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Enlarging bullae and spontaneous pneumothorax associated with CPAP use: A case series of three patients

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Abstract

Objectives
Spontaneous pneumothorax among patients with obstructive sleep apnea treated by nocturnal continuous positive airway pressure (CPAP) has not been well documented.
Methods
We present three cases of patients on chronic CPAP who experienced spontaneous pneumothorax without clear predisposing factors. Their personal and family medical histories, imaging characteristics, and CPAP settings are reviewed.
Results
In all three cases, the patients had bullae ipsilateral to the pneumothoraces that either formed (n = 1) or grew significantly (n = 2) after CPAP initiation. No other risk factors for pneumothorax or bullae were identified.
Conclusions
This case series demonstrates a need for further investigation into a possible connection between spontaneous pneumothorax, bullae development, and CPAP use.

Keywords: obstructive sleep apnea, continuous positive airway pressure, bullae, complications of noninvasive mechanical ventilation, spontaneous pneumothorax

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Current Knowledge: Few reports of spontaneous pneumothorax or bullae formation in association with nocturnal CPAP use for obstructive sleep apnea are reported. Given the high prevalence of obstructive sleep apnea and the efficacy of continuous positive airway pressure in treating this disorder, it is important to identify any possible adverse impacts of this therapy.

Study Impact: This is the first case series of patients with obstructive sleep apnea who developed spontaneous pneumothorax, which is associated with new or enlarged bullae after being placed on nocturnal continuous positive airway pressure. This highlights the need for additional studies to identify the relationship between noninvasive positive airway pressure and bullae formation.

Introduction

Spontaneous pneumothorax among patients with obstructive sleep apnea (OSA) treated by continuous positive airway pressure (CPAP) has not been well documented. The following case series describes three patients with OSA treated by CPAP who developed enlarging bullae followed by spontaneous pneumothorax. Bullae are air-containing spaces within lung parenchyma, of 1 cm or greater in diameter, that arise distal to the terminal bronchioles and are confined by connective tissue septa. The pathophysiology of bullae development or pneumothorax from positive airway pressure and the difference between bullae and blebs will be reviewed in this manuscript. In describing these cases, we aim to elucidate any risk factors that would identify other patients on CPAP who may be at risk for pneumothorax, and thereby develop better management strategies. The terms CPAP and auto CPAP are used interchangeably in this report. Auto CPAP refers to a CPAP unit that adjusts the delivered pressure within a preset range based on the CPAP unit's detection of resistance or obstruction to air flow. All of the patients were on Auto CPAP with a relatively narrow range of pressures specified below. Obstructive sleep apnea is a common disorder in the United States, with a prevalence of approximately 20% for at least mild cases and 10% for moderate to severe cases. [1] CPAP is the cornerstone for therapeutic intervention. It is thus essential to identify any potential adverse associations.

Report of cases

Case 1

A 63-year-old man with a past medical history of hypertension, obesity, gastroesophageal reflux disease (GERD), paroxysmal atrial fibrillation, and OSA treated with CPAP for 11 years returned for his annual follow-up for sleep apnea. His CPAP settings at the time of presentation are listed in Table 1. He reported a two-day history of feeling unable to take a deep breath. Five days prior to the presentation, he had returned from an international trip on a standard 11-hour commercial airline flight. He did not notice symptoms on the plane, and he did ambulate during the flight. There was no history of recent chest trauma. The night his symptoms started, he took off his CPAP and went back to sleep. The next day, he still felt slightly short of breath but could do his usual workout with his trainer. Tilting his head back made him cough slightly. He also had a vague sensation of something moving in the right side of his chest. The patient was in no distress, his vital signs were stable, and his exam was unremarkable.

The patient was assessed by chest radiograph and by chest computed tomography (CT) scan, which revealed a bulla in the right middle lobe and a moderate-sized right-sided pneumothorax (Fig 1C-D). The patient chose watchful waiting over the next week and did not restart CPAP. The pneumothorax decreased in size but did not completely resolve. He was then referred to thoracic surgery, and the right middle lobe bulla was resected without complication. The patient restarted CPAP several months later without recurrence of pneumothorax during the subsequent five years of follow-up.

The patient had no occupational exposure, family history of lung disease, or personal history of recurrent cough, wheezing, or respiratory illness. He had a 15-pack-year smoking history and had quit 30 years before presentation. The chest CT scan, taken before the initiation of CPAP 11 years before the event, did reveal a small right middle lobe bulla (Fig 1A). An abdominal CT 2 months before presentation revealed a slight increase in the size of the bulla (Fig 1B).

Case 2

A 64-year-old man with a past medical history of gastrointestinal (GI) bleeds, GERD treated with Nissen fundoplication, melanoma, and OSA treated with CPAP for six years (settings at the time of presentation included in Table 1), presented to the emergency department (ED) after having woken from sleep with severe pleuritic chest pain and shortness of breath. He had been in his usual state of health with no preceding symptoms of cough, wheezing, dyspnea, chest pain, or illness. In the ED, the patient was found to have a tension pneumothorax (Fig 2B-D). A chest tube was placed to wall suction, and the pneumothorax resolved over two days. The chest tube was changed to a water seal, and the patient restarted CPAP at 16-18 cmH_20 but had a recurrence of a small pneumothorax. The chest tube was then placed back to suction, and the pneumothorax resolved. The patient briefly retried CPAP at 10 cmH_20 while awake in the hospital with the chest tube to water seal without recurrence of the pneumothorax. The chest tube was pulled; his subsequent chest CT revealed multiple right lower lobe bullae without recurrent pneumothorax (Fig 2E-F). The patient was instructed to remain off CPAP for a month during which time the pneumothorax did not recur. He started treatment for OSA with an oral appliance and stopped using CPAP.

The patient had no known pulmonary disease. He had a 12-pack-year smoking history and had quit 30 years before admission. The patient had no preceding cough, wheeze, or dyspnea on exertion

before the event. Although he did typically lift heavy boxes at work at a supermarket, he had done no unusual lifting or activity prior to admission. Approximately 17 years before this event, he had worked as a welder and machinist for 26 years, cutting metals and shaping “mild steel” or “cold roll”. He also worked with cast iron, stainless steel, and aluminum and believes there may have been minor asbestos exposure. His alpha-1-antitrypsin level was within normal limits. There was no family history of lung or liver disease.

On review of prior imaging, pulmonary nodules had been noted on an abdominal CT taken ten years prior to presentation for a GI bleed (Fig 2A). The nodules were followed for four years and remained stable. Those CTs did not reveal bullae in the lung bases at that time.

Case 3

A 67-year-old woman with obesity, hypertension, gallstone-related pancreatitis, fibromyalgia, seronegative rheumatoid arthritis, allergic rhinitis, and moderate OSA (apnea-hypopnea index (AHI) of 21 events per hour) on auto CPAP for 11 years returned to our sleep clinic for annual follow-up. Although she was a non-smoker, she had significant second-hand smoke exposure as a child and during ten years of adulthood. She worked in an office setting and had no history of occupational exposure. Her initial CPAP settings of 13-15 cmH_20 were decreased to 10-14 cmH_20 five years prior to presentation because of pressure intolerance following weight loss, mask leak, and recurrent sinusitis. She had intermittent flares of rhinitis and sinus headaches despite heated humidification, and regular use of intranasal fluticasone, montelukast. She also took sublingual immunotherapy.

Four years before the annual follow up, the patient had presented to her PCP with dyspnea on exertion and was found to have an elevated D-dimer. She was referred to the ED where a chest CT (Fig 3B-C) revealed a large right mid-lung field bulla that had grown significantly based on comparison to a chest CT taken 13 years prior, which had shown a small right middle lobe bulla (Fig 3A). Her CPAP pressure was lowered again to 6-10 cmH_20 due to ongoing pressure intolerance, mask leak, and concern about the enlarging bullae noted on a CT scan. Her auto CPAP settings at the time of presentation are shown in Table 1.

At her annual follow-up visit, the patient used CPAP consistently, but her sleep was fragmented by chronic back, neck, and joint pain for which she was doing physical therapy. She had occasional non-exertional chest tightness with her chronic musculoskeletal pain and occasional palpitations but no dyspnea, cough, wheezing, or pleuritic pain at that time.
She presented to the ED of a separate institution six months after that last annual visit for unrelated symptoms of spinal cord compression with bilateral arm and leg pain, weakness, and difficulty walking. Her ED chest radiograph revealed a pneumothorax. Her lung ultrasound revealed loss of lung sliding, and a chest tube was placed. She subsequently had pleurodesis for incomplete resolution of the pneumothorax with the chest tube. She later underwent posterior decompression and fusion of the 2nd through 5th cervical vertebrae. She resumed CPAP with the previous setting of 6-10 cmH_2O and had no further recurrence of pneumothorax.

