-event alveolar ventilation, contributes to nocturnal CO_2 accumulation. In specific diseases, such as OHS with severe OSA, addressing sleep apnea prevents or resolves hypercapnic respiratory failure. Indirect evidence suggests that treating OSA might reduce or prevent respiratory decompensations in patients with other causes, multifactorial causes, or undifferentiated cases of hypercapnic respiratory failure.[31–33] However, the degree of benefit would depend on how large the contribution of OSA is amongst different etiologies of hypercapnic respiratory failure. The remainder of this article focuses on quantifying the role of untreated OSA in hypercapnic respiratory failure encountered in various clinical settings.

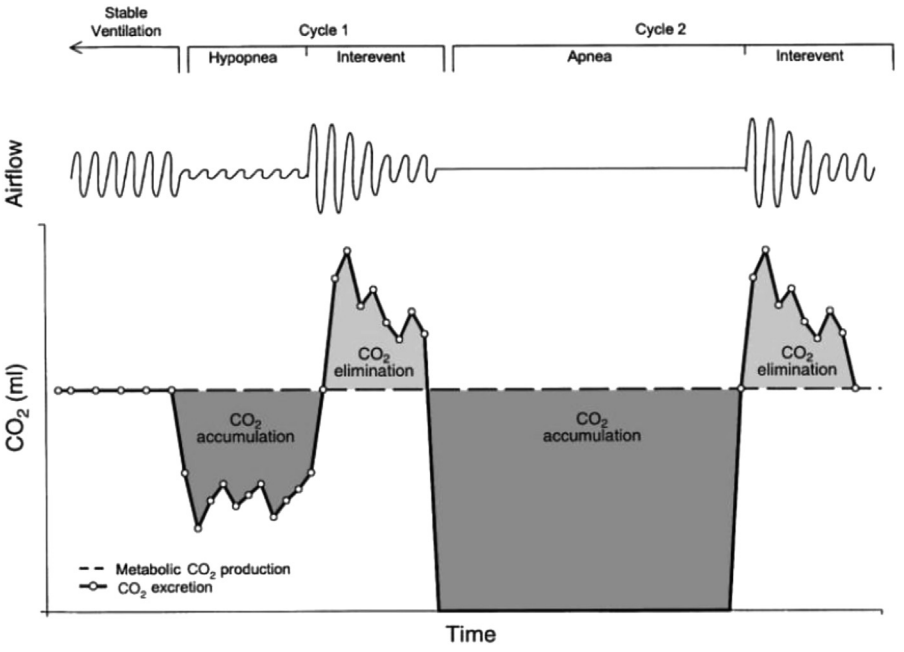

Fig. 2. CO_2 loading during apneas and hypopneas. Apneas and hypopneas can lead to an accumulation of CO_2 in the arterial blood, particularly if the inter-event ventilation is not able to increase because metabolic CO_2 production continues while alveolar ventilation drops. According to this model, more frequent events (a higher Apnea-Hypopnea Index), longer events, or a limited ability to increase the amount of ventilation between obstructions will lead to progressive nocturnal CO_2 accumulation. In combination with any underlying respiratory system abnormalities, bicarbonate retention by the kidneys to minimize the change to blood pH is then hypothesized to lessen the tendency to normalize the nocturnal loading, eventual leading to daytime hypercapnic respiratory failure. (*From* Berger and colleagues J Appl Physiol 88:257 to 264 (2000)[12,24]; with permission.)

EPIDEMIOLOGY

Research on hypercapnic respiratory failure has generally focused on what factors differ between patients with or without hypercapnia among patients who have specific diseases that can cause hypercapnic respiratory failure, such as COPD,[34] obesity with SDB (OHS[35–37]), restrictive chest wall disease,[38,39] or neuromuscular disease (NMD)[40,41]. However, clinicians often face an "inverse problem"[42,43] where hypercapnic respiratory failure has been identified, but the conditions that have led to hypercapnia must be determined (**Fig. 3**).

This question is important for clinicians because hypercapnic respiratory failure is often identified in acute care settings (ICU, emergency department, or inpatient ward), where definitive diagnostic studies such as spirometry, polysomnography, and electromyography have not been performed and cannot be obtained immediately. In the specific case of OSA, care must be transitioned to an outpatient sleep physician to diagnose and manage OSA, as the qualification criteria for respiratory assist devices (in the United States) limit empiric management.[44] The urgency of this referral depends on whether OSA is commonly an important cause of hypercapnia or not.

