ONLINE SUPPLEMENT

TITLE: Tidal flow variability measured by impedance pneumography relates to childhood asthma risk

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MORE DETAILED METHODS SECTION

Measurement methods

Impedance pneumography measurement

The overnight signals were acquired using custom designed recording devices (design of Tampere University of Technology, Finland as a modified version of that presented by Vuorela et al. [1]) storing lead I electrocardiogram (ECG), IP and tri-axial acceleration (Article Figure 1). The three signals were sampled at 512, 256 and 64 Hz rates, respectively. Impedance was measured in a 4-electrode fashion, placing the electrodes bilaterally on the thorax and arms close to the armpit. This configuration has been shown to yield very high linearity between impedance and lung volume [2]. Ambu BlueSensor BRS (Ambu A/S, Ballerup, Denmark) pre-wired hydrogel electrodes were used.

Skin electrodes and the IP device, held in a special shirt were set up by a research nurse at the hospital. Parents kept diary of sleeping time, eventual symptoms and medication at home.

No calibration was required on IP since the derived flow parameters do not depend on absolute measures of flow. It is, however, strictly required that the IP signal is highly linear with the flow signal. This was ensured by one-minute simultaneous IP and pneumotachography (Medikro, Pro, Kuopio, Finland) tidal breathing recording in sitting and laying positions while the child was still at the hospital. The linearity was found acceptable and similar (data not shown) to a previous validation study on similar children [3].

Whether the relation of the varying lung volume and the measured thoracic electrical impedance is linear (desired) or non-linear depends mainly on the electrode placement strategy. In most earlier studies the electrodes have been placed bilaterally on the thorax at different levels on the midaxillary line. This tends to yield a non-linear volume-impedance-ratio [4], but the recently introduced electrode placement strategy [2] used in this study produces a highly linear ratio. This linearity was demonstrated earlier also in preschool children during induced bronchial obstruction [3] and in healthy adults under mechanical respiratory loading [5].

Differentiating a naturally volume-oriented signal of IP to yield a flow-oriented signal pronounces any noise in the signal decreasing the signal to noise ratio. This places additional challenges to the filter algorithm that suppresses the cardiogenic signal that must leave minimal traces of (cardiac) noise in the signal while carefully preserving the respiratory part of the signal, especially its linearity with instantaneous lung volume.

IP signal pre-processing

All signal processing and statistical analysis was performed using MATLAB software (MATLAB R2015a, MathWorks Inc., Natick, MA, USA). One experienced investigator who was blind to patient information screened the signