



ACTIVE LUNG VOLUME RECRUITMENT TO PRESERVE VITAL CAPACITY IN DUCHENNE MUSCULAR DYSTROPHY

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Objective: To consider the effect of active lung volume recruitment (“air stacking”) on rate of decline in vital capacity.

Design: Retrospective cross-sectional design.

Patients: People with Duchenne muscular dystrophy.

Methods: Vital capacity was measured at every patient visit and then graphed. Air stacking using volume-preset ventilation or manual resuscitator bag was introduced to all patients after their vital capacity plateaued (reached a lifetime maximum).

Results: For 151 consecutive patients with multi-year data, the 1-year rate of greatest decline in post-plateau vital capacity was 104 ml (8.8%)/year and occurred from age 20 to 21 years. For 53 patients with multi-visit data for whom air stacking was begun at the immediate post-plateau visit, the 1-year rate of greatest decline in vital capacity was 118 ml (8.5%) and occurred from age 20 to 21 years. Between annual visits, vital capacity and maximum insufflation capacity increased 26.4% and 43.3% of the time, respectively. The peak of maximal vital capacity decline occurred more than 5 years later than previously reported without air stacking.

Conclusion: For patients with Duchenne muscular dystrophy, active lung volume recruitment may help to preserve vital capacity. Effects on post-plateau vital capacity may be a useful outcome measure for therapeutic trials.

Key words: air stacking; lung volume recruitment; maximum insufflation capacity; noninvasive ventilatory support; pulmonary compliance.

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Duchenne muscular dystrophy (DMD) is caused by a mutation of the dystrophin gene at locus Xp21 that prevents linkage of the cytoskeleton of a muscle fiber to its basal lamina (1), causing excessive calcium leakage across the membrane and into the muscle sarcolemma. This results in necrosis of muscle fibers (2) and their replacement by fibrofatty tissue (3). The muscle length-tension relationship is altered, and muscle elasticity and plasticity are decreased (3–5). In addition, loose connective tissue within the muscle

becomes dense and fibrotic, further worsening tissue elasticity. The tendons and ligaments of the rib cage stiffen and ankylose, and the respiratory muscles weaken and become contracted (6, 7). As a result, not only do lung volumes diminish, but also it becomes more difficult for the inspiratory muscles to ventilate the lungs, and vital capacity (VC) decreases. Loss of deep breathing further alters alveolar surface tension, thereby increasing the risk of alveolar collapse, atelectasis (8), chronic lung hypoinflation, and mucus retention (6). Excess mucus retention results from an ineffective cough, in part due to low lung volumes and typically results in respiratory failure and death in DMD (9). However, lung volumes can be increased by lung volume recruitment (LVR), thereby improving lung compliance, decreasing work of breathing, and increasing lung recoil pressures for greater cough flows (10, 11).

LVR can be effected by passive insufflation via a manual resuscitator with the exhalation valve blocked, via mechanical insufflation (CoughAssist™, Philips Respironics Inc., Murrysville, PA, USA), or via pressure-preset ventilation at pressures greater than 50 cmH₂O. On the other hand, active LVR, or “air stacking,” involves the glottis holding consecutively delivered volumes of air to a “maximum insufflation capacity” (MIC). Air delivery for air stacking can be via oral, nasal, or oronasal interface from a manual resuscitator or volume-preset ventilator, with the goal of approaching the predicted inspiratory capacity (12). The MIC is a function of pulmonary compliance and strength of glottis closure (12, 13). Exhalation is passive.

In people without neuromuscular disease, the lifetime maximum “plateau” VC occurs at around 20 years of age. Subsequently, males lose 1%/year, while females lose 1.2%/year (14). For people with DMD, the mean age of plateau VC has been reported to be between 11 and 14 years of age (range 9–17 years) (15–18). Following the plateau, VC decreases exponentially with the maximum rate of decrease described from ages 14 to 16 years (15, 18) before VC asymptotically levels off (17).

The purpose of this study was to consider the effect of air stacking on rate of decline in VC and to consider VC plateau and maximum rate of decrease as potential medical trial outcome measures.

METHODS

This retrospective chart review was approved by our Institutional Review Board. The VC was measured at every visit for all patients with DMD referred to a Muscular Dystrophy Association Clinic from 1996 to 2015 who were diagnosed by DNA-based genetic testing (23.3%), muscle biopsy (27.3%), both (19.4%), or family history and clinical phenotype (30.0%) (Mark 8 Wright Respirometer, Ferraris, Anesthesia Associates Inc., Tulsa, OK, USA). Only patients who were non-compliant or incapable of air stacking were excluded from analysis. During the study, patients continued use of noninvasive ventilatory support (NVS) as indicated. Nocturnal NVS was initiated when the patient became symptomatic for nocturnal hypoventilation. Its use was extended during the daytime when dyspneic upon discontinuation. Eventually, patients required NVS continuously. Graphs were made of all VC data-points, of data-points for every patient with multiple post-plateau visits, and of data-points for patients with 5 or more visits (increasing 2 points, plateauing, then decreasing 2 points) that permitted establishment of plateau VC. This permitted determination of the ages at which the VC plateaued and its subsequent rate of diminution.

The age at maximum rate of loss of VC was established by determining the maximum negative slope of VC over time. Since the problem of selecting suitable “predicted” values for partially paralyzed and severely impaired subjects has never been satisfactorily resolved, and use of percentage of predicted normal VC obliterates the plateau phase of DMD, the absolute VC was measured rather than percentage of predicted normal VC, as recommended by Rideau et al. (15).

Following the plateau, which was measured directly or assumed to be passed (for all patients whose VC was documented to be decreasing and all patients over 17 years of age), the patients were trained in and prescribed air stacking 3 times daily with 10–15 stackings each time. The VC and MIC were measured on all subsequent visits via mouthpiece or oronasal interface when lip weakness limited MIC. Post-plateau inter-visit changes in MIC and VC were analyzed. The number of times: (i) both MIC and VC increased; (ii) MIC increased but VC decreased; (iii) VC increased but MIC decreased; and (iv) both MIC and VC decreased were determined.

RESULTS

Fig. 1 shows the 1,033 VC data-points for all 232 patients by age. The maximum 1-year rate of decline in VC (maximum slope) was 106 ml (9.1%)/

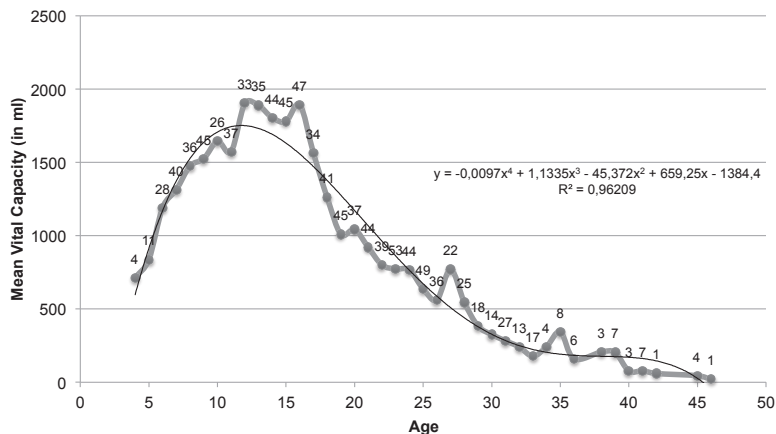


Fig. 1. Data from 232 patients and 1,033 data-points was included in analysis of vital capacity (VC) as a function of age. The maximum slope of rate of decrease in VC occurred from age 20 to 21 years and was 106 ml (9.1%)/year. R-squared is 0.96. The sample size is included above each time-point.

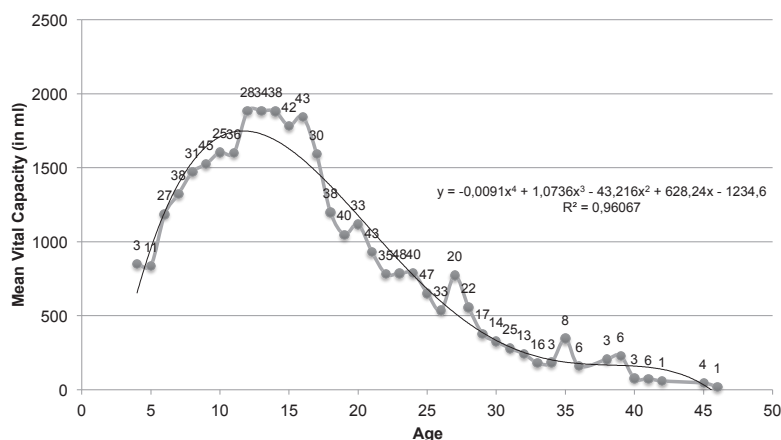


Fig. 2. For patients with multi-year data, 151 patients and 956 data-points were included in analysis of vital capacity (VC) as a function of age. The 1-year rate of greatest decline in post-plateau VC was 104 ml (8.8%)/year and occurred from age 20–21 years. R-squared is 0.96. The sample size is included above each time-point.