Table 1: Summary of Patient Characteristics. AHI: apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; CT: computed tomography; PTX: pneumothorax; SpO_2: oxygen saturation

	Case 1	Case 2	Case 3
Age	63	64	67
BMI (kg/m^2)	33.3	26.3	38.1
Height (cm)	180	175	164
Tobacco Use	Prior Smoker (15 pack-year history, quit 30 years prior)	Prior Smoker (12 pack-year history, quit 30 years prior)	Secondhand Smoke Exposure (as a child and 10 years of adulthood)
Baseline AHI	13 (on a split study)	9 (74 in supine REM sleep)	21
Baseline Nadir SpO_2	89%	82%	59%
Median/95%/Max CPAP Pressure Prior to PTX (cm H_2O)	11.9/13.6/14.6	16/16.5/16.9	9.1/9.7/9.8
Years on CPAP	11	6	11
Bulla Site	Right middle lobe	Right lower lobe	Right middle lobe
Bullae on CT Prior to Initiation of CPAP	Yes (11 years prior to presentation) with subsequent growth after CPAP initiation (CT 2 months prior to presentation)	None in lung bases (prior abdominal CT)	Yes (13 years prior, with subsequent growth on CT 4 years prior)
Risk Factors	International flight (3 days prior to symptom onset)	Lifting heavy boxes	None

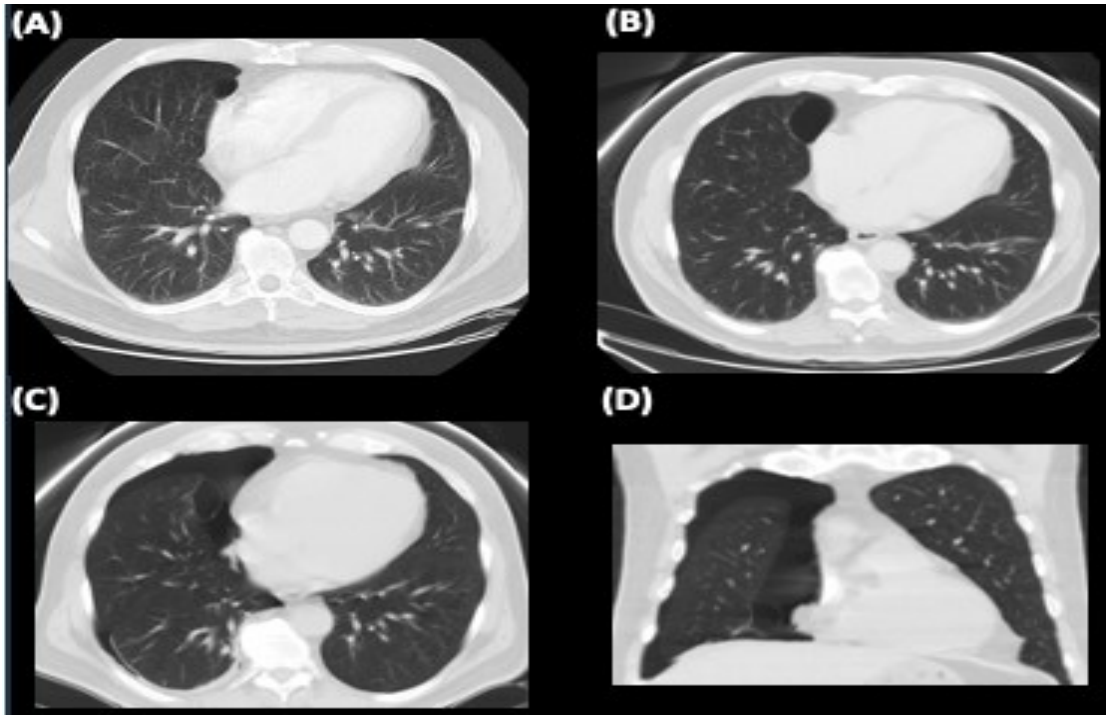

Figure 1: Case one. (A) Chest CT taken 11 years prior to presentation showing right middle-lobe bulla. (B) Chest CT Scan 2 months prior to presentation for an unrelated reason. Note the interval growth of the bulla from Fig 1A. (C-D) Chest CT was obtained at presentation with axial (C) and sagittal (D) images showing the bulla and right-sided pneumothorax.