Both clinicians and researchers are interested in what portion of hypercapnic respiratory failure cases would be averted if OSA were prevented or treated because this guides the extent to which addressing SDB should be prioritized in this group. In each patient, OSA can be an important driver, a weak contributor, or unrelated to the development of hypercapnia. Frequent co-occurrence alone is, therefore, insufficient evidence that OSA is an important cause of hypercapnia. However, an important role is supported if OSA is more common in patients with hypercapnic respiratory failure than otherwise appropriately matched patients who do not have hypercapnia.[45,46] The current literature, with few exceptions,[47] does not contain matched control groups. Inferences about the excess risk caused by OSA therefore rely on implied comparisons, which limits the strength of evidence.

In the following section, the authors consider the evidence supporting OSA's role as a cause of hypercapnic respiratory failure in various settings. The patient mix and the methodologies of studies

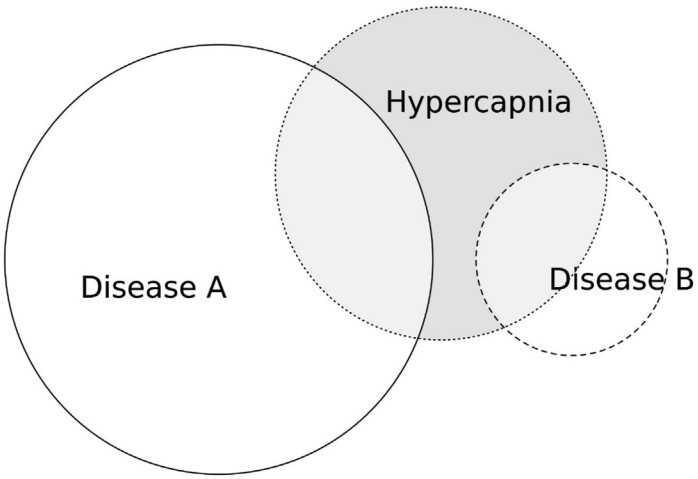

Fig. 3. Spatial representation of the "inverse problem" of conditional probability. The probability of having a disease among patients identified with hypercapnia (represented as: P [disease | hypercapnia] in statistical notation) may be much different from the probability that a patient with a disease develops hypercapnia (P[hypercapnia | disease]). This is an important difference because clinicians often recognize hypercapnia before knowing the cause, and thus, P (disease | hypercapnia) is the expected rate for finding that disease in subsequent investigations. In this case, only 1 in 5 cases of "Disease A" develop hypercapnia, while 1 in 2 cases of "Disease B" do. However, because disease A is much more common, the likelihood of hypercapnia being caused by disease A is double that of Disease B. It has been suggested that obesity hypoventilation syndrome is the most common current cause of hypercapnia (see **Table 3**), despite most patients with obesity and obstructive sleep apnea not developing hypercapnia.[37] (Figure generated using 'eulurr' package.[94])

differ between the intensive care, inpatient, emergency, and outpatient settings. Thus, the authors have subdivided our discussion into those groups.

Intensive Care Unit

The diagnosis of hypercapnic respiratory failure is often made in the ICU, where patients with the most severe respiratory decompensation who require ventilatory support are encountered. A summary of studies evaluating comorbidities of patients with hypercapnic respiratory failure in the ICU is shown in **Table 1**.

All studies included patients using an arterial blood gas criterion (either a $Paco_2$ over 45 mm Hg or 6 kPa) and either a pH consistent with uncompensated respiratory acidosis (Contou and colleagues[48] and Ouanes-Besbes et al.[49]) or requirement that patients received non-invasive (NIV) or invasive mechanical ventilation (IMV) (Thille and colleagues[50] Adler and colleagues[51] Gursel and colleagues[52]). OSA/OHS was uncommon (12% of 230 patients) in the single study that relied on clinician attribution (Contou and colleagues[48]).

