

Long-term accuracy of 5 current pulmonary function instruments in the measurement of DL_{CO}

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ABSTRACT

Five new pulmonary function test (PFT) instruments (Collins CPL, JaegerUSA Masterscreen Diffusion TP, Morgan Transflow Test PFT System, Medical Graphics Profiler DX™ System, SensorMedics Vmax 22D) were tested with a DL_{CO} simulator using 3 precision gas mixtures and 3 different inspiratory volumes. An additional precision gas mixture was supplied to each instrument, as its normal DL_{CO} test gas, so that accurate differences between inspired and expired gas concentrations could be determined. Testing was performed on days 0, 30, 60, and 90. At each testing session, each gas mixture and volume (total of 9 test conditions) was manually injected into each device 5 times (45 total tests). Simulator-derived target values were calculated from the breath-hold time reported from the instrument and precision gas concentrations. Individual instrument measurements of DL_{CO} were compared to their simulator-derived target values. The mean absolute bias in DL_{CO} across all 45 tests (observed DL_{CO} – target DL_{CO}) for each PFT instrument on each test day is presented in Figure 1:

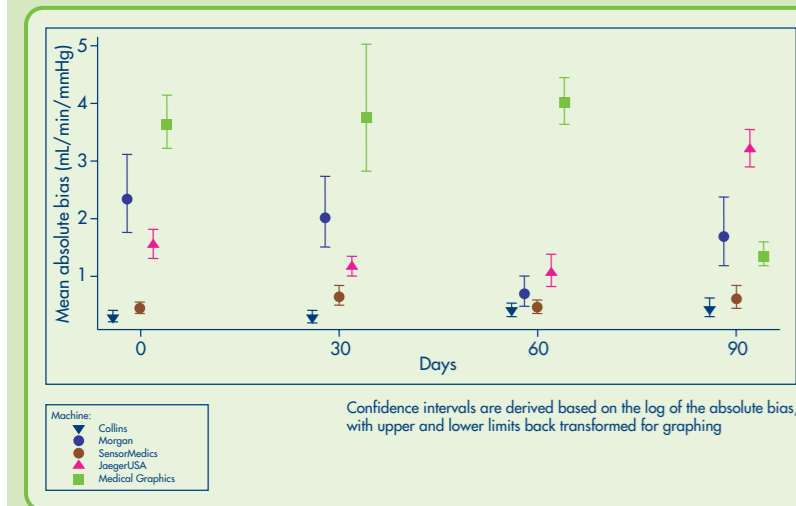


Figure 1. Mean (95% CI) absolute bias by machine and day - DL_{CO}.

Conclusions: This study suggests that the accuracy of DL_{CO} measurement can vary among commercially available PFT instruments. Such biases need to be confirmed in additional instruments, expanded test conditions, and human subjects.

BACKGROUND

Longitudinal measurement of pulmonary function is an integral component of assessing the safety and efficacy of drugs delivered by inhalation. An understanding of instrument accuracy and variability is essential in clinical trial design, as well as in the interpretation of longitudinal PFT measurements in disease states. Methods for assessing the accuracy and variability associated with repetitive pulmonary function measurements using modern PFT instruments are, however, largely lacking. The following study was performed to assess the longitudinal accuracy and precision of 5 commercially available PFT instruments in the longitudinal measurement of pulmonary diffusing capacity (Single-breath DL_{CO}), and to support the PFT methodologies utilized in the Exubera® (inhaled insulin) clinical development program.

