Sleep Disordered Breathing in Isolated Unilateral and Bilateral Diaphragmatic Dysfunction

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Introduction: The effect of isolated unilateral or bilateral diaphragmatic dysfunction (DD), in the absence of a generalized neuromuscular disorder, on sleep disordered breathing (SDB) is not well understood. The type of positive airway pressure (PAP) device needed to treat SDB in patients with isolated DD is also not well established.

Methods: We retrospectively analyzed data on patients with isolated unilateral or bilateral DD who were referred for polysomnography (PSG) for clinical symptoms or abnormal oximetry between 1994 and 2006.

Results: We found 66 patients who met criteria, of whom 74.2% were males with an average age of 58.8 ± 10.9 years. 56 had isolated unilateral DD, and 10 had isolated bilateral DD. All had significant SDB with an apnea-hypopnea index (AHI) of 26.6 ± 28.4 . There were no significant differences in PSG measures, arterial blood gas analysis, pulmonary function tests, or echocardiographic data, except for lower maximal inspiratory

pressure in patients with bilateral DD compared to unilateral DD ($40.2\% \pm 17.8\%$ vs. $57.7\% \pm 20.5\%$, $p = 0.02$). Control of SDB with continuous PAP (CPAP) was possible in only 37.9% of patients with the rest requiring bilevel PAP (BPAP). Patients with isolated bilateral DD and SDB were 6.8 times more likely to fail CPAP than those with unilateral DD ($p = 0.03$).

Conclusions: Most patients with isolated DD failed CPAP and required BPAP. Patients with bilateral DD were more likely to require BPAP than those with unilateral DD. Patients with isolated DD should be considered for in-lab titration to determine adequacy of therapy.

Keywords: diaphragmatic weakness, diaphragmatic paralysis, sleep disordered breathing, obstructive sleep apnea, isolated diaphragmatic dysfunction, diaphragmatic dysfunction

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Normal function of the diaphragm is essential for effective ventilation during sleep in normal subjects.¹ Diaphragmatic dysfunction (DD), defined as either weakness or paralysis depending on the degree of diaphragm impairment, can lead to daytime symptoms of exertional dyspnea as a consequence of reduced respiratory system capacity.² Patients with DD can also present with disturbed sleep (increased nocturnal arousals and decrease in REM sleep percentage) and sleep disordered breathing (SDB) (both obstructive and central sleep apnea).^{3,4} In a recent case series, individuals with isolated unilateral DD had position-dependent hypopneas in REM sleep with frequent desaturations.⁵ The effects of DD on nighttime sleep are not well understood, and studies are limited by inconsistencies and small sample size.³⁻⁸ Part of the inconsistency reflects the selected patient population with DD (unilateral vs. bilateral) and the added ventilatory load (isolated DD vs. DD associated with generalized neuromuscular disorders).

DD, specifically bilateral DD, is associated with alveolar hypoventilation, particularly during REM sleep.⁹ Bilateral DD, when associated with neuromuscular weakness, appears to be a common cause for ventilatory failure, presumably due to the lack of reserve caused by a concurrent reduction and/or inhibition of intercostal and accessory respiratory muscle activity, accentuated during REM sleep.^{3,7} Respiratory failure due to isolated (defined as idiopathic or excluding neuromuscular disorders) bilateral DD, though possible, appears to be

BRIEF SUMMARY

Current Knowledge/Study Rationale: The effect of isolated unilateral or bilateral diaphragmatic dysfunction on sleep disordered breathing in the absence of systemic neuromuscular disease and how the type of positive airway pressure device used influences treatment success has not been extensively studied.

Study Impact: Most patients with isolated diaphragmatic dysfunction, either unilateral or bilateral, failed continuous positive airway pressure (CPAP) therapy and required bi-level positive airway pressure therapy. Failure of CPAP was more common in bilateral than in unilateral diaphragmatic dysfunction.

rare, presumably due to the role of other muscles in ventilation during wake and sleep.^{6,10,11} Unilateral DD leads to sleep hypoventilation, albeit to a lesser degree than bilateral DD.^{5,12} Similar to isolated bilateral DD, it is rare that isolated unilateral DD leads to respiratory failure unless there are associated comorbidities.^{5,6,13}

