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Comparison of Sitting and Supine Forced Vital Capacity in Collagen VI-Related Dystrophy and Laminin α2-Related Dystrophy

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Summary.

Background: Progressive, restrictive, respiratory insufficiency is the major cause of morbidity and mortality in Congenital Muscular Dystrophy (CMD). Nocturnal hypoventilation precedes daytime alveolar hypoventilation, and if untreated, may lead to respiratory failure and cor pulmonale. CMD consensus care guidelines recommend screening for respiratory insufficiency by conventional and dynamic (sitting to supine) pulmonary function testing (PFT) and evaluating for sleep disordered breathing if there is more than 20% relative reduction from sitting to supine FVC(L) (ΔFVC).

Objective: The objective of this retrospective study was to explore and characterize dynamic FVC measures in 51 individuals with two common subtypes of CMD, COL6-RD, and LAMA2-RD.

Methods: We compared sitting and supine FVC in patients with confirmed mutation(s) in either *COL6* or *LAMA2*. We investigated influences of age, CMD subtype, gender, race, ambulatory

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status, and non-invasive positive pressure ventilation (NIPPV) status on FVC percent predicted (FVCpp) and ΔFVC.

Results: COL6-RD participants exhibited a significant difference between sitting and supine mean FVCpp (sitting 66.1, supine 55.1; $P < 0.0001$) and were 5.4 times more likely to have –ΔFVC >20% than those with LAMA2-RD when controlling for ambulant status. FVCpp sitting correlated inversely with age in individuals ≤18 years.

Conclusion: FVCpp sitting decreases progressively in childhood in both CMD subtypes. However, our results point to a difference in diaphragmatic involvement, with COL6-RD individuals having more disproportionate diaphragmatic weakness than LAMA2-RD. A ΔFVC of greater than 20% should continue to be used to prompt evaluation of sleep-disordered breathing. Timely initiation of NIPPV may be indicated to treat nocturnal hypoventilation.

Keywords

vital capacity; neuromuscular disorders; dynamic spirometry; congenital muscular dystrophy; pulmonary function testing

INTRODUCTION

Congenital muscular dystrophies (CMD) comprise a group of phenotypically and genetically heterogeneous disorders characterized by progressive, early onset muscle weakness, axial, and peripheral skeletal contractures, and progressive respiratory insufficiency evidenced by a predictable annual rate of decline in forced vital capacity (FVC).[1–4] Progressive, restrictive pulmonary defect is the major cause of morbidity and mortality in CMD. Nocturnal hypoventilation often precedes daytime respiratory insufficiency, and if untreated, may lead to respiratory failure and cor pulmonale.[3] This respiratory insufficiency primarily stems from the combination of progressive muscle weakness, thoracic deformity, decreased compliance of the chest wall and lungs, and costo-vertebral limitation.[4–9]

Pulmonary function screening allows for earlier detection and treatment of nocturnal alveolar hypoventilation, especially when ambulatory status may not correspond to the degree of respiratory limitation.[1,2,10] To identify individuals at risk, the 2010 CMD consensus care guidelines suggest screening for respiratory insufficiency by conventional and dynamic (sitting to supine) pulmonary function testing (PFT) in ambulant and non-ambulant individuals with CMD.[2] To further identify early sleep-disordered breathing, these guidelines also recommend nocturnal oximetry be performed if there is a >−20% relative change from sitting to supine FVC(L) (ΔFVC) and FVC percent predicted sitting (FVCpp) is <80%, or if FVCpp sitting alone is <60% predicted.[2] Nocturnal oximetry was recommended by Wang et al.,[2] because polysomnography (PSG) is not always available. However, the gold standard to assess sleep disordered breathing, including hypoventilation and hypercapnea, involves PSG or the use of nocturnal oximetry with capnography because both O_2 and CO_2 readings may be required to make informed decisions about a potential intervention. In addition, the CMD standard of care recommendations do not yet address specific CMD subtype differences because there currently is insufficient specific data. The use of non-invasive positive pressure ventilation (NIPPV) to correct nocturnal hypoventilation has

resulted in improved survival and quality of life in various neuromuscular disorders.[1,2,11,12] Recent retrospective cohort studies in two CMD subtypes, Collagen VI-related dystrophy (COL6-RD) and Selenoprotein N,1 (SEPN1)-related myopathy, highlight the potential need for NIPPV even in ambulant individuals.[4,13]

CMD subtypes present with differing phenotypic spectra. In COL6-RD, the phenotype ranges from a severe Ullrich CMD presentation to the mild Bethlem Myopathy. Ullrich CMD presents with either the inability to achieve ambulation or a loss of ambulation at a mean age of 10 years (typical Ullrich CMD, or "moderate progressive").[14] In the intermediate form of COL6-RD "mild,"[14] individuals achieve ambulation but do not run or hop, lose ambulation at a mean age of 19 years, and may develop respiratory insufficiency while still ambulant. In the mildest phenotype, Bethlem Myopathy, individuals can achieve and maintain ambulation through adulthood.[4] In laminin alpha 2-related dystrophy (LAMA2-RD), individuals with complete deficiency of laminin alpha 2 (or complete merosin deficiency) typically do not achieve ambulation.[1,2,11] Individuals with partial deficiency of laminin alpha 2 have a more variable phenotype in regard to pattern of weakness and may achieve ambulation.[15]

Studies describing pulmonary function in specific CMD subtypes are limited. Although some neuromuscular disorders may behave similarly, a varying degree of involvement of distinct respiratory and abdominal muscles may be subtype-specific and account for different rates of decline in FVC.[4,8,13,16,17] The diaphragm is the most important muscle involved in respiration and is affected by posture. In the seated position, the diaphragm contributes approximately 70% to tidal breathing and the intercostal muscles approximately 30%. However, in the supine position, the diaphragm contribution can increase to nearly 90%.[18,19] An excessive fall in FVC from sitting to supine thus is a good indicator of diaphragm weakness, even in subjects who might have global inspiratory muscle dysfunction.[20] Thus, individuals with neuromuscular disorders in which the diaphragm is selectively involved are at greater risk for nocturnal hypoventilation. FVC is commonly used to evaluate respiratory muscle strength in patients with these disorders.[21] Variables that influence FVC include age, weight, height, gender, race, ambulatory status, and NIPPV status. The objective of our retrospective study was to explore and characterize FVC measures in the sitting and supine positions of individuals with COL6-RD and LAMA2-RD, and we hypothesized that there is a relationship between the decrease in ΔFVC and NIPPV status in both disease subtypes.

MATERIALS AND METHODS

This retrospective study included 51 participants with genetically confirmed CMD between the ages of 4 and 61 years: 30 with COL6-RD and 21 with LAMA2-RD. Participants were recruited at the National Institutes of Health through two clinicaltrials.gov protocols (NCT01568658 and NCT00004568). Both studies were approved by the NIH Combined Neurosciences Institutional Review Board. Informed consent and assent (when appropriate) was obtained for each participant at the time of enrollment.

Demographics

Demographic variables are recorded in Table 1. Compared with LAMA2-RD, more COL6-RD participants were >18 years of age ($P = 0.04$) and ambulatory ($P = 0.0002$) (see Table 1). Of the participants with COL6-RD, 22 (73%) were ambulatory, and 5 (42%) of the COL6-RD participants with FVCpp <60% were ambulatory. In contrast, four (21%) of LAMA2-RD participants were ambulatory, and none of LAMA2-RD participants with FVC <60% were ambulatory. There were no significant differences in race, gender, or NIPPV status between the two subtypes.

All PFTs were performed in the Pulmonary Function Laboratory of the National Heart, Lung, and Blood Institute at the National Institutes of Health using the VMAX™ Encore PFT system, software v. 21.1A; CareFusion Corporation, San Diego, CA, as part of an annual evaluation of participants in the above protocols. ATS/ERS guidelines were followed.[22] Testing included FVC in the sitting and supine positions, with results reported in both absolute values (in liters, L) and FVCpp using established reference equations.[23,24] Participants completed spirometry in the sitting position first, then in the supine position. Approximately, 10–30min elapsed between tests to allow for recovery and to minimize fatigue. Standing height was measured for participants who were capable of standing and were without contractures. For individuals with lower extremity contractures or who could not stand, a Rosscraft segmometer was used to measure the ulna length, and height was consequently derived.[25]

Ambulatory status was defined as the ability to walk 10 m without orthotics or assistive devices. NIPPV status was defined as the use of non-invasive mechanical ventilatory support as either <16hr per day, or >16hr per day.

Descriptive analyses were performed with calculation of means, standard deviations and medians for continuous variables. Categorical variables were summarized using frequencies and percentages. Descriptive analyses were implemented using SPSS Statistics 19; all other analyses were implemented in SAS 9.3. Fisher's exact test was used to identify significant differences between COL6-RD and LAMA2-RD with respect to categorical variables (Table 1).

Multivariate Analysis of Covariance (MANCOVA) was used to compare FVC in sitting and supine positions, in liters and in FVCpp. The response variable for liters was FVC(L) in both sitting and supine. Covariates included CMD subtype, age, gender, race, ambulatory status, and NIPPV status in the analysis of FVC(L). For FVCpp, (sitting and supine) the covariates included diagnosis, ambulatory status, and NIPPV status, because the percent predicted equation accounts for age, height, and race. Least-squares means and 95%CI are reported for each model. Results were considered statistically significant if $P < 0.05$.

We performed Pearson correlations to assess the relationship between each FVC measure and age. A partial Pearson correlation was performed to determine the association between ΔFVC and age while adjusting for sitting FVCpp, which served as the "baseline" FVC in this study. Because of the significant difference in the number of adults between the two

subtypes, all Pearson correlations included the total n = 51 and were also subdivided for subjects by age ≤18 versus >18 years.

We performed logistic regression to determine how the odds of having –ΔFVC>20% may be impacted by ambulatory or NIPPV status.

Multiple linear regression was used to analyze the relationship between ΔFVC and each of the following variables: CMD subtype, age, gender, race, ambulatory status, and NIPPV status. The response variable was ΔFVC as defined above.

The current cut-off point for recommending a sleep study is either when FVCpp is <60%, or when –ΔFVC is >20% even with normal FVCpp. Because these cutoffs were determined by expert opinion,[2] we queried our sample to see how many patients were using NIPPV and what their PFT result was for ΔFVC, specifically. To do this, we counted the number of individuals using NIPPV identified at four different ΔFVCs: <−10%, −10 to −14%, −15 to −20%, and >−20%.We also calculated the positive predictive value of the current guideline of −ΔFVC of >20% for need for NIPPV by using McNemar's test for the all subjects and by disease subtype.

RESULTS

FVC (L)

Table 2 shows the range of FVCpp for COL6-RD and LAMA2-RD in both sitting and supine participants. Participants with COL6-RD had a statistically significant difference in mean FVC(L) when comparing sitting to supine, whereas LAMA2-RD participants did not (Table 3). Because there was a significant difference in age between the two subtypes, a sensitivity analysis was performed by excluding subjects over 21 years of age. This removed the significant difference in age between the two groups, however, COL6-RD remained the only group with a significant difference between sitting and supine mean FVC(L).

FVC (PP)

For all participants, the mean sitting FVCpp was 64.67% and the mean supine FVCpp was 57.04%. There was no significant difference in the mean sitting FVCpp or mean supine FVCpp between the two disease subgroups. As with mean FVC(L), participants with COL6-RD had a statistically significant difference in mean FVC(L) when comparing sitting to supine, whereas LAMA2-RD participants did not (see Table 4 and Fig. 1). We repeated the sensitivity analysis by excluding subjects over 21 years of age as described above, and the results did not change. FVCpp sitting correlated inversely (i.e., decreased) with age in individuals ≤18 years only (Table 5).

FVCpp correlated negatively with age (Table 5).

ΔFVC

In general, a decrease in ΔFVC of up to approximately 10% in moving from the sitting to supine position is expected because of upward pressure on the diaphragm from the abdominal contents and displacement of air due to blood pooling in the thorax.[18,19] In

contrast, when analyzing the within subject differences between sitting and supine in our cohort, almost twice as many subjects with COL6-RD experienced a >20% decrease in FVC from sitting to supine compared to subjects with LAMA2-RD (Fig. 2). ΔFVC did not correlate with age, even when adjusting for FVCpp sitting as the "baseline value" by partial correlation (data not shown). We performed a sensitivity analysis to see if this changed in participants ≤18 only, but did not find this to be the case.

ΔFVC and Ambulatory and NIPPV Status

We also examined the relationships between participants' decrease of >20% ΔFVC and ambulatory status and NIPPV status (Figs. 3 and 4).

Logistic regression of >20% decrease in ΔFVC on covariates CMD subtype and ambulatory status further showed the CMD subtype was significantly associated with >20% decrease ΔFVC but ambulatory status was not. When controlling for ambulant status, the odds for participants with COL6-RD to have ΔFVC>−20% were 5.4 times greater than for those with LAMA2-RD and 17.6 times greater for a ΔFVC>15%.

Logistic regression of >20% decrease on the covariates subtype and NIPPV status showed neither of the covariates were statistically significant (i.e., neither the subtype nor NIPPV status was associated with a significant postural difference in FVC). This was also only the case in participants ≤18 years of age.

To analyze whether any covariates (CMD subtype, age, gender, race, ambulatory status, and NIPPV status) contributed to ΔFVC, we performed a linear regression of ΔFVC while controlling for FVCpp sitting ("baseline") and identified gender as the only significant covariate ($P = 0.019$), suggesting females experienced a greater ΔFVC than males. Of those participants with a relatively high sitting FVCpp (>60%), ΔFVC did not differ by NIPPV status (Fig. 3).

ΔFVC Cut Off Points

We evaluated the numbers of individuals with a decrease of <10%, −10 to −14%, −15 to −20%, and >20% in ΔFVC (Table 6). There were equal numbers of individuals in NIPPV with a decrease of <10% as there were with a decrease of >20% (four individuals in each category). However, more LAMA2-RD individuals were prescribed NIPPV at a milder decrease in ΔFVC of <10%. In contrast, COL6-RD individuals were usually prescribed NIPPV with a −ΔFVC of >10%. On the other hand, only4/19 (21%) individuals with a −ΔFVC of >20% were treated with NIPPV. Of note, 12 COL6-RD individuals had an FVCpp sitting of <60%, of which only 3 (25%) were using NIPPV. For LAMA2-RD, nine individuals had an FVCpp sitting of <60%, and four (44%) were using NIPPV.

The positive predictive value of ΔFVC ≤−20% for need for NIPPV was low for all groups: the proportion of NIPPV users among all individuals who had ΔFVC ≤−20% was 0.15, among COL6-RD who had ΔFVC ≤−20% was 0.11, and among LAMA2-RD who had ΔFVC ≤−20% was 0.19 (Fig. 4).

DISCUSSION

Progressive respiratory failure in CMD is an important cause of morbidity and mortality related to the early onset of muscle weakness affecting respiratory muscles, related thoracic, and spinal deformities, increasing stiffness and contractures of the ribcage, and decreased respiratory compliance.[6–10] Systematic screening, timely recognition, and institution of appropriate intervention when necessary are among the most important components of care in an individual with CMD. NIPPV use is recommended when day- or night-time hypoventilation have been detected as it improves symptoms such as morning headaches and daytime fatigue, reduces the frequency of intercurrent respiratory infections, and, once initiated, is used long term to manage progressive respiratory failure.[1,2,5] Failure to intervene may lead to significant morbidity and mortality.[2,26] It is likely that the relative importance of the various contributors to respiratory failure and the resulting natural history of respiratory impairment differ between the various genetic subtypes of CMD. Moreover, disproportionate diaphragmatic involvement may have an additional negative impact on prognosis in neuromuscular disease.[27,28]

This is the first study to our knowledge to present dynamic spirometry results specifically in LAMA2-RD and the first to compare dynamic spirometry findings in individuals with LAMA2-RD and COL6-RD. Upon initial analysis, disease subtype was a contributing factor to having a significant decrease in FVCpp when moving from the sitting to supine position. However, we identified the change was only significant for the COL6-RD group of subjects. Participants with COL6-RD were 5.4 times more likely than LAMA2-RD participants to have a >20% decrease in ΔFVC when controlling for ambulant status and 17.6 times greater for a ΔFVC >−15%.

This is an important finding regarding disease specificity, as the decrease in FVCpp between sitting and supine was seen in COL6-RD, but not in LAMA2-RD, indicating differences in pathophysiology. There appears to be to early disproportionate diaphragmatic involvement in COL6-RD specifically, consistent with the observation that nocturnal hypoventilation may be observed in children and adults who are still ambulant.[4] Quijano-Roy et al. recently showed diaphragmatic involvement by spontaneous breathing in the upright position in Ullrich CMD and intermediate COL6-RD individuals.[7] Use of a maximal voluntary maneuver (sniff) showed the same finding in early severe, moderate-progressive, and mild individuals.[7] In the first mouse model of COL6-RD, the diaphragm also appeared to be the most affected muscle.[29,30]

Although we did not observe a significant decrease in FVCpp between sitting and supine positions in participants with LAMA2-RD, this lack of differential does not imply lack of diaphragmatic involvement in these individuals. Rather, it is reasonable to assume that the diaphragmatic contribution to respiratory compromise in LAMA2 is not as disproportionate as it is in COL6-RD but rather correlates more with the overall skeletal muscle weakness in the patient. In contrast, the disproportionate diaphragmatic weakness compared to other muscles in COL6-RD is supported clinically by the finding that ambulatory COL6-RD individuals sometimes require NIPPV whereas this is not the case in ambulant LAMA2-RD.

[4] Additional factors that may differentiate the respiratory physiology in the two subtypes remain to be explored.

We also found that FVCpp sitting correlated inversely (i.e., decreased) with age in individuals ≤18 years only, suggesting a significantly greater progressive rate of decline in lung function in childhood. We attribute this at least in part to the fact that some younger patients have a more severe early onset clinical presentation and the older patients are more likely to represent the milder disease form. This finding is consistent with the predictable and progressive decline in FVC documented for COL6-RD by our group in a large international cohort,[4] which has also been observed by others,[17] and substantiates that the degree and time course of respiratory compromise is directly correlated with the overall severity of the disease.

Of those participants with a relatively high sitting FVCpp (>60%), ΔFVC did not differ by NIPPV status, suggesting that nocturnally NIPPV-dependent individuals did not have a greater drop in FVC from sitting to supine. In most cases, this is likely because both parameters decline and thus the differential between FVCpp sitting and supine did not widen. Of potential relevance to future studies, supine FVCpp has been shown to be a highly correlated predictor of transdiaphragmatic pressure (Pdi), with a cutoff of supine FVCpp of <75% being 100% sensitive and specific for predicting an abnormally low Pdi.[31]

Notably, in contrast to FVCpp we did not find that ΔFVC worsens with age, meaning the differential is established early and remains similar with declining FVCpp. Being ambulant or having NIPPV did not decrease the likelihood of a >20% decrease in ΔFVC in our study, but our findings suggest females experienced a greater ΔFVC than males. On the other hand, Chen et al. showed that ΔFVC in a mixed population of neuromuscular patients using NIPPV exceeded ΔFVC in those with spontaneous breathing by 14-fold ($P = 0.001$).[21] We speculate that this difference in findings may be due to the fact that we only included two neuromuscular disease subtypes in our study whereas Chen et al.,[21] included more, and FVC varies greatly between subtypes. Although Lyager et al.[32] showed a correlation between FVC <30% sitting in individuals with Duchenne muscular dystrophy needing mechanical ventilation but did not find this correlation in individuals with spinal muscular atrophy, the positive predictive value of ΔFVC ≤−20% for NIPPV was low in our total cohort and in both disease subtypes. We therefore agree with Chen et al.,[21] that a prospective longitudinal study to assess the predictive value of ΔFVC would help identify a threshold value for initiating NIPPV, but add that these thresholds may be disease and/or gender specific.

Limitations of the current study include the small numbers in each CMD subtype, but given the rare nature of CMD, even this limited sample size has provided useful information and insights. Also, the data were collected and analyzed retrospectively and thus matching of subjects between the two CMD subtypes by age, gender, race ambulatory status, and NIPPV status was not possible. Despite this, there were no significant differences between the two groups with regard to race, gender, or NIPPV status. The difference in age between the two subtypes was a limitation, but we performed sensitivity analyses to overcome this difference, which supported our finding that only COL6-RD individuals had significant change in sitting to supine FVCpp. Furthermore, 28/51 subjects (55%) were not able to meet ATS

criteria, primarily due to (1) an inability to exhale on the FVC maneuver for more than 3 sec (if a child) and more than 6 sec (if an adult) and (2) the difference between the two largest FEV1 values was >0.15 L.[33] Nevertheless, when the analysis was repeated with only those individuals who met ATS criteria, COL6-RD remained the only group with a significant difference between sitting and supine mean FVC. Finally, we did not have detailed retrospective data about degrees of scoliosis in our cohort, which may be a contributing factor to respiratory failure in this population and, although a complex factor to isolate in regard to its contribution, may be an important one to consider in future studies.

In our cohort, only 4/18 participants (22%) with a −ΔFVC >20% were using NIPPV and only 7/21 (33%) with an FVCpp sitting of <60% were using NIPPV, despite current recommendations.[2] This may be due to multiple factors such as a high “baseline” sitting FVCpp, practice variability among clinicians, or the fact that these participants’ pulmonary function may have worsened since their previous PFT. However, it does highlight the critical need for systematic screening, particularly in ambulatory COL6-RD individuals, as previous studies have confirmed that nocturnal hypoventilation requiring nocturnal respiratory support can manifest while an individual with COL6-RD is still ambulant.[4,16,17] Adherence to the current recommendations is crucial to reducemorbidityandmortalityinindividualswithCOL6-RD and LAMA2-RD.

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ABBREVIATIONS

CMD	Congenital muscular dystrophies
FVC	Forced vital capacity
FVC(L)	Forced vital capacity in liters
FVCpp	Forced vital capacity percent predicted
ΔFVC	Relative percent change in FVC(L) from sitting to Supine = [FVC(L)sitting-FVC(L)supine]/[FVC(L)sitting] × 100
COL6-RD	Collagen VI-related dystrophy
LAMA2-RD	Laminin α2-related dystrophy
PSG	Polysomnogram

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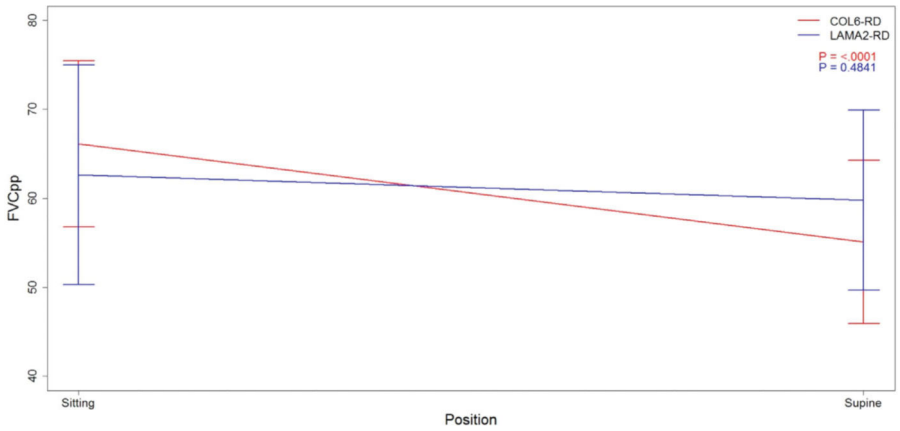

Fig. 1.

FVC percent predicted (FVCpp) sitting and supine by subtype (red, COL6-RD; blue, LAMA2-RD). Only COL6-RD patients had a significant decline by MANCOVA (COL6-RD FVCpp sitting mean = 66.1, FVCpp supine mean = 55.1 $P < 0.0001$).

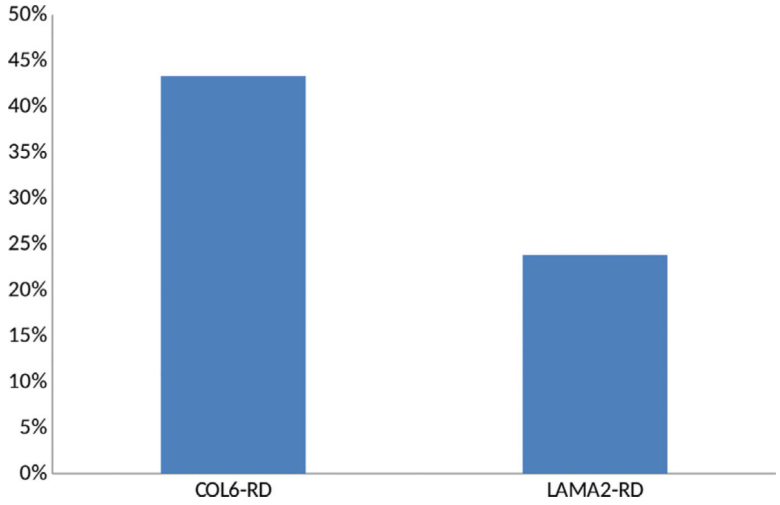

Fig. 2.

Percent of patients with >−20% ΔFVC by disease subtype. Almost twice as many subjects with COL6-RD experienced a >20% decrease in FVC from sitting to supine compared to subjects with LAMA2-RD.

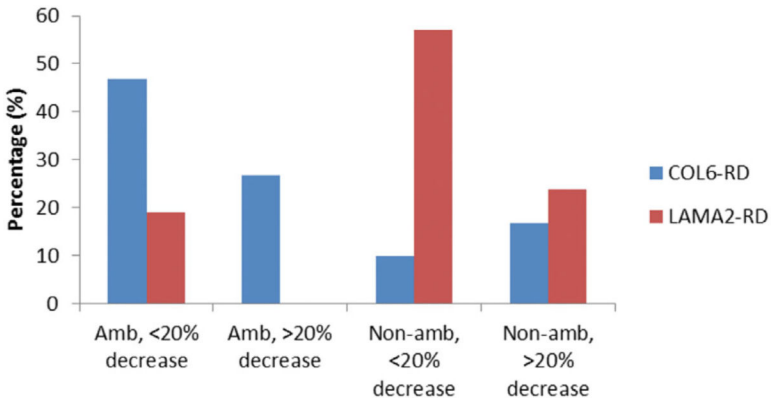

Fig. 3.

ΔFVC and ambulation status in both disease subtypes. Comparison of ambulation and ΔFVC in subjects with COL6-RD to subjects with LAMA2-RD. More subjects with COL6-RD were ambulatory than subjects with LAMA2-RD. The only ambulatory subjects with a −ΔFVC of >20% were those with COL6-RD.

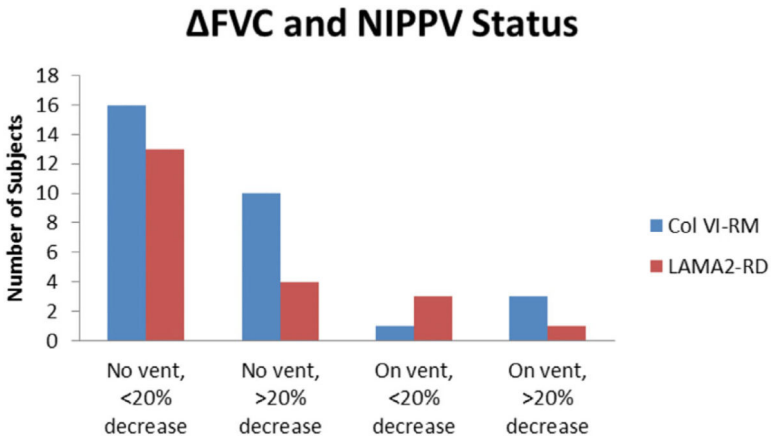

Fig. 4.

ΔFVC and NIPPV status in both disease subtypes. There were three subjects with COL6-RD and one with LAMA2-RD on NIPPV who had a −ΔFVC of >20%. However, there wer 14 subjects (10 with COL6-RD and four with LAMA2-RD) with a −ΔFVC of >20%, who had not been started on NIPPV.

TABLE 1—

COL6-RD and LAMA2-RD Categorized by Disease Subtype, Age, Race, Gender, Ambulatory Status, and Ventilatory Status

	COL6-RD patients, N=30 No. (%)	LAMA2-RD patients, N=1 No. (%)	Total, N=51 No. (%)	*P**
Age range				
Total range	4–61 years	5–54 years	4–61 years	0.04
≤18 years	21 (70)	20 (95)	41 (82)	0.18
>18 years	9 (30)	1 (5)	10 (18)	
Race				
Asian	2 (7)	2 (10)	4 (8)	0.76
Black	0 (0)	1 (5)	1 (2)	
Caucasian	27 (90)	18 (86)	45 (88)	
Hispanic	1 (3)	0 (0)	1 (2)	
Gender				
Male	18 (60)	9 (43)	27 (53)	0.27
Female	12 (40)	12 (57)	24 (47)	
Ambulatory status				
Ambulatory	22 (73)	4 (19)	26 (51)	0.0002
Non-ambulatory	8 (27)	17 (81)	25 (49)	
Ventilation status				
Non-ventilated	26 (87)	17 (81)	42 (82)	0.99
Ventilated	4 (13)	4 (19)	9 (18)	
	30 (100)	21 (100)	51 (100)	

Percentages of category subsets in parenthesis; percentages based on disease subtypes. Totals for each category in the right-hand column; totals by disease at top. Fisher exact test was used to examine the differences in characteristics between the COL6-RD and LAMA2-RD group. The majority of subjects were age 18 years or younger, were Caucasian, and were non-ventilated. The number of males and females was nearly equal, and the number of ambulant/non-ambulant subjects was also equal. Between the two subtypes, there were significantly more adults with COL6-RD than with LAMA2-RD. There was also a significant difference in ambulatory status between the two subtypes (COL6-RD had more ambulant individuals).

* Fisher's-exact test.

TABLE 2—

Range of FVC(L) and FVCpp by Subtype

Subtype	FVC (L) sit	FVCpp sit	FVC(L) supine	FVCpp supine	ΔFVC
COL6-RD					
Max	4.52	113	4.3	102	0
Min	0.38	10	0.27	7	–40
LAMA2-RD					
Max	2.22	113	2.21	106	51
Min	0.32	22	0.41	28	–33

The range of volumes FVC(L) and FVC percent predicted (FVCpp) was larger for subjects with COL6-RD than for subjects with LAMA2-RD, in both sitting and supine positions. The only category where subjects with LAMA2-RD had a larger rangewas in ΔFVC because the ΔFVC actually increased for at least one subject with LAMA2-RD.

TABLE 3—

MANCOVA of COL6-RD and LAMA2-RD Comparing the Difference in Mean FVC(L) Between Sitting and Supine Positions

	n	Variable	Mean FVC(L)	STDV (L)	*P*	Partial Eta^2
Total	51	FVC(L) sitting	1.488	0.934	0.0015 *	0.194
		FVC(L) supine	1.302	0.870		
COL6-RD	30	FVC(L) sitting	1.838	1.023	<0.0001 *	0.526
		FVC(L) supine	1.541	1.008		
LAMA2-RD	21	FVC(L) sitting	0.989	0.467	0.427	0.036
		FVC(L) supine	0.960	0.458		

Partial Eta^2 is a measure of effect size.

Covariates included diagnosis ($P < 0.0001$), ambulatory status, and ventilation status. We repeated the analysis by the specific disease subtypes. The total population showed a significant difference in FVC (L) between sitting and supine positions. Controlling for disease subtype, only subjects with COL6-RD showed a significant difference in FVC(L) between sitting and supine positions.

* Indicates statistical significance for 95%CI.

TABLE 4—

MANCOVA of COL6-RD and LAMA2-RD Comparing the Difference in Mean FVCpp Between Sitting and Supine Positions

	n	Variable	Mean FVCpp	STDV	*P*	Partial Eta^2
Total	51	FVC (%) sitting	64.67	25.69	0.02*	0.110
		FVC (%) supine	57.04	23.51		
COL6-RD	30	FVC (%) sitting	66.10	25.02	<0.0001*	0.594
		FVC (%) supine	55.10	24.54		
LAMA2-RD	21	FVC (%) sitting	62.62	27.11	0.484	0.028
		FVC (%) supine	59.81	22.25		

Partial Eta^2 is a measure of effect size.

There was a significant difference in FVC percent predicted (FVCpp) in the total population between sitting and supine positions. Covariates included diagnosis ($P = 0.0021$), ambulatory status, and ventilation status. Because disease subtype was the only significant covariate, we repeated the analysis by the specific disease subtypes, and only COL6-RD participants had a significant decrease in mean FVCpp between sitting and supine positions.

*Indicates statistical significance for 95%CI.

TABLE 5—

Pearson Correlation of FVC Percent Predicted Sitting and Age

Pearson correlation of FVCpp sitting and age			
	n	**Age**	***P*-value**
Total	51	−0.154	0.282
<18 years	41	−0.406	0.008
>18 years	10	−0.013	0.972

There was a negative correlation between age and FVC percent predicted (FVCpp). Older children (and adults) presented with lower FVCpp. The correlation was only statistically significant for the population that was ≤18 years of age.

TABLE 6—

ΔFVC Cutoff Points

	Total individuals	On NIPPV	<60% FVCpp
ΔFVC	**COL6RD/LAMA2RD**	**COL6RD/LAMA2RD**	**COL6RD/LAMA2RD**
<10%	7/15	1/3	1/8
10–14%	5/0	1/0	3/0
15–20%	5/1	0/0	1/0
>20%	13/5	3/1	7/1
Total	30/21	5/4	12/9

In the COL6-RD cohort 4/30 participants (13%) were using NIPPV, 13/30 (43%) had a −ΔFVC >20%, and 3 of those 13 (23%) were using NIPPV. In the LAMA2-RD cohort, 4/21 (19%) were using NIPPV, 5/21 (%) showed a −ΔFVC >20% and 1 of those 5 (20%) was using NIPPV. More LAMA2-RD than COL6-RD were started using NIPPV before having a −ΔFVC >20% because they had a sitting FVCpp of <60%.