The FIVC should be used as an acceptable substitute for the FVC when evaluating the FVC in neuromuscular disease; experience in a clinical trial for adult myotonic dystrophy

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Rationale

The FVC is used to evaluate respiratory muscle function in neuromuscular disease, both clinically and in clinical trials. The 2019 ATS/ERS spirometry standards[1] strongly recommend the performance of a forced inspiratory vital capacity (FIVC) maneuver upon completing the forced exhalation.

Comparison of the FVC with the FIVC that followed allows verification that the forced exhalation started from full inflation. If the FIVC is more than 105% of the FVC (or > 0.100L larger, if the FVC is < 2.00L), this indicates the forced exhalation started before the patient reached full inflation.

The ATS/ERS 2019 spirometry standards imply equivalence of FVC and FIVC yet sponsors of clinical trials are uncertain about the ability of patients to provide both FVC and FIVC for each spirometry effort. Sponsors are also reluctant to offer the FIVC as a surrogate for the FVC to regulators when the comparison shows the forced exhalation started before the patient reached full inflation.

Methods

We evaluated forced spirometry measurements in a clinical trial of patients with adult myotonic dystrophy collected in both sitting and supine positions at 3 study visits: Baseline, 3 months and 6 months.

50 patients were screened, and 37 patients were able to complete Baseline through 6-month measurements.

The 2019 ATS/ERS spirometry standards were employed, including the measurement of the FIVC upon completion of the forced exhalation.

We present data on how often the FIVC was too small to allow evaluation of full inflation and how often the FIVC showed the forced exhalation was started too early.

No data on study outcomes is presented here.

Results

21 (9.8%) of the 102 acceptable upright spirometry measurements and 21 (17.6%) of the supine spirometry measurements showed a FIVC < 90% of FVC and provided no utility for evaluating full inflation.

When a proper FIVC was performed, patients were able to demonstrate full inflation in 98.0% of sitting measurements and 99.0% of the supine measurements.

Results (cont.)

One sitting measurement showed a FIVC 0.53L larger than the FVC in that measurement.

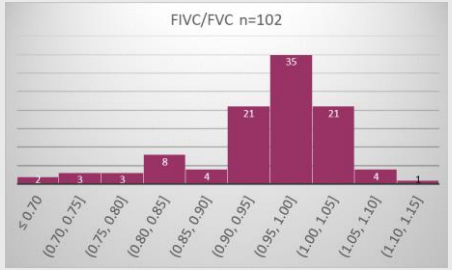
The FIVC was larger than the FVC in 28 (23.5%) of the sitting measurements and 62 (42.1%) of the supine measurements.

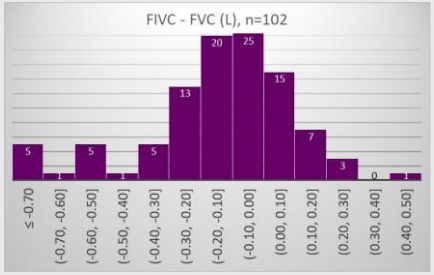
The FIVC averaged 0.080 L (SD 0.40L) less than the FVC for sitting measurements and 0.101 L (SD 0.63L) less for supine measurements.

The mean coefficient of variation during the study period was 3.4% (SD 2.4%) for the sitting FVC and 3.8%(SD 3.4%) for sitting VCmax.

The mean coefficient of variation during the study period was 6.1% (SD 8.8%) for the supine FVC and 5.8% (SD 8.8%) for the supine VCmax.

The frequency distribution of FIVC/FVC and FIVC – FVC





Conclusion/Discussion

1. Phase 4 of forced spirometry, the measurement of the FIVC upon completing the forced exhalation, provides objective verification that forced exhalations start from full inflation.
2. Successful measurement of the FIVC, comparable or larger than the FVC, was demonstrated in 90.2% of upright and 82.4% of the supine forced spirometry measurements in a clinical trial of patients with adult myotonic dystrophy,
3. The FIVC provided a slightly higher value than the FVC in 24% of the upright forced spirometry measurements and 42% of the supine forced spirometry measurements in this clinical trial of patients with adult myotonic dystrophy.
4. When the forced exhalation was shown to start before full inflation was reached, the repeatable larger FIVC provided a value comparable to other previous and subsequent measurements on the subject and could prevent a missed data point.
5. When the vital capacity is the sole parameter of interest (e.g., IPF, neuromuscular disease), performance of a FIVC maneuver provides two opportunities to obtain the patient's largest vital capacity in each forced spirometry effort.

Reference

1. Graham BL, et al. Standardization of spirometry, 2019 update. Official ATS and ERS Technical Statement. Am J Respir Crit Care Med. 2019

Poster 4052

Conflicts of Interest: Authors McCarthy, Lake, Patterson, Baumle and Ramos are full-time employees of Clario. C Heusner was a full-time employee of Avidity Biosciences

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