Most patients with obstructive sleep apnea (OSA) can be successfully treated with continuous positive airway pressure (CPAP), which effectively stabilizes the upper airway. However, patients who have concurrent hypoventilation, as seen in obesity hypoventilation syndrome may require bilevel positive airway pressure (BPAP).¹⁴⁻¹⁶ Similarly, noninvasive positive pressure ventilation with BPAP is indicated for patients with neuromuscular disorders (NMD), including

patients with DD who have diaphragmatic weakness as part of their NMD.^{14,17} In contrast, the type of positive airway pressure device (i.e., CPAP vs. BPAP) needed to treat patients with isolated DD (i.e., patients without NMD) who present with OSA is not well established. Clinical experience suggests that some patients do well with CPAP while others require BPAP. To help better understand the role of PAP devices in treating DD patients with SDB and to evaluate the characteristic features of such patients, we reviewed and analyzed the clinical and polysomnographic data and treatment administered to patients with isolated unilateral and bilateral DD at Mayo Clinic Sleep Disorders Center.

METHODS

We identified all patients diagnosed with DD at the Mayo Clinic between 1994 and 2006 who also had an overnight polysomnography (PSG) due to symptoms suggestive of SDB or referred based on an abnormal overnight oximetry. Clinical data, tests, and final diagnoses were extracted retrospectively by chart review. DD was initially identified by documentation of the presence of elevated hemidiaphragm on chest x-ray. All cases were subsequently confirmed with either chest fluoroscopy (sniff test) and/or phrenic electromyogram (EMG). We excluded patients with generalized neuromuscular disorders (based on consult notes and documentation in the chart) and restrictive lung diseases due to causes other than diaphragmatic paralysis, thereby including only patients with isolated unilateral or bilateral DD. Unilateral DD was defined as the presence of weakness or paralysis on one side of the diaphragm while the other side was functioning well as documented either by chest fluoroscopy and/or EMG. Bilateral DD was defined by the presence of weakness or paralysis documented on both diaphragms by chest fluoroscopy and/or EMG. Also, the absence of both diaphragms to descend or move upward during inspiration, was defined as bilateral DD. Weakness was defined as either segmentally elevated anterior or posterior portions of the hemidiaphragm with movement impaired or paradoxical under fluoroscopy relative to the other portions; paralysis was defined as the absence of paradoxical movement of the diaphragm under chest fluoroscopy and/or lack of phrenic EMG activity. Clinical records of consults and follow-up visits were reviewed and data were collected including age, gender, body mass index (BMI), pulmonary function tests (PFT), arterial blood gas analysis (ABG). PSG data including apnea hypopnea index (AHI), type of PAP devices used, and echocardiogram findings within 1 year of their PSG were also recorded.

PSG was performed using a digital polygraph (NCI-Lamont Medical Incorporated; Madison, WI; or Bio-logic Systems Corporation; Mundelein, IL, or Viasys, Conshohocken, PA). The following parameters were recorded: electroencephalography, electrooculography, submental and anterior tibialis electromyography, snoring by laryngeal microphone, oxygen saturation (finger or ear oximeter), and respiratory effort (thoracic, abdominal, and summated inductive plethysmography). Airflow and respiratory effort were monitored using oronasal thermocouple and later thermocouple, nasal pressure transducer, and respiratory inductive plethysmography (RIP)

during the diagnostic study and, during titration, using the flow channel from the CPAP and BPAP plus RIP.

PAP titration was performed during PSG. Treatment was considered successful when the AHI was effectively reduced to less than 10/h, oxygen saturation was maintained $\geq 88\%$, and the patient tolerated the treatment pressure during the titration. CPAP failure was defined as persistent oxygen saturation $< 88\%$ despite control of SDB events as defined by an AHI of $< 10/h$, and/or the patient could not tolerate CPAP (at any pressure). A pressure cutoff for CPAP (such as 15 or 20 cm of water) was not used as failure criterion, as some patients tolerated higher pressures better than others. For the split-night protocol, patients identified with an AHI ≥ 5 after 2 h of sleep during diagnostic recording underwent a CPAP titration.¹⁸ If CPAP failed and there remained ≥ 2 h of anticipated sleep, a BPAP titration was performed during the last portion of the study. If a satisfactory BPAP titration could not be accomplished, or the patient had initially been started on CPAP but did not tolerate treatment, an additional PSG with BPAP titration was performed to determine settings.