In contrast, moderate or severe OSA was very common in the 3 studies where patients underwent sleep testing ranging from 63% to 88% (75% of 37 patients in Adler and colleagues,[51] 88% of 16 patients in Thille and colleagues,[50] and 63% in Ouanes-Besbes et al.[49]). Notably, these 3 studies used either in-lab polysomnography 3 months after ICU discharge (Adler and colleagues[51] and Thille and colleagues[50]) or home sleep apnea tests 3 weeks after discharge (Ouanes-Besbes et al.[49]). All had very low rates of follow-up among patients invited for testing (46%,[51] 47%,[50] and 76%,[49] respectively).

This low follow-up rate, even among the patients who consent to participate in research, suggests that many patients are lost when transitioning from inpatient to outpatient care and thus may not receive definitive evaluation in routine clinical care. These patients often encounter issues preventing timely access to follow-up, and recognition for the need for treatment may be lacking for both patients and providers. This is particularly problematic given the high likelihood of early readmissions for patients with hypercapnic respiratory failure.[4] Gursel and colleagues[52] reported that respiratory polygraphy during ICU admission identified OSA in 8 of 11 patients diagnosed with OHS and 12 of 21 patients with COPD and hypercapnia (overall rate of OSA of 64%). Alternatively, Adler and colleagues reported that the absence of hyperinflation (as assessed by plethysmography) might select survivors of hypercapnia with a particularly high likelihood of moderate-severe OSA.[53] However, plethysmography is also not easily performed in acute care settings.

Overall, OSA is identified in ICU patients with hypercapnic respiratory failure at a roughly 5-fold higher rate (63%–88%) when sleep testing is performed compared to when clinicians' assessment of the cause is used (12%). While OSA is likely common and unrecognized among all ICU patients (for example, Bucklin and colleagues[54] estimate that 40% of ICU patients have moderate or

Table 1
Prevalence of obstructive sleep apnea among intensive care unit survivors of hypercapnic respiratory failure

Author	Year, Location	Enrollment Criteria	Exclusion Criteria	Method of Assessment	Loss to Follow-up	Rate of Mod-Severe OSA
Prospective without Protocolized Comorbidity Assessment.						
Contou et al,[48] 2013	France, 2008–2011	pH < 7.35 and $Paco_2$ > 45 mm Hg	Invasive Mechanical Ventilation or DNI	Chart review	Not Applicable	30 of 242 (12%)
Prospective Studies with Protocolized Ascertainment						
Adler et al,[51] 2017	France 2012–2015	$Paco_2$ over 47.25 mm Hg. NIV or IMV treatment	neuromuscular disease, prognosis < 3 mo, iatrogenic hypercapnia, persistent confusion	PSG 3 mo after discharge	53%	28 of 37 (75%)
Thille et al,[50] 2018	Prior to 2018 (precise dates not reported)	pH < 7.35 and $Paco_2$ 45 mm Hg treated with NIV or IMV	none	PSG 3 mo after discharge	54%	14 of 16 (88%)
Ouanes-Besbes et al,[49] 2021	Tunisia, 2015–2018	pH < 7.35 and $Paco_2$ > 45 mm Hg	Previously diagnosed OSA.	HSAT 3 wk after discharge	24%	104+ of 164 (63%); 34 not tested (STOP-BANG < 3 points, indicating low risk)
Gursel et al,[52] 2015	Turkey, not reported.	Hypercapnia treated with NIV	None	Respiratory Polygraph during ICU	0%	20 of 31 (64%), hypopneas not assessed.

Abbreviations: DNI, do not intubate advanced directive; HSAT, home sleep apnea testing; IMV, invasive mechanical ventilation; Mod-Severe obstructive sleep apnea (OSA), apnea-hypopnea index over 15 events/hour; NIV, Non-Invasive Ventilation; $Paco_2$, arterial gas tension of CO_2; PSG, polysomnogram; STOP-BANG (Snoring, Tiredness, Observed Apneas, high blood Pressure, BMI over 35 kg/m2, Age over 50 years, Neck cirumfrence over 40cm, male Gender), risk stratification score for OSA.[112]

severe OSA), a more likely explanation is that OSA at least contributes to the development of hypercapnia in many more cases than are commonly recognized in practice or coded in documentation.

