**Online data supplement to:**

# Performance of noninvasive airway occlusion maneuvers to assess lung stress and diaphragm effort in mechanically ventilated critically ill patients

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## Supplementary methods

**Measurement setup and Calibration**

The ancillary study design and experimental setup have been described previously.1 In short, all patients received a nasogastric catheter with an esophageal and gastric pressure balloon (Nutrivent, Sidam, Italy). Correct positioning of the catheter was confirmed with a chest x-ray and by inspection of the pressure traces. Correct filling and pressure transmission of the esophageal balloon was confirmed by progressively inflating the balloons with steps of 0.2ml until the ratio of the drop in airway pressure (Pao) and esophageal pressure (Pes) during an occluded breath was between 0.8 – 1.2 (preferably 1.0), with as little volume as possible, as recommended previously.2,3 The pressure balloons were connected with stiff 4mm tubing to a TSD104A attached to a TSD100C signal amplifier, which was in turn connected to a MP160 signal acquisition setup. A differential flow sensor (Adult Flow Sensor, Hamilton Medical, Swiss) was placed in series to the patient’s ventilatory circuit, and was connected to a TSD160F differential pressure transducer to measure flow. The tubing originating from the proximal (patient) side of the flow sensor was split close to the acquisition device with a Luer-lock three-way valve and connected to a TSD104A pressure transducer to measure Pao. Using a gain of 1000 on the sensors, the expected error is ~0.2 cmH2O according to the manufacturer.
Before each measurement commenced in a patient, all of the pressure sensors (for Pao, Pes and Pga) were calibrated by constructing a two-point calibration curve. First, the sensors were opened to the atmosphere for 30 seconds, and the average recorded signal was then set at 0 cmH2O. Next, a known pressure of 30 cmH2O was generated by a calibration device (Citrex H4, IMT Analytics, Swiss) for 30 seconds. The average recorded signal by the sensors over this period was then set at 30 cmH2O. The acquisition software (Acknowledge, BIOPAC, USA) then constructed a calibration curve. Flow was calibrated by opening both ends of a differential pressure transducer to the atmosphere for 30 seconds and setting the average recorded signal to 0 L/s. Next, a large syringe containing 1000mL was injected and then refilled through the differential pressure sensor in ~10 seconds. The calibration curve of the flow sensor was adjusted until the integral of flow during one full inhalation and exhalation by the syringe measured 1000 ± 20mL, thus accepting a 2% error.

**Signal analysis**

Esophageal pressure (ΔPes), respiratory muscle pressure (ΔPmus), transdiaphragmatic pressure (ΔPdi) and transpulmonary pressure (ΔPL) were calculated as the absolute difference between baseline and peak (or nadir) in each available breath (**Figure 1** of the main manuscript). The occluded inspiratory airway pressure (Pocc) was calculated as the maximal drop in airway pressure during an airway occlusion maneuver.4 P0.1 was calculated as the absolute drop in airway pressure during the first 100ms of the same end-expiratory occlusion.5,6 Pmus was calculated as the absolute difference between the chest wall recoil pressure (calculated as tidal volume \* chest wall elastance) and Pes. The chest wall elastance was calculated as (Pes during an inspiratory plateau – Pes during an expiratory occlusion) / tidal volume; measurements with a rise in Pga >2 cmH2O during the occlusions were discarded because of suspected expiratory muscle activity. Each breath was indexed by a computer script based on flow. Breaths with suspected artefacts (such as coughs and swallows) were discarded by having the script remove breaths that met the following criteria: Inspiratory or expiratory volume >2L; ΔPes, ΔPga, ΔPdi and ΔPL >100 cmH2O; the first and last sample of Pes, Pdi, Pga and PL >30 cmH2O or <30cmH2O from the average Pes, Pdi, Pga and PL of that subject. This selection step discarded ~2% of all breaths.

Several parameters were calculated in the 60 minutes immediately preceding the airway occlusion maneuvers: the average ΔPdi, ΔPmus and ΔPL; the pressure-time product of the diaphragm (PTPdi, calculated as the time-integral of Pdi divided by 60 to convert the unit to cmH2O**⋅**s**⋅**min-1); and the transpulmonary mechanical power (MPL, calculated as the area enclosed by the PL-volume loop of an ‘averaged breath’ **(Figure E1)**, multiplied by 0.098 and the respiratory rate to convert the unit to J/min.7 To obtain an average breath representative for an hour of measurements, 100 breaths (based on the onset of inspiratory flow) were selected at random and stacked on top of each other. Breaths that had a minimum, maximum or median PL or tidal volume that was more than 2 standard deviations different from all breaths recorded in that hour were discarded. Next, these pressure-volume loops were averaged in two dimensions to obtain a single ‘average’ pressure-volume loop representative for that hour as described previously.8,9