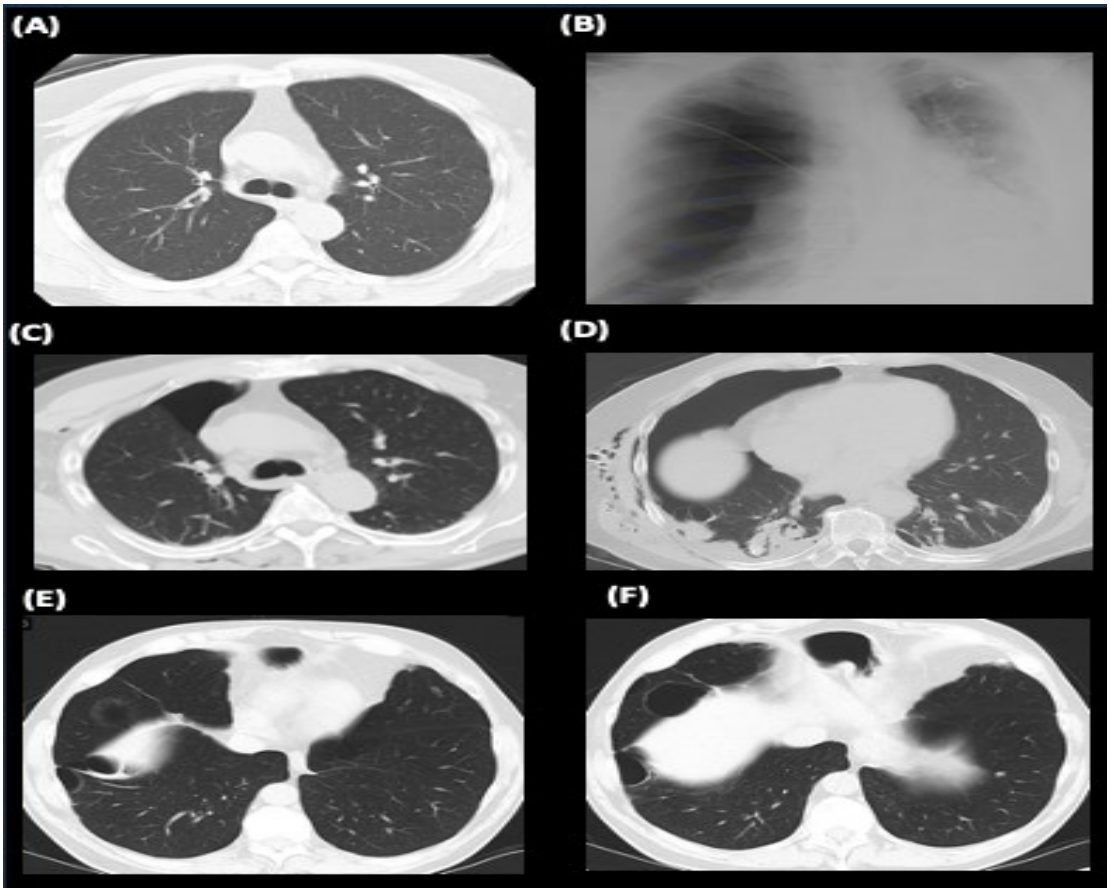

Figure 2: Case two. (A) Chest CT taken six years prior to presentation for pulmonary nodule follow-up. No bullae were visible at the time. (B) Chest radiograph taken at admission showing the right-sided pneumothorax. (C-D) Chest CT taken at admission showing pneumothorax with bulla visible in the right lower lobe in (D). (E-F) Follow-up chest CT images taken two months after initial presentation showing multiple right lower lobe bullae.

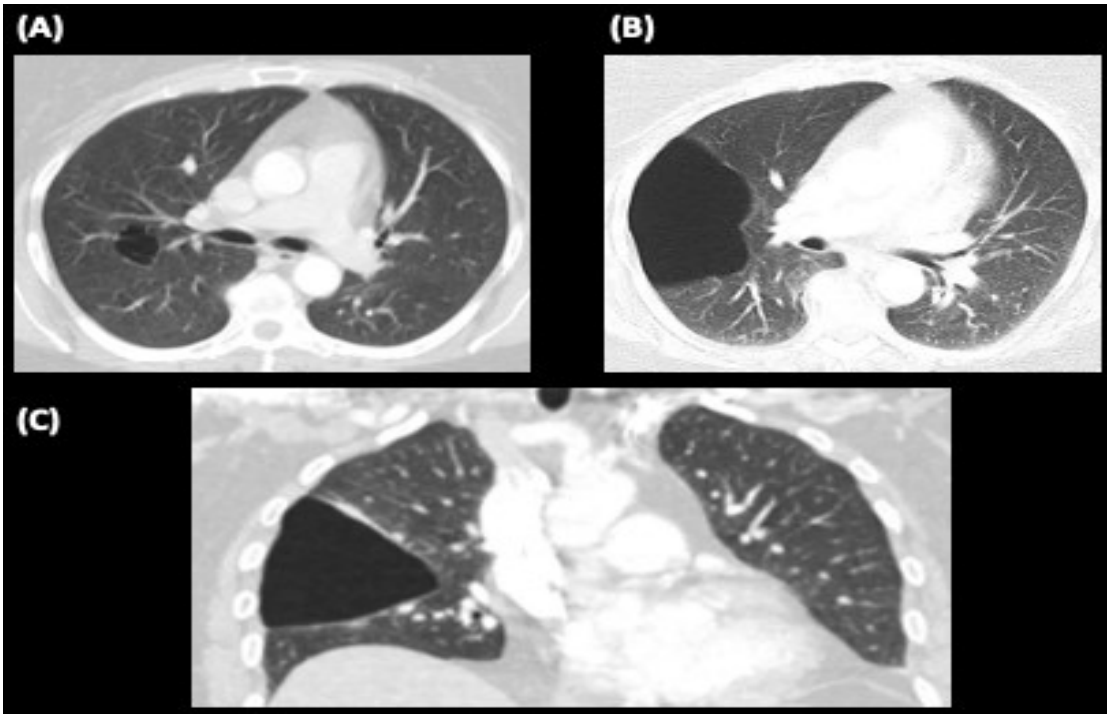

Figure 3: Case threw. (A) Chest CT image taken 13 years prior to presentation showing a small right middle lobe bulla. (B) Transverse and (C) sagittal chest CT images taken 4 years prior to presentation showing significant interval growth of the bullae.

Discussion

Bullae are located within the lung parenchyma. As noted above, these air-containing spaces arise distal to the terminal bronchioles and are confined by connective tissue septa. They are distinct from blebs, found between the inner and outer elastic layers of visceral pleura, and lung cysts, which are epithelial-lined cavities. [2] Bullae are commonly associated with emphysema, connective tissue disorders, and pulmonary fibrosis but have been documented in various other clinical settings, including COVID-19 pneumonia, intravenous drug users, and marijuana smokers. [3–5] There is also a “vanishing lung syndrome” in which bullae rapidly replace normal lung parenchyma. [2]

The pathogenesis and natural history of bullae are not precisely understood. There are likely multiple processes that contribute to bullae, given the broad range of settings in which bullae develop and the clustering of bullae characteristics by causal factors (i.e., bullae associated with intravenous drug use are typically found in the upper lobes while those associated with alpha-1 antitrypsin deficiency are typically found in the lower lobes). [4,6] The time course of bulla evolution appears highly variable with multiple reports of bullae developing over days while in other cases, bullae remain stable for years or resolve spontaneously. [3,7–9]

There are multiple proposed mechanisms of bullae formation. In emphysema, bullae may result from the same connective tissue-destroying processes associated with the development of emphysema. In lung fibrosis, the scarred portion of the lung may become relatively fixed, and the resulting increased traction on surrounding lung parenchyma may lead to over-distention of those areas during inspiration. In marijuana smokers, the repeated Valsalva maneuvers characteristic of this type of smoking in the presence of pro-inflammatory high-temperature inhaled particles are hypothesized to contribute to bullae development. [5] In tall, thin patients, the increased traction on the apices of upper lobes resulting from the mechanical constraints of narrow anterior-posterior diameter chests may explain the higher prevalence of apical upper lobe bullae typically found in young men. [10] In intravenous drug users, coalescence of cavities produced by foreign body emboli within the pulmonary capillary bed may result in bullae.4 In patients undergoing lobectomies, tension along the staple line has been proposed to affect the likelihood of post-operative bullae formation. [11] A check-valve mechanism, in which a contained parenchymal air leak dissects pleura and connective tissue, has also been proposed. [7]

Whether long-term positive airway pressure for obstructive sleep apnea leads to bullae neogenesis or evolution is unclear. There is a report in which a 68-year-old patient on CPAP for many years for OSA presented with spontaneous pneumothorax and basal bullous emphysema. [12] Another report described recurrent pneumothorax after five years of NPPV, along with blebs that had not previously been identified on prior chest radiograph (no CT was available). [13] It is possible that barotrauma from high pressures could lead to bulla neogenesis, although set auto CPAP pressures are typically lower than levels suspected to cause barotrauma. As CPAP is known to cause regional hyperinflation in patients with chronic obstructive pulmonary disease (COPD), it is reasonable to

hypothesize that once bullae exist, positive airway pressures could hyperinflate the bullae further and thereby accelerate their growth. [14]

It is also possible that OSA itself could contribute to the development of bullae independent of NPPV. In Tulek et al.'s case report of bullous disease-associated pneumothorax as the initial presentation of OSA, the authors hypothesized that OSA may have contributed to bullae formation through barotrauma associated with increased negative inspiratory pressures during upper airway closure. [15]

Even in the absence of bullae or blebs, pneumothorax is a known but rare complication of CPAP and other forms of non-invasive positive pressure ventilation (NPPV). [16–18] Five cases of pneumothorax related to NPPV for OSA were recently summarized by Rajdev et al. [19] The duration of NPPV exposure prior to the pneumothoraces in these reports ranged from hours to years. [20]

Although it is possible that the bullae were not related to the pneumothoraces observed in our patients, the co-location of the bullae and pneumothorax in the same lung suggests there may be an association between these entities. Common risk factors for primary spontaneous pneumothorax include tobacco smoking, a tall and thin physique, and male gender. Risk factors for secondary spontaneous pneumothorax include COPD, HIV, lung malignancy, and concurrent lung infections. [21,22] Although two out of three cases had remote smoking histories, there were no known symptoms of COPD among these patients. There was no prior history of lung disease or concurrent lung infection in any of the patients. None of the patients possessed the tall, thin physique often associated with primary spontaneous pneumothorax. One patient had a recent history of air travel, a known risk factor for pneumothorax via bullous expansion. [23] However, as there was a three-day delay between the travel and symptom onset, the possibility remains that the bulla grew because of prolonged CPAP exposure. While one patient did have a history of lifting heavy boxes, the evidence associating weight-lifting or physical activity with pneumothorax is inconclusive and based on limited case reports. [22,24–26]

Bullae are typically managed conservatively and followed with serial imaging. Pulmonary function testing is helpful both to determine if emphysematous disease is present in the remaining normal lung, which is reflected in the diffusing lung capacity (DLCO), and to quantify the degree of air trapping in the bulla (the difference in functional residual capacity measured via helium dilution versus plethysmography). Complications of bullae include sterile fluid accumulation, infection, pneumothorax, bronchogenic cancer, hemoptysis, or angina-like retrosternal chest pain. Surgical management of bullae is indicated for symptomatic patients who are good surgical candidates with high volumes of trapped lung but preserved DLCO. Those with radiographic evidence of compressed lung adjacent to the bulla are most likely to benefit from procedural intervention. [2]

Additional studies are required to determine if there is an association of CPAP with bullae neogenesis or enlargement. The increasing availability of annual low-dose CT scans offers an opportunity to assess bullae neogenesis and evolution. National databases such as the National Inpatient Sample or the National Emergency Department Sample could be used to determine whether the incidence of pneumothorax and bullae is elevated among patients using CPAP and/or patients with OSA. High-resolution CT scans could potentially be used to assess the short-term effects of varying CPAP pressures on bullae volume in patients with known bullae; this has been demonstrated in patients with COPD and acute respiratory distress syndrome. [14,27] Although the routine ordering of screening chest radiographs before CPAP initiation is too resource-intensive, clinicians could use periodic imaging to monitor the smaller subset of patients on CPAP with known bullae.

Conclusion

This case series describes the occurrence of enlarging bullae associated with spontaneous pneumothorax in three patients with CPAP use. This is the first case series identifying a potential association between the use of CPAP, bullae formation, and pneumothorax. This case series suggests an association between the use of CPAP and bullae enlargement. However, larger studies are needed to further assess the causality between them. We propose a protocol to follow those patients on CPAP who are concurrently enrolled in an annual low-dose chest CT screening program to monitor for bullae progression. This may further elucidate the impact of positive airway pressure on bullae formation and evolution.

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