While it is common to document the "single cause" of hypercapnic respiratory failure, as encouraged by device-qualification practices (which often require the absence of other contributors in the United States, thus dissuading searching for and documenting their presence[44]), there is both physiologic and epidemiologic evidence that multiple conditions often contribute to the occurrence of hypercapnia. Physiologically, the model of CO_2 loading during apneas (see **Fig. 2**) predicts that limitations on the ability to increase interapnea ventilation will lead to the early development of hypercapnia.[24] This is corroborated empirically, as hypercapnia develops in patients with OSA-COPD overlap syndrome with milder obstruction than in the pure COPD case and milder obesity.[55] In the 3 prospective ICU cohorts, very high rates of multiple contributors were noted. Adler and colleagues found that 36% of their cohort had COPD and OSA, 61% had OSA and congestive heart failure (CHF), and 54% had CHF and COPD.[51]

In summary, the available evidence on ICU patients treated for hypercapnic respiratory failure suggests a very high rate of undiagnosed sleep apnea that is often not recorded as a contributor to hypercapnic respiratory failure. The prospective ascertainment of comorbidity status is a notable strength of these studies, though low follow-up rates for sleep studies limit the strength of conclusions.

Emergency Department and Inpatient Ward

Several studies have investigated hypercapnic respiratory failure in hospitalized and emergency room patients, mostly relying on retrospective health record data (**Table 2**).

Chung and colleagues leveraged data from a single hospital serving a defined population in Liverpool, Australia, to publish several informative studies.[1,47,56] They included patients with a measured arterial $Paco_2$ over 45 mm Hg within 24 hours of hospital presentation, after excluding iatrogenic causes, from 2013 to 2017. By standardizing the rate of hypercapnia to the region's demographics, they estimated the yearly period prevalence of hypercapnia in acute care settings to be 163 per 100,000 person-years, and the prevalence roughly doubling with each decade of age above 50[1].

Next, they investigated conditions that may have led to the development of hypercapnia. In the cohort, obstructive lung disease codes were the most common diagnostic code (n = 389, 44.6%), followed by CHF (n = 278, 31.8%).[56] In contrast to other studies, only 6.0% (n = 52) had a SDB diagnosis code, and only 13% had diagnostic codes for multiple contributing conditions.

They then selected a subset of patients with hypercapnia (cases) and a matched sample of patients in the community (controls) to determine which diseases occurred in excess among people with hypercapnic respiratory failure.[47] Among the subsample, 43% of patients with hypercapnia (vs 12% of controls) reported they had OSA. However, home sleep apnea tests found moderate-severe OSA at equivalent rates between cases and controls (28% cases, 34% controls). Response rates with follow-up testing were very low in both cases and controls (roughly 1 in 10), reinforcing the difficulty of establishing the diagnosis of OSA once patients are discharged from the hospital.

Comparatively little is known about the epidemiology of sleep-breathing disorders among hospitalized patients.[57,58] Several groups have attempted to estimate the prevalence of OSA among general inpatients, and compare it with the prevalence of OSA in those patients with hypercapnia. Using a screening program based on STOP-BANG (the presence of five or more of the following criteria: snoring, tiredness, observed apneas, high blood pressure, BMI over 35 kg/m2, age over 50 years, neck circumfrence over 40cm, and male gender; which is validated to predict a high risk of OSA) and high-resolution pulse oximetry, the estimated prevalence of sleep apnea among patients with obesity was 19.7% at a single center.[59] Higher rates (48%) are seen in patients with cardiovascular disease.[60] Among the subset of hospitalized patients referred for inpatient sleep testing, Johnson and colleagues[61] found that patients usually had either nocturnal or diurnal hypoventilation (65% of 326 patients) on inpatient polysomnogram with CO_2 monitoring. Patients also had high rates of sleep apnea (17% mild, 21% moderate, and 56% severe), OHS (59%, operationally defined as other factors not *entirely* explaining the hypoventilation), and other comorbidities (68% had CHF and 35% had COPD).