Sleep staging and arousals were scored according to established guidelines from American Academy of Sleep Medicine guidelines.¹⁹⁻²¹ Until April 30, 2002, hypopnea was defined as $\geq 30\%$ decrease in airflow for ≥ 10 sec despite respiratory effort and accompanied by $\geq 2\%$ decrease in oxyhemoglobin saturation. For the remaining period, the desaturation criterion for hypopnea was 4% or less. Obstructive apnea was defined throughout as cessation of airflow for ≥ 10 sec despite respiratory effort. Pulmonary function testing was performed according to standard American Thoracic Society guidelines.^{22,23}

Statistical analysis was done comparing groups using a t-test for normally distributed continuous variables, or χ^2 for categorical variables, as appropriate using Stata/IC 13.1 (StataCorp LP College Station, TX). A probability (p) value < 0.05 was considered significant. Unless otherwise specified, parametric data are expressed as mean $\pm$ standard deviation (SD), and proportions as count (percentage).

RESULTS

Sixty-six patients were included in the final analysis. Of these, 56 (84.8%) patients had isolated unilateral DD and 10 (15.2%) had isolated bilateral DD. Basic demographics are displayed in **Table 1**. Snoring was noted in 28.8% of patients. Abnormal oximetry at baseline was present in 37.3% of patients, while 11.9% had an Epworth Sleepiness Scale score ≥ 10 . There were no statistically significant differences in these measures between unilateral and bilateral DD groups. Orthopnea was present in 15.3% of patients. Patients with bilateral isolated DD were more likely to have orthopnea, with an odds ratio of 31.3 (95% CI 5.12-191.8, $p < 0.0001$). Average AHI was 26.6 ± 28.4 (95% CI 18.9-34.2). AHI in REM sleep was significantly higher than the total AHI in both isolated unilateral and bilateral DD. There were no significant differences between isolated unilateral and isolated bilateral DD with regards to the AHI, AHI in REM sleep, REM duration in minutes or %, REM supine duration in minutes, oxygen saturation nadir in N-REM and REM sleep, and time spent with oxygen saturation $< 90\%$ during the diagnostic or PAP

titration portion of the PSG (**Table 2**). However, the relatively small amount of REM sleep during the diagnostic PSG may explain the lack of difference in oxygen desaturation between the two groups. Evaluation of ABG, PFT, and echocardiography data showed no significant differences between unilateral and bilateral DD except for maximum inspiratory pressure (Pimax%), expressed as a percent of normal predicted value (**Tables 3**).²³⁻²⁵ The Pimax% was lower in bilateral DD than unilateral DD (40.2 ± 17.8 vs 57.7 ± 20.5 , $p = 0.022$). Five patients in the bilateral DD (50%) group and 17 in the unilateral DD (32%) had $pCO_2 > 45$ mm Hg.

Treatment of DD and SDB is summarized in **Table 4**. Successful CPAP titration in patients with isolated DD and OSA was possible in only 25 (37.9%) patients. The majority of patients in both groups, 57.1% ($n = 32$) with unilateral DD and 90% ($n = 9$) with bilateral DD, failed CPAP and required BPAP (**Table 5**). In patients who failed CPAP, the mean CPAP pressure was 10.3 ± 3.7 cm H₂O compared to those successfully titrated with CPAP who had a mean pressure of 8.8 ± 2.6 cm H₂O. In 61% of patients who failed CPAP, failure was due to persistent oxygen desaturation of less than 88% despite the absence of apneic events. Four patients were unable to tolerate CPAP despite the pressures being < 10 cm of water and had to be switched over to BPAP. The remaining 12 patients did not have a documented reason to switch to BPAP from CPAP, but in the absence of persistent desaturation, presumably it had to do with patient comfort. In a logistic regression, the odds ratio for CPAP failure with isolated bilateral DD and SDB was 6.75 (95% confidence interval 1.15 to 128.75; $p = 0.0322$) compared to unilateral DD. Even in patients with isolated unilateral DD, successful titration with CPAP occurred in only 42.9%. Eight patients (5 with isolated unilateral DD and

3 with isolated bilateral DD) required BPAP in a spontaneous/timed mode (BPAP-ST) due to evidence of continued desaturations suggesting hypoventilation on CPAP and on BPAP-spontaneous mode (BPAP-S). Patients requiring BPAP-ST had higher serum HCO₃ levels (31.8 ± 7 vs 27.1 ± 3.5 , $p = 0.012$). There were no significant differences in age, sex, BMI, unilateral or bilateral diaphragmatic paralysis, AHI, or AHI in REM sleep between the groups. The sample size was, however, small to allow clinically meaningful conclusions. Patients with isolated bilateral DD and OSA had a higher IPAP requirement on the BPAP settings (14.7 ± 2.9 vs 12.0 ± 2.8 , $p = 0.04$).