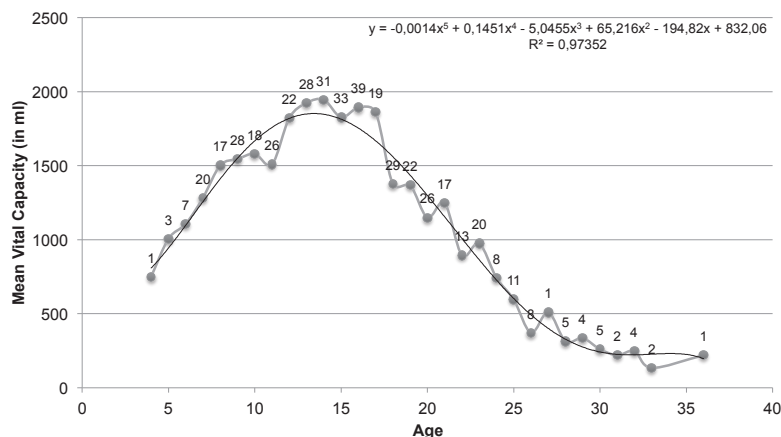


Fig. 3. For patients with a minimum of 5 data-points around the vital capacity (VC) plateau, 53 patients and 470 data-points were included in analysis of VC as a function of age. The maximum 1-year decline in VC occurred from age 20 to 21 years and was 118 ml (8.5%)/year. R-squared is 0.97. The sample size is included above each time-point.

year. It occurred from age 20 to 21 years. The R-squared value was 0.96. Fig. 2 graphs the 956 data-points for 151 patients with multiple post-plateau visits. From the best-fit curve, the maximum 1-year decline in VC occurred from age 20 to 21 years and was 104 ml (8.8%). Fig. 3 presents 470 data-points from 53 patients with 5 or more points around the plateau who began air stacking immediately upon determination of the plateau. From the best-fit curve, the maximum 1-year decline in VC occurred from age 20 to 21 years and was 118 ml (8.5%). Although 3 additional patients were unable to air stack due to cognitive impairment, no patients were non-compliant since all required air stacking to independently increase cough flows and voice volume.

The mean MIC-VC difference was 640 ml. Both MIC and VC increased 50 times, with MIC increasing by a mean of 189 ml (standard deviation (SD) 225) (19.9%) and VC increasing by 58 ml (SD 83) (17.9%) from the previous year. There were 78 instances in which MIC increased by a mean of 211 ml (SD 281) (22.8%), while VC decreased by 88 ml (SD 74) (17.8%). There were 28 instances in which MIC decreased by a mean of 180 ml (SD 144) (13.8%), while VC increased by 38 ml (SD 40) (15.2%). Both MIC and VC decreased 139 times, with MIC decreasing by a mean of 270 ml (SD 230) (17.3%) and VC decreasing by 162 ml (SD 159) (23.7%).

DISCUSSION

In addition to air stacking, nocturnal use of NVS must be considered to have potential bearing on the preservation of VC. In her 1987 study, Delaubier et al. (19) reported a post-plateau annual rate of decline in absolute VC of mean 206 ml for 75 untreated patients with DMD. For 20 other patients, she prescribed sleep nasal NVS from the point of VC plateau. For these 20, the maximum annual VC decline was 161 ml/year and occurred from age 15 years 10 months to 17 years 9 months (19). Delaubier et al. attributed the decrease in fall off of VC to the use of NVS without taking into account the asymptotic leveling off of VC decline that occurs naturally, but a possible treatment effect of NVS could not be ruled out (19). Subsequently, a multicenter study (20), albeit one with significant methodological flaws (21), concluded that sleep NVS had no effect on preserving VC in DMD.

In our study, maximum 1-year VC decline for patients beginning LVR upon reaching plateau VC (Fig. 3) was 118 ml (8.5%)/year, but it occurred 5 years after the point of maximum decline reported by Delaubier et al. (19). Furthermore, our patients began NVS at a mean of 18.8 years (SD 2.4) of age with VCs less than 700 ml, or approximately 5 years after the VC plateau, and only became continuously dependent on

it with VCs under 300 ml at 22.3 years of age (SD 4.7), which was just after the point of their maximum VC drop off (22). Therefore, it is less likely that NVS played a significant role in the apparent preservation of VC seen in our patients.

Our observed maximum decline in VC occurring between ages 20 and 21 years can also be compared to the maximum annual rate of decline of 39% and median 8%/year over multiple years reported by Wagner et al. for untreated patients (23) and to decreases of 8.5–14%/year over multiple years reported in other studies that identified neither maximum rates of VC decline nor plateau VC (15, 16, 18, 24–29). These studies reported decreases in the percentage of predicted VC over ages 10–20 years, of 8.5%/year, or 85% over 10 years (3), 5%/year over ages 5–24 years ($n=60$) (26), 8%/year over ages 10–18 years ($n=58$) (27, 30, 31); 10.7%/year over ages 12–15 years ($n=10$) (28), and 4.2%/year at mean age 13 years ($n=25$) (16). Therefore, all of these studies included pre-plateau data-points for which absolute VCs would have been increasing and points for which VC percentage of predicted normal would have been changing only minimally (16, 23, 29).

In a graph of VC over time for 120 patients with childhood onset rapidly progressive muscular dystrophy that, in retrospect, included patients with milder conditions, such as limb-girdle muscular dystrophy and other non-DMD myopathies initially confused with DMD, the maximum rate of loss of VC was 13.5%/year between ages 10 and 15 years despite the fact that a more moderate rate of loss might have been expected for a group that included patients with milder conditions (18).

McKim et al. (24) reported that beginning active LVR once VC decreases below 80% of predicted normal decreased the rate of decline in percentage of predicted VC from 4.7% to 0.5%/year. However, that study was small and also did not distinguish pre- from post-plateau patients and so included patients whose absolute values of VC were spontaneously increasing and percentage of predicted normal was still relatively stable without treatment (24). In a follow-up study, use of active LVR also demonstrated significant attenuation in VC decline and a stable MIC-VC difference over time of approximately 700 ml (32). This is comparable to the 640 ml MIC-VC difference observed in this study. In another study, a small and not statistically significant increase in VC was reported for 10 DMD patients by using mechanical insufflation-exsufflation, a form of passive LVR (25).

The early stability, and late leveling off, of VC that occurs for DMD (17), amyotrophic lateral sclerosis (33), and other neuromuscular disorders have misguided investigators into thinking that interventions

including prophylactic institution of sleep nasal ventilation (19, 34), and diaphragm pacing (33) have had a beneficial effect on preserving VC. Likewise, concerning medication trials, in an idebenone trial (35), significant results were confounded by grouping pre- with post-plateau patients. By including pre-plateau patients in studies, natural VC trends are ignored. In future studies, benefits should be established by demonstrating a decrease in maximum rate of loss, as noted here.

The absolute value of VC increased 78 out of the 295 times following VC plateau in this study. Although this was only 26.4% of the time, it is remarkable considering the normal decline in post-plateau VC. The MIC increased 43.3% of the time, demonstrating that it can increase with practice even though inspiratory muscles are weakening. This indicates some combination of relative sparing of bulbar-innervated musculature, diminished inspiratory muscle contractures (9), and improvement in dynamic pulmonary compliance with practice (15). Increasing lung volumes by air stacking also improves cough flows to help avert episodes of respiratory failure (13, 36).

Limitations of the study include that, with absence of a control group, it is not possible to know for certain that LVR helps preserve VC or that post-plateau VC does not increase spontaneously from time to time. Likewise, the fact that 8.6% of our subjects had taken glucocorticoid therapy could have affected the results and comparisons with other centers, assuming that a smaller percentage of their patients had also been taking glucocorticoids. Cardiac, mobility, cognitive, and psychiatric considerations, as well as scoliosis may also affect patient motivation and effort for accurate VC measurements and compliance with air stacking (29). Another shortcoming was the inability to accurately determine how often our patients were air stacking other than by their say so. A more accurate method to quantify compliance with air stacking is needed. Selection bias must also be considered, since 78 patients with only single data-points and 3 who could not air stack were excluded from the analyses in Figs 2 and 3. However, for all 3 analyses, the ages and rates of maximum 1-year decline were essentially identical. Most subjects with single data-points came from out-of-state, but it has never been suggested that the incidence of DMD varies from one state to another.

Because of the need to maximize cough flows and the other benefits of active LVR (10, 11), all patients with DMD should be trained in air stacking and have their efficacy using it measured at least annually.

Numerous medication trials now underway for DMD have relatively imprecise primary outcome measures (37–39), such as percentage of patients walking as a

function of age and 6-min walk distances that vary with practice, learning, steroid intake (40), lower limb orthopedic interventions (41), and by as much as 30% by motivation and degree of encouragement. Such measures also exclude subjects with advanced disease who can no longer walk. On the contrary, age at VC plateau and maximum rate of loss of VC are objective, quantifiable, and reproducible, reflect the function of 68 respiratory muscles (42), and should be considered as outcome measures for treatment trials.

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