Several other studies show similar distributions of comorbidities as assessed by diagnostic codes. Rates of recognized OSA vary from 10% to 25%, with either COPD[2,3,62,63] or CHF[5] being the most common comorbidity. The frequency of obesity ranges from a mean BMI of 36.4 kg/m^2 (Meservey and colleagues[4]) to a median of 25.8 kg/m^2 (Cavalot and colleagues[2]) and age

Table 2
Prevalence of obstructive sleep apnea among patients presenting to the emergency room or admitted to the hospital with hypercapnic respiratory failure

Author	Year/Location	Enrollment Criteria	Exclusion Criteria	Method of Assessment	Loss to Follow-up	Prevalence of OSA
Prospective, arterial blood gas assessment in all patients, but no structured OSA assessment						
Nowbar et al,[8] 2004	USA, before 2004 (not stated)	Arterial blood gas $Paco_2$ > 2 SD above norm (elevation-adjusted).	Severe obstruction (FEV1/FVC < 0.5); lung resection	Inferred from lack of other identified causes	Not Applicable	31%
Retrospective, all patients received polysomnography						
Johnson et al,[61]	USA 2015–2018	Inpatient PSG ordered, $Paco_2$ > 45 mm Hg or $TcCO_2/EtCO_2$ > 50 mm Hg for 10+ minutes	No titration study performed	Inpatient PSG	None	65%[a]
Prospective with structured comorbidity ascertainment						
Chung et al,[47] 2023	Australia 2013–2017	$Paco_2$ over 45 mm Hg	Iatrogenic causes, trauma, post-arrest.	HSAT (case-control study)[b]	90%	28% in cases (vs 34% in controls)
Retrospective Studies						
Chung et al,[1] 2022; Chung et al,[56] 2022	Australia 2013–2017	$Paco_2$ over 45 mm Hg	Iatrogenic causes, trauma, post-arrest.	Diagnosis code	Not Applicable	6%
Cavalot et al,[2] 2021	Canada 2017	ABG: CO_2 > 45 mm Hg & pH < 7.35 or VBG: CO_2 > 50 mm Hg & pH < 7.34	Cystic fibrosis, neuromuscular disease, ILD, lung cancer, drug overdose, or tracheostomy.	Diagnosis code	Not Applicable	19.3%
Meservey et al,[4] 2020	USA 2016	Diagnostic Code for Hypercapnic Respiratory Failure	Advanced cancer, trauma, stroke, seizure, cardiac arrest, advanced neurologic disease, serious non-pulmonary illness.	Chart review	Not Applicable	24%

Vonderbank et al,[3] 2020	Germany 2015–2016	Arterialized capillary blood gas CO_2 > 45 mm Hg	None	Health record review	Not Applicable	10.8%
Wilson et al.[5] 2021	USA 2018	$Paco_2$ > 50 mm Hg and pH > 7.35	Admitted at psychiatric or inpatient rehabilitation hospitals.	EMR problem list	Not Applicable	22.4%
Domaradzki et al,[63] 2018	USA 2009–2015	Diagnostic code for chronic obstructive pulmonary disease (COPD) or respiratory failure & VBG	tracheostomy	Home CPAP (or BPAP)	Not Applicable	10% (and 5%)
Bülbül et al,[62]	Turkey 2009–2010	Initial and follow-up (stable) $Paco_2$ > 45 mm Hg	Acute hypercapnia	Inferred from lack of other identified causes	Not Applicable	25%
Fox et al,[95] 2022	Israel 2012–2017	Referral for NIV on discharge	Death during admission	Chart Review	Not Applicable	5%
Calvo et al,[96] 2012	Spain 2008–2009	$Paco_2$ over 45 mm Hg and pH < 7.35	None	Chart Review	Not Applicable	6%
Brandão et al,[97] 2016	Portugal 2012–2013	NIV use outside an ICU (90% Hypercapnic)	Elective admissions	Chart Review	Not Applicable	23%

Abbreviations: ABG, arterial blood gas; VBG, peripheral venous blood gas; ILD, interstitial lung disease; SD, standard deviation, FEV1/FVC: forced expiratory volume in 1s over forced vital capacity; EMR, electronic medical record; CPAP, constant positive airway pressure; BPAP, bilevel positive airway pressure.

[a] Only patients referred for inpatient sleep testing included.

[b] Cases come from the hospital, but controls are taken from the general population.

from the mean of 60.5 years in (Wilson and colleagues)[5] to median age of 70 years (Domardzki and colleagues[63]). All studies have shown high rates of death (1-year mortality of roughly 30% in Wilson and colleagues,[5] 25% in Vonderbank and colleagues[3]) and re-presentation to the hospital (23% were readmitted within 30 days, usually for recurrent hypercapnic respiratory failure[4]; 66% within 1 year[2]).

The unreliability of diagnostic codes is a significant challenge for this literature because many respiratory conditions are not diagnosed, and many are misdiagnosed, particularly in obese patients.[64–66] This makes it challenging to disentangle the influence of these conditions on each other, the rates of (mis) diagnosis, and the likelihood of hypercapnia.[67] In addition, the definition of OHS—hypercapnic respiratory failure occurring in the context of SDB and *in the absence of other contributing conditions*[26]—is particularly challenging to apply in health record-based epidemiologic research because OHS is underrecognized[8,66] and one cannot infer which contributing conditions have been considered and excluded, particularly in the presence of missing data.

Despite these limitations, several patterns emerge. First, hypercapnia is common in acute care settings, is associated with substantial morbidity, and often occurs in the context of multiple potentially contributing diagnoses, including OSA. Data on the excess rate of OSA among patients with hypercapnia are conflicting and vary substantially based on the method used for ascertaining OSA.

OUTPATIENTS

Determining the contribution of SDB to outpatient hypercapnic respiratory failure is particularly challenging because neither elevated arterial CO_2 levels nor sleep breathing abnormalities are reliably assessed in the outpatient population. One approach to investigating the community-dwelling population with hypercapnic respiratory failure is to evaluate the patients who receive home NIV. However, only a subset of patients receiving home NIV have hypercapnic respiratory failure, given that NIV is started before overt respiratory failure for conditions such as neuromuscular disease. Conversely, not all patients with hypercapnic respiratory failure qualify for, or obtain, home NIV.

Twenty-two identified studies evaluated the composition of patients enrolled in home mechanical ventilation programs and commented on OSA or the prevalence of related comorbidities (**Table 3**). The estimated population prevalence of hypercapnia presenting to the hospital by Chung and colleagues (163 per 100,000)[1] is between 3 and 100 times higher than estimates of the prevalence of patients in domiciliary home ventilation programs (1–47 per 100,000[68]). It is reported that 25% to 50% of patients in home mechanical ventilation programs are enrolled after a hospitalization for acute (on chronic) respiratory failure.[69–72]

Mirroring the ICU and inpatient literature, studies with universal assessment of sleep breathing when home NIV is initiated generally show that most patients have OSA,[73,74] while studies relying on clinician documentation of the "primary cause" of hypercapnia result in much lower estimates. Several cohorts listed NMD, COPD, and OHS as the most common indications for non-invasive ventilation.

Longitudinal studies report an overall increase in the prevalence of patients receiving home mechanical ventilation over the past several decades and also an increase in the proportion of those patients who have OHS .[70,75,76] Demographic and comorbidity data suggest that OSA likely contributes to many more patients with hypercapnic respiratory failure than is documented. For example, the patients who are labeled as having "COPD" as their primary cause for home ventilation in these cohorts tend to have much higher BMI (generally, above 30 kg/m^2) and less severe airflow limitation on spirometry obstruction compared to the cohorts of patients with hypercapnia and COPD when OSA was excluded. For example, in the trials of home ventilation by Kohnlein and colleagues and in the subset of patients with hypercapnia in the National Emphysema Treatment (NETT) trial of lung volume reduction the mean BMI of included patients was 24 to 25 kg/m^2.[34,77,78] This pattern would be expected if many of these patients have an overlap syndrome, which results in hypercapnia at milder obstruction.[79]

Even among patients with neuromuscular disease, sleep apnea may contribute to the earlier occurrence of respiratory failure. Boentert and colleagues[41] showed that OSA was present in 45.6% of the patients with amyotrophic lateral sclerosis (ALS) before they developed an indication for NIV, and patients with OSA had 1.9 times higher odds of having nocturnal hypoventilation, which is known to predict the subsequent development of daytime hypoventilation.[23] Duchenne muscular dystrophy is another condition where OSA is highly prevalent early in the course of the disease but progresses to nocturnal hypoventilation and ultimately hypercapnic respiratory failure.[80,81] Lastly,

Table 3
Constitution of home non-invasive ventilation programs

Author	Location Year	Enrollment Criteria	Exclusion Criteria	Method of Assessment	Most Common Cause	Prevalence of OSA
Cohorts on Home NIV; Polysomnography Performed						
Poh Tan et al,[74] 2018	AUS, 2005–2010	Records review of a clinic, sole provider of services to their region.	Home mechanical or non-invasive prescribed	Routine PSG performed at NIV initiation.	neuromuscular disease (NMD)	15% 240 with obesity hypoventilation syndrome (OHS) as reason for Vent; but OSA present in most patients of all other classifications.
Patout et al,[73] 2020	UK and France, 2008–2014	Established via inpatient study at 2 centers (London and Rouen	CPAP, ASV, tracheostomy	Patients received inpatient titration studies at initiation	OHS	29.5% of 1746 with OHS. 12.7% with Overlap Syndrome. 10.5% with OSA (non-OHS) listed as a cause.
Cohorts on Home NIV; provider determination of cause or survey						
Cantero et al,[70] 2020	2016–2018, Switzerland	Receipt of Home NIV—which generally though not always requires hypercapnia. (all regional providers)	Adaptive servo ventilation, tracheostomy	Clinical determination of pulmonologist	COPD	26% OHS 11% COPD-Overlap 4% with OSA as part of 'other' SDB
Budweiser et al,[98] 2007	2002–2004 Germany	Home NIV for 3 or more months (single center)	None reported	Clinician diagnosis	COPD	30% of 231 with OHS or OVS
Neill et al,[76] 2022; Garner et al,[99] 2013	2018 New Zealand	Receipt of Home NIV (country-wide)	None reported	Clinician diagnosis	OHS	47.3% of 1188 with OHS additional 23% with Overlap Syndrome

(*continued on next page*)

Table 3
(*continued*)

Author	Location Year	Enrollment Criteria	Exclusion Criteria	Method of Assessment	Most Common Cause	Prevalence of OSA
Hannan et al,[100] 2016	2013, Australia	Provision of Home NIV	Non-English speaking, survey nonresponse (43.4%)	Patient self-report	NMD	31% with OHS
Hannan et al,[100] 2016	2013, Canada	Provision of Home NIV	Non-English speaking, survey nonresponse (43.4%)	Patient self-report	NMD	8.1% with OHS
Rose et al,[101] 2015	Canada, 2012–2013	Ventilation provision (Service providers identified prescribers, then surveyed)	None	Provider determination	NMD	14% with OHS
Maquillon et al,[102] 2021	Chile, 2008–2017	Admission for inpatient initiation of NIV (Nationwide)	Smoking, drug use, lack of power or resources at home.	Provider determination	COPD	23.9% with OHS
Schwarz et al,[103] 2005	UK, 2008–2018	Death while enrolled in a large weaning and HMV service; $Paco_2$ > 45 mm Hg	Still alive (roughly half of enrolled patients)	Provider determination	NMD	17% with OHS 4% with Overlap Syndrome
Lloyd-Owen et al,[68]	16 European countries, 2002	Survey estimates of NIV or IMV for 3+ months delivered at home.	Negative pressure vent, phrenic stim, positional therapies.	Provider determination.	COPD	<31% OHS (lumped with "chest wall restriction")
Laub and Midgren[71] 2007	Sweden, 1995–2005	National register of patient receiving Home Ventilation	None	Diagnosis provided to register	OHS	28% of 422 OHS

Nasilowsky et al,[104] 2015	Poland, 2000–2010	Treated at an Experienced HMV program	None	Provider determination; survey	NMD	11% with hypoventilation syndromes[a]
Valko et al,[105] 2018	Hungary, 2018	Survey to centers providing HMV	None	Provider determination; survey	OHS	60% with hypoventilation syndromes[a]
Windisch et al[106] 2003	Germany, prior to 2003	4 hospitals, established in HMV clinic	First visit with HMV clinic, acute decompensation, tracheostomy	Provider determination	COPD	5.3% OHS of 226
Biggelaar et al,[107] 2022	Netherlands 1991–2020	4 centers that provision home NIV	None	Diagnosis provided to register	NMD	~15% 'Sleep Disorders' indication.
Cohorts on Home NIV; Documentation of Comorbidity present						
Jimenez, Akrivo, et al,[108] 2023	Mich. USA, 2012–2021	$Paco_2$/$PtCO_2$ 45+mm Hg and pH over 7.35;	Tracheostomy, not on NIV at first visit.	Diagnostic Codes	NMD	14% of 48 OHS
Povitz et al,[72] 2017	Canada 2000–2012.	Request for NIV or IMV equipment from provincial administrative data	Private acquisition of supplies; long-term care facility residents	Diagnostic codes;	NMD	15.9% 'Obesity' (OSA and OHS not directly assessed)
Borel et al,[69] 2013	France 2003–2008	Initiation of NIV at one of five facilities; obesity is the main explanation of NIV.	Neuromuscular disorder, severe pulmonary fibrosis, FEV1/VC < 30%	Chart review	OHS	67% of 107 OHS
Tissot et al.[109] 2015	France 2009–2014	Referral for NIV (3 hospitals)	Death or loss to follow-up within 6 mo	Patient survey	OHS	42% of 264 OHS
Poh Tan et al,(b)[110] 2019	Singapore, 2009–2015	Single center HMV service	None	Chart Review	NMD (ALS)	2% of 112 with OSA listed as contributor
Rentala et al,[111] 2021	Finland, 2012–2015	Referral for home NIV	None	Chart Review	OHS	47.3% OHS 57.1% OSA as contributor