Inspiratory airway support (Pinsp) was defined as the inspiratory support set on the ventilator (in cmH2O) in pressure support mode as opposed to the peak inspiratory airway pressure minus PEEP used in an earlier study4 based on observations made during the analysis. While conducting the signal analysis it was noticed that some patients have a sharp increase in airway pressure right before inspiratory support is terminated by the mechanical ventilator. Upon inspection of the esophageal pressure tracings (**Figure E2**), we concluded that these rises in airway pressure were caused by continued inspiratory pressure support by the ventilator while the patient’s respiratory muscles were already starting to relax, evidenced by a rise in Pes (blue shaded areas below), consistent with delayed cycling. Adding these sharp rises in airway pressure to the formula to predict PL resulted in substantial overestimation of cyclic lung stress in these patients. Therefore, the predicted ΔPL was calculated using the support set on the ventilator (consistent with the plateau in airway pressure during the first part of pressurization). In the external validation cohort, Pinsp was calculated as the average increase in airway pressure at the peak of Edi during each NAVA-level.

**Statistics**

The correlations of ΔPdi with ΔPmus and ΔPes were assessed breath-by-breath in dynamic conditions using all breaths in the main cohort. To assess the diagnostic capacities of a bedside Pes-measurement for assessing potentially-injurious diaphragm effort in the preceding hour, 10 breaths were selected at random by a computer script from each hour of the recordings to simulate random bedside measurements. Next, the drop in Pes in these breaths was compared with the average Pdi in the preceding hour. This procedure was repeated 1000 times; the average AUROC from all these runs is reported. The same procedure was repeated after averaging 3 consecutive Pes-measurements to assess to which degree this would improve the correlations and diagnostic properties.

**Potential magnitude of measurement errors**

To assess the potential magnitude and influence of measurement errors in our analysis, we critically assessed the properties of the measurement setup and ran several simulations based on our data. The TSD100C has a noise level of ±0.010 volts according to the manufacturer. With the gain levels used in our setup, one volt corresponds to 33 mmHg, meaning random noise is expected to be ~0.3 mmHg or ~0.4 cmH2O. However, the influence of random noise was further reduced in our analysis by collecting data at 250 Hz, and using moving average filters averaging the signal every 25 samples. To assess how much this filtering step reduced random noise, we analyzed 17 of the calibration files that we still had available. The first 1000 samples (i.e., 4 seconds) after applying 30 cmH2O with the calibration device (after initial calibration) were assess from each calibration in filtered and unfiltered conditions. We found that the average measured pressure at this period was cmH2O was 30.11 ±0.52 cmH2O in the unfiltered signal, and 30.10 ± 0.11 cmH2O after filtering.

To assess whether our conclusion that Pes cannot replace Pdi could be heavily influenced by measurement errors, we simulated 1000 breaths for each subject in our statistical software (R, R Foundation for Statistical Computing, Austria) and used both conservative and high measurement errors. First, we constructed Pes\_true in each subject by generating a normal distribution using the average and standard deviation of ΔPes as it was observed in each subject to simulate biological variation. For the conservative error estimation, we constructed Pes\_error as random Gaussian noise with mean 0 and standard deviation of 0.156 cmH2O as observed in the analyses on random variations shown above. The 0.156 was obtained by taking the square root of (0.112 + 0.112), as the Pes and Pga measurements are deltas and thus the random noise is present at both the peak and nadir. For the high error estimation, we used a SD of 0.778 cmH2O as if the data was unfiltered (square root of 0.552 + 0.552). Next, we added additional random noise with a mean of 0 and a SD of ±1.44% of Pes\_true to Pes\_error to account for errors induced by the inaccuracy of the calibration device (Square root of 1% + 1%). Pes\_observed was calculated as Pes\_true + Pes\_error. The same procedure was repeated to construct Pga\_true, Pga\_error and Pga\_observed. Finally, Pdi\_true was constructed as Pga\_true + Pes \_true, and Pdi\_error as Pga\_error + Pes\_error. Pdi\_observed was calculated as Pdi\_true + Pdi\_error.

Next, we correlated Pes\_true to Pdi\_true and Pes\_observed to Pdi\_observed, calculated the correlation coefficients with mixed linear models and constructed the Bland-Altman plots with all available simulated data as described in the methods section. The process was repeated with conservative and maximal error estimates.

We found that the correlation between Pes\_true and Pdi\_true had an r2 of 0.97, bias 0.2 cmH2O, and 95% limits of agreement from -4.2 to 4.6 cmH2O**.** With conservative error estimates, the correlation was r2 = 0.97, bias 0.2 cmH2O, with 95% limits of agreement from -4.3 to 4.7 cmH2O**.** With maximal error estimates, the correlation was r2 = 0.95, bias 0.2, limits of agreement -4.5 to 4.9 cmH2O**.**

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