DISCUSSION

Reports of occurrence and treatment of SDB in patients with isolated unilateral or bilateral DD are very few, have shown conflicting results, and have been restricted to case reports and

Table 1—Demographic data ($n = 66$)

	Total	Unilateral	Bilateral	p-value
Diaphragm paralysis (n)	66	56	10	
Age (years)	58.77 ± 10.9	58.8 ± 11.3	58.4 ± 9.5	0.9
Gender				
Male	49 (74.2%)	41 (73.2%)	8 (80%)	0.6
Female	17 (25.8%)	15 (26.8%)	2 (20%)	
Body mass index (BMI)	35.6 ± 7.5	36 ± 7.9	33.3 ± 4.03	0.3

* p value between unilateral and bilateral diaphragmatic dysfunction.

Table 2—PSG indices in unilateral vs. bilateral diaphragmatic dysfunction

PSG data	Subjects with data available	Total	Unilateral diaphragmatic dysfunction	Bilateral diaphragmatic dysfunction	p-value*
Diagnostic Study					
AHI	55	26.6 ± 28.4	28 ± 29.2	16.4 ± 20.7	0.32
REM – AHI	44	42.5 ± 31.7	44.4 ± 31.5	27.4 ± 32.2	0.26
O ₂ Sat $< 90\%$ (%)	43	27.3 ± 29.9	26.6 ± 30.7	32.3 ± 25.7	0.7
Lowest REM – O ₂ %	41	77.4 ± 9.5	77.1 ± 9.7	80 ± 8.5	0.53
Lowest NREM – O ₂ %	50	81.6 ± 6.9	81.3 ± 7.2	84 ± 3.6	0.37
TST (min)	43	151.7 ± 80.2	145.9 ± 69.5	195.5 ± 142	0.2
REM (min)	45	17.5 ± 19.8	15.6 ± 16.8	29.3 ± 33	0.11
REM (%)	45	11.4 ± 9.5	11.1 ± 9.6	13.4 ± 8.8	0.58
PAP Titration					
O ₂ Sat $< 90\%$ (%)	48	30.9 ± 38.2 (CPAP & BPAP)	30.8 ± 38.8 (CPAP)	31.0 ± 38.3 (BPAP)	0.99
Lowest REM – O ₂ sat %	30	83.1 ± 8.8	83.5 ± 8.9	78 ± 8.5	0.41
Lowest NREM – O ₂ sat %	37	86 ± 5.5	86.2 ± 5.5	83.8 ± 5.3	0.41
TST (min)	38	132.2 ± 81.0	130.8 ± 80.8	144.2 ± 83.8	0.76
REM (min)	38	28 ± 27.2	28.9 ± 27.7	20.1 ± 24.1	0.55
REM (%)	38	18.6 ± 14.2	19 ± 14.3	15.2 ± 14.2	0.62
NREM (min)	38	50.5 ± 60.5	49.2 ± 57.7	60.9 ± 91.3	0.72

* p value between unilateral and bilateral DD. AHI, apnea hypopnea index; Min, minutes; O₂, oxygen; PSG, polysomnography; CPAP, continuous positive airway pressure; BPAP, bilevel positive airway pressure; Sat, saturation; TST, total sleep time.

Table 3—ABG, PFT, and echocardiographic data in unilateral vs. bilateral diaphragmatic dysfunction

	Subjects with available data	Total	Unilateral diaphragmatic dysfunction	Bilateral diaphragmatic dysfunction	p value
O ₂ sat %	55	93.4 ± 4.9	93.6 ± 5.1	91.9 ± 3.5	0.38
pCO ₂ mm Hg	53	47.4 ± 11.5	47.4 ± 11.8	47.0 ± 10.5	0.92
pH	52	7.39 ± 0.04	7.39 ± 0.04	7.4 ± 0.05	0.8
HCO ₃	38	27.7 ± 4.4	27.3 ± 4.2	29.3 ± 5.2	0.29
FEV1 %	62	51.4 ± 16.9	52.3 ± 16.8	47.0 ± 19.1	0.38
FVC %	61	55.1 ± 17.6	56.1 ± 17	49.0 ± 21.2	0.27
DLCO%	56	67.6 ± 19.4	68.7 ± 18.4	61.9 ± 24.7	0.34
TLC %	58	70.6 ± 14.4	71.5 ± 14.1	65.9 ± 16.1	0.29
Pimax %	52	54.6 ± 21	57.7 ± 20.5	40.2 ± 17.8	0.022 *
Pimax (cm H ₂ O)	45	56.6 ± 24.7	59.7 ± 25.4	42.3 ± 15.6	0.07
Pemax %	51	62.5 ± 19.4	60.6 ± 17.7	72.4 ± 25.7	0.12
MVV %	56	48.6 ± 19.1	48.8 ± 19.2	47.0 ± 20.4	0.82
EF%	42	59.6 ± 12.1	59.4 ± 12.5	62.7 ± 7.5	0.66
RVP	30	39.6 ± 12.8	39.2 ± 12.7	34 ± 14.7	0.52

*p value, significant between unilateral and bilateral diaphragmatic dysfunction; O₂, oxygen; CO₂, partial pressure of carbon dioxide; HCO₃, serum bicarbonate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; Pimax, maximal inspiratory pressure; Pemax, maximal expiratory pressure; MVV, maximal ventilatory ventilation; EF, ejection fraction based on echocardiogram; RVP, right ventricular systolic pressure; Sat, saturation.

Table 4—CPAP, IPAP, and EPAP pressures in subjects with diaphragmatic dysfunction and sleep disordered breathing

	Total	Unilateral diaphragmatic dysfunction	Bilateral diaphragmatic dysfunction	p value
CPAP *	9.7 ± 3.3	9.7 ± 3.4	9.2 ± 3.4	0.75
IPAP	12.8 ± 3	12.0 ± 2.8	14.7 ± 2.9	0.042 *
EPAP	6.9 ± 3	6.8 ± 2.8	7.3 ± 3.6	0.71

* Values only in those who were successful. CPAP, continuous positive airway pressure; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

Table 5—CPAP failure and success in unilateral vs. bilateral diaphragmatic dysfunction

CPAP	Unilateral diaphragmatic dysfunction	Bilateral diaphragmatic dysfunction	Total
CPAP failure	32	9	41
CPAP success	24	1	25
Total	56	10	66

In a logistic regression, the odds ratio for CPAP failure with bilateral diaphragmatic dysfunction was 6.75 (95% confidence interval 1.15 to 128.75; p = 0.0322) compared to unilateral diaphragmatic dysfunction.

small case series. In our retrospective analysis of 66 patients referred for suspected SDB, with either unilateral (n = 56) or bilateral (n = 10) DD, most patients had significant OSA. Therapeutically, most of these patients failed CPAP and required some form of BPAP. We believe our study is the first to analyze the influence of isolated DD (unilateral or bilateral) on management of patients with SDB using positive airway pressure devices. We found that patients with both isolated unilateral and bilateral DD had worse AHI in REM sleep compared to the total AHI, and most patients with isolated DD required BPAP to control SDB rather than CPAP.

The increased prevalence of SDB in our patient population may be related to our patient selection criteria. Our patients were referred to the sleep disorders center because of symptoms suggestive of SDB or abnormal findings on overnight oximetry, and DD was not the primary reason for evaluation. Also, most of our patients were obese (mean BMI 35.5 ± 7.56) and may have had an increased risk for OSA. Previous reports have suggested a lack of SDB in patients with isolated bilateral DD, though there was evidence for mild but clinically nonsignificant sleep hypoventilation predominantly during REM

sleep.^{6,11} A case report by Kreitzer et al. on isolated bilateral DD showed ventilatory failure though the underlying mechanism was not studied.²⁶ Subsequent studies revealed significant sleep (predominantly REM sleep) and wake hypoventilation leading to ventilatory failure when bilateral DD was associated with neuromuscular disorders.⁸ Excluding patients with neuromuscular disorders and focusing on isolated bilateral DD, studies from both Stradling et al.⁴ and White et al.⁸ showed presence of significant SDB. The presence of SDB in these studies was due to hypoventilation manifesting as central hypopneas leading to nocturnal hypoxemia, but not to daytime hypoxemia or ventilatory failure. The degree of impairment of diaphragmatic function was an important determinant of nocturnal oxygenation.⁸ Though hypoventilation appeared to be the predominant pathophysiology, they could not rule out underlying OSA. We were surprised to find that both isolated unilateral and isolated bilateral DD showed no statistically significant differences in nocturnal hypoxemia, AHI, or arterial blood gas values including pCO₂ in our retrospective cohort. We expected to find a greater degree of nocturnal hypoxemia in the bilateral DD than the unilateral DD group. We are unable to explain these

findings clinically as there were no statistically significant differences in factors such as the total amount of REM sleep or supine REM sleep between the two groups. However, the relatively small amount of REM sleep during the diagnostic PSG may explain the apparent lack of difference in oxygen desaturation between the two groups. Speculatively, this may also be a function of referral bias, wherein we evaluated more obese patients with unilateral DD (and hence prone to greater hypoxemia and hypercapnia), and slimmer patients with bilateral DD.

Similar to previous reports, in our study patients with both unilateral DD^{6,12,27} and bilateral DD^{3,4,8,11} had a restrictive ventilatory defect with a low forced vital capacity (FVC) and total lung capacity (TLC). The reduction in FVC in our study was greater than other studies and may have been related to underlying obesity.²⁸⁻³⁰ Supine spirometry is usually more sensitive to detect reduced FVC in patients with neuromuscular disorder, such as patients with diaphragmatic dysfunction. None of our patients had supine spirometry. Clinically, orthopnea was more common in patients with bilateral DD, and we suspect supine spirometry could have demonstrated significant abnormalities had it been obtained. Patients with underlying neuromuscular disorder have been shown to develop hypercapnia and ventilatory failure with the requirement for noninvasive positive pressure ventilation (NIPPV) when the respiratory muscle strength as measured by $P_{i_{max}}$ is less than 40% of predicted³¹ and FVC is less than 50%³², predominantly due to hypoventilation. Our patients with isolated bilateral DD and OSA had mean $P_{i_{max}}$ values $40.2\% \pm 17.8\%$ of predicted and may have failed CPAP as it may have not effectively corrected nocturnal hypoventilation, especially with the added ventilatory load from obesity. The mean $P_{i_{max}}$ % and FVC% were not in the range ($< 40\%$ and $< 50\%$, respectively), which is associated with ventilatory failure.^{17,31,32}

Our patients had diurnal hypercapnia with mean awake PCO_2 levels of 47.1 ± 11.3 and HCO_3 levels of 27.5 ± 4.4 . PCO_2 levels were not measured during sleep. Most if not all patients with NMD with or without diaphragm involvement had hypercapnia due to alveolar hypoventilation.³³ Similarly, OSA patients can develop hypercapnia and the exact reason remains unknown.^{34,35} It is not possible to determine if the hypercapnia in our patients was related to OSA or non-obstructive alveolar hypoventilation, or to both.

Our patients had increased right ventricular systolic pressures on echocardiography. Thirteen of 30 patients (43.3%) had estimated systolic pulmonary artery pressures estimated ≥ 40 mm Hg. This could have been due to obstructive sleep apnea or nocturnal hypoxia from hypoventilation, both of which have been associated with pulmonary hypertension.³⁶⁻³⁸ We do not have data on right heart catheterization on our patients.

Though NIPPV with BPAP is a well-established treatment modality for respiratory failure in patients with NMD, both with and without DD,^{14,17} guidelines for use of positive airway pressure devices to treat isolated DD and SDB have not been established. The goal of therapy is to correct the underlying hypoventilation from DD and SDB. CPAP has been shown to improve sleep hypoventilation disorders in many but not all patients with obesity hypoventilation syndrome (OHS) and hypercapnia with OSA.^{35,39-43} The mechanism has been suggested as stenting of upper airways³⁵ and increasing lung

volume improving gas exchange and overcoming intrinsic positive end expiratory pressure (iPEEP).^{42,44,45} This may be the reason that some of our patients (24 patients [48%] with unilateral DD and one patient [10%] with bilateral DD) had resolution of SDB with CPAP, while most (62% with unilateral DD and 90% with bilateral DD) required BPAP and some (8 patients) even required BPAP-ST to control SDB (**Table 5**). Although all of our patients requiring BPAP-ST had elevated serum HCO_3 levels, we did not find any clinical or laboratory features statistically predictive of the need for BPAP-ST, perhaps due to our small sample size. The backup rate was likely needed in patients who did not generate enough negative inspiratory pressure to trigger the BPAP. This is most commonly seen during REM sleep and in those with severe DD (paralysis vs. weakness).⁴⁶ The mean IPAP required for control of SDB was higher in patients with isolated bilateral than isolated unilateral DD and fits with the underlying pathophysiology of sleep hypoventilation. A greater IPAP on BPAP for higher minute ventilation may be needed to correct the greater degree of hypoventilation in patients with bilateral DD.⁴³

Our study has several limitations. A true prevalence estimate for SDB in DD patients is not possible, as our retrospective design carries referral and selection bias. Being a tertiary care center, it is possible our patient population included sicker patients which may explain the severity of SDB in our isolated DD patients compared to other studies. Also, patients were referred to our sleep center because of symptoms of SDB or abnormal findings in an overnight oximetry, while DD may not have been the primary reason. This may be different from the studies where patients with DD were evaluated for SDB. Also, due to the retrospective design, not all recorded data on the analyzed variables were available and may have contributed to the nonsignificant findings. The exact reasons for pressure intolerance related to CPAP use for some patients could not be ascertained from our records retrospectively. ABGs, PFTs, and PSG data were not available in all patients and the numbers are listed in **Table 2**. Similarly, not all studies were performed around the time of DD diagnosis. While our study reflects the common clinical practice in assessing for DD, the clinical diagnosis of isolated DD based on fluoroscopy may not have always been accurate as not all patients had phrenic EMGs and none had transdiaphragmatic pressures measured. Due to the retrospective nature of our study, the influence of medications and/or alcohol could not be clearly ascertained and the exclusion of neuromuscular disorders were based on consult and progress notes alone. The small number of patients in the bilateral DD group and wide range of values (**Table 2**) for AHI and oxygen desaturation may have resulted in a type II error in determining clinical features predictive of CPAP failure. Future prospective studies with higher sample size may help to address these limitations. CPAP failure, in our study, was defined as persistent oxygen desaturation $< 88\%$ despite control of SDB events as defined by an AHI of < 10 /hour. It is important to emphasize that this is not hypoventilation as per the AASM scoring manual, which recommends documenting an increase in $PaCO_2 \geq 10$ mm Hg during sleep compared to awake supine values. Though there are noninvasive methods to monitor $PaCO_2$ values during PAP titration such as transcutaneous PCO_2 to document hypoventilation, this was not performed in our study. These noninvasive

methods are currently being used more often lately, after establishing reliability and validity within each sleep center.

Our study also leaves several questions unanswered for future investigation. Does OSA in patients with isolated DD, either unilateral or bilateral predispose to significant hypoventilation leading to nocturnal hypoxemia and hypercapnia and subsequent respiratory failure? Which patients with DD and SDB develop cor pulmonale? Is the severity of SDB important in patients with DD? Also, other factors like the duration of isolated DD prior to diagnosis without treatment, degree of diaphragm impairment (paralysis vs. weakness), associated comorbidities including neuromuscular disorder, and obesity may contribute to right heart failure. The retrospective design of our study prevents us from making any conclusions on these questions. Further prospective studies are needed to address this question.

CONCLUSIONS

We present the largest retrospective analysis to date of patients with isolated DD (without concurrent neuromuscular disorder) and SDB that serves to broaden both awareness and knowledge of this condition for further prospective studies. Our investigation examined the effect of positive airway pressure therapy on SDB in patients with isolated DD and found that, although CPAP was effective in some patients, most patients with either unilateral or bilateral DD with SDB require BPAP during sleep and some may require BPAP-ST. We recommend that patients with isolated DD should undergo an in-lab positive airway pressure therapy titration due to high risk of CPAP failure and the possibility of inadequate treatment.

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