$PtCO_2$, transcutaneous partial pressure of CO_2; ASV, Adaptive Servo-Ventilation; HMV, home mechanical ventilation; SDB, sleep-disordered breathing.

[a] Includes obesity hypoventilation, congenital central hypoventilation syndrome, and central apneas.

extremely high rates of SDB (above 60%[82]) and nocturnal hypoventilation (30%[83,84]) are seen in patients with spinal cord injuries, where PAP treatment has been shown to improve respiratory events and autonomic symptoms.[85] While the complex respiratory control abnormalities[86] and simultaneous onset SDB and muscle weakness hamper the ability to isolate the contribution of OSA, both the epidemiologic and physiologic evidence support the role of OSA in accelerating the development of hypercapnia in patients with spinal cord injury. However, under recognition of SDB likely results from challenges accessing traditional sleep lab testing due to complex care needs of patients with neuromuscular disease.[87] Innovative management pathways may facilitate early recognition of patients with nocturnal hypoventilation,[88] who are difficult to identify with clinical criteria[83] and have been shown to benefit from NIV in randomized trials.[89]

In summary, though significant limitations exist with applying the data from home-mechanical ventilation to the question of OSA's contribution to hypercapnia in outpatients, the available data suggest that OSA is frequently present in patients who providers have not labeled as having OHS as their primary indication. Furthermore, both the prevalence of domiciliary ventilation and the diagnosis of OHS are increasing, likely as a result of the increasing prevalence of obesity.[90]

SUMMARY

A burgeoning literature describing the epidemiology of hypercapnic respiratory failure has developed over the last 2 decades. Sleep apnea is prevalent among patients recognized to have hypercapnia in a variety of settings but is often not diagnosed. Both physiologic understanding and epidemiologic evidence support that OSA is a contributing cause in many cases, though better ascertainment of potentially contributing conditions would improve the strength of evidence. Additionally, hypercapnic respiratory failure is common (167 per 100,000 persons in Chung and colleagues,[1] which, for frame of reference, is roughly as common as decompensated cirrhosis[91]), occurs in patients with multiple morbidities,[92] and is associated with high health care expenditure,[93] morbidity, and mortality. As sleep apnea is treatable and likely contributes to the occurrence of hypercapnic respiratory failure with consequent increases in health care burden, determining the exact contribution of OSA and the effectiveness of improved identification or management of OSA in this population should be a public health priority.

CLINICS CARE POINTS

- Hypercapnic respiratory failure is common, becoming more prevalent, and sleep apnea contributes to its development.
- Sleep apnea is found in most patients with hypercapnic respiratory failure if sleep testing is sought, though far fewer are recognized to have OSA during routine clinical care.
- Patients who have OSA and other causes of hypercapnia tend to develop hypercapnia at a milder stage of the disease, suggesting OSA contributes to its occurrence.
- While the current documentation requirements and the existing evidence base encourage categorizing patients as having a single cause, recognizing that many patients with hypercapnic respiratory failure have multiple contributing comorbidities may allow more patients to receive beneficial treatments.
- Significant loss to follow-up is seen in all studies when patients identified in acute settings are recommended to return for sleep testing after discharge, suggesting that approaches to encourage higher follow-up rates or more immediate testing are needed for clinical care and research.

DISCLOSURE

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