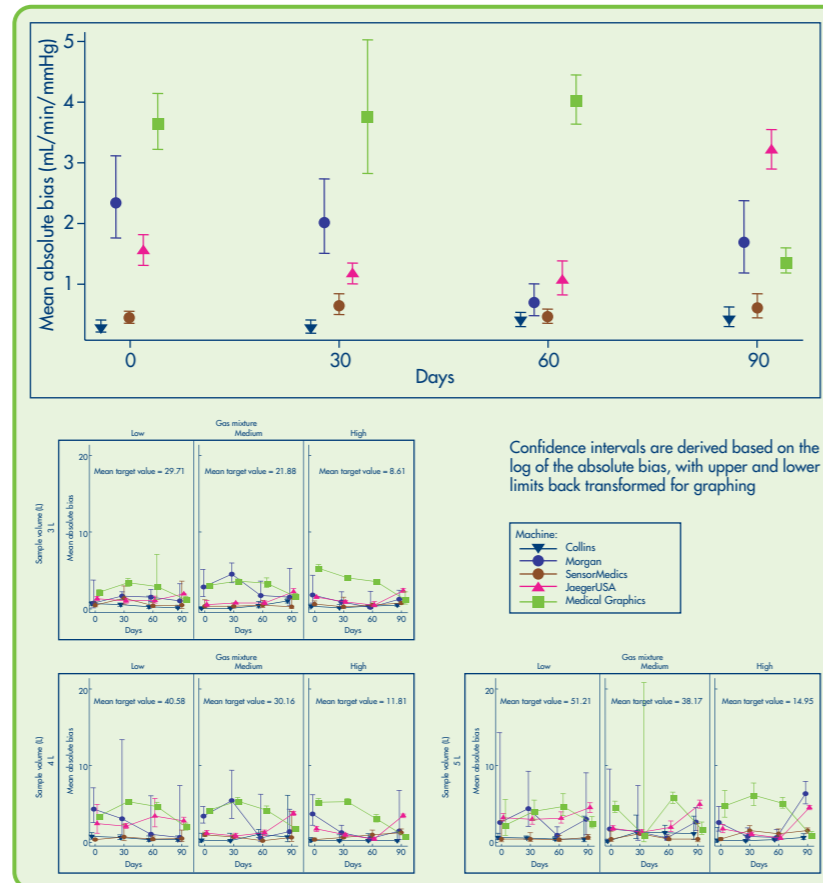


Figure 2. Mean (95% CI) absolute bias by machine and day - DL_{CO} (mL/min/mmHg).

METHODS

- One new instrument model from 5 different PFT equipment manufacturers was purchased to perform these studies. The models were:
 - Collins CPL
 - Morgan Transflow Test PFT System
 - SensorMedics Vmax 22D
 - JaegerUSA Masterscreen Diffusion TP
 - Medical Graphics Profiler DX™ System.
- Each instrument was set up and maintained throughout the study according to manufacturer's specifications.
- All instruments remained powered on for the duration of the study.
- All testing was done at LDS Hospital in Salt Lake City and performed by 2 experienced technicians.
- All instruments were calibrated on days of testing.
- We used a DL_{CO} simulator (Hans Rudolf, Kansas City, MO) to simulate a broad range of DL_{CO} values.
 - DL_{CO} was simulated by varying the inspired volume and, after the breath-hold, injecting gases with known concentrations of CO and the tracer gas.

DL_{CO} SIMULATOR

- The DL_{CO} simulator works with 2 precision syringes, 1 that is used to precisely inhale a known volume of test gas (V_{insp}) and the other to inject a precision gas mixture where concentrations are known to 1% of the manufacturer's reported value (eg, a CO concentration of 0.101% would be accurate to within 0.00101%).
- Three different gas mixtures were developed that "simulate" different physiologically relevant levels of exhaled gases that can be observed in patients with a broad range of DL_{CO} values.
- With these 3 "known" values (V_{insp}, FA_{CO}, and FA_{tracer}) along with a breath hold time, the simulator software calculates a target DL_{CO} value for each DL_{CO} test.
- For each individual test, the difference between the measured and target DL_{CO} values was calculated.

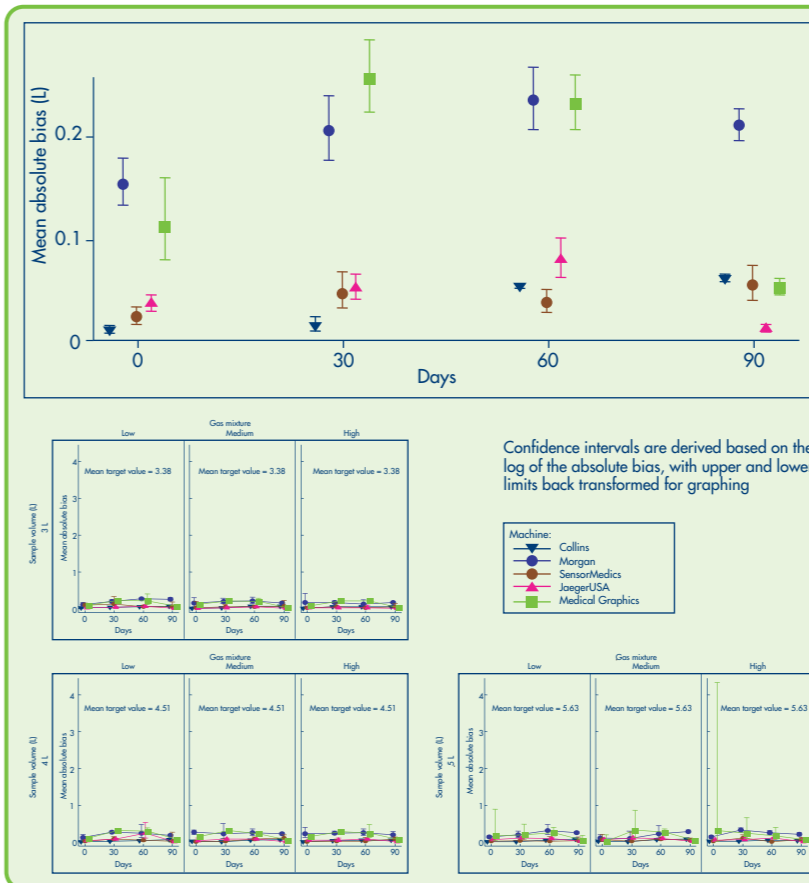


Figure 3. Mean (95% CI) absolute bias by machine and day - alveolar volume (L).

STUDY DESIGN

- Six repetitions of 9 test gas/inspiratory volume combinations were injected into each instrument over a 90-day period according to the schedule in Table 1.
- To ensure complete flushing of the system, the first trial of a group of 6 repetitions was deleted from the analysis.

Table 1.

Instrument	Day 0 (Repetitions × gas-volume combination)	Day 30 (Repetitions × gas-volume combination)	Day 60 (Repetitions × gas-volume combination)	Day 90 (Repetitions × gas-volume combination)	Total observations analyzed per instrument
Collins	6×9	6×9	6×9	6×9	180
Morgan	6×9	6×9	6×9	6×9	180
SensorMedics	6×9	6×9	6×9	6×9	180
Jaeger	6×9	6×9	6×9	6×9	180
Medical Graphics	6×9	6×9	6×9	6×9	180

- As outlined in Table 2, each of 3 test gas mixtures was combined with 3 inspiratory volumes to produce the 9 simulated DL_{CO} maneuvers utilized in the protocol:

Table 2.

Gas mixture	Inspiratory volume (L)
Low	3, 4, and 5
Medium	3, 4, and 5
High	3, 4, and 5

Simulator gas mixtures

Table 3.

	% Carbon dioxide	% Carbon monoxide	Tracer gas, as % of inspired	% Oxygen	% Nitrogen
Low gas mixture	5.000	0.080	75	16.000	balance
Middle gas mixture	5.000	0.100	67	16.000	balance

Analysis

- The following DL_{CO} end points were recorded:
 - Diffusion capacity (DL_{CO})
 - Alveolar volume (VA)
 - Inspiratory volume (VI).
- Instrument mean absolute Bias: [observed – target].

RESULTS

- The mean absolute biases in DL_{CO}, VA, and VI across all test conditions, and for each individual test gas-inspiratory volume condition are presented in Figures 2, 3, and 4.

DISCUSSION

- This is the first large-scale study utilizing a DL_{CO} simulator to test DL_{CO} instruments.
- The methods employed in this study represent an approach to assessing the longitudinal accuracy of PFT instruments in the measurement of DL_{CO}.
- The results represent analyses obtained on 1 instrument per manufacturer and may not be representative of all of their models.
- Our observations need to be expanded to additional units, longer time intervals, altitude, and human testing.
- Overall biases associated with the measurement of DL_{CO}, VA, and VI varied significantly among the PFT instruments tested.
- There was no apparent systematic drift in bias observed over the 90-day period of the study.

CONCLUSIONS

Based on these results, we conclude that some instruments may be preferable in the measurement of DL_{CO} over time in a clinical or research setting. The choice of DL_{CO} instrument may impact clinical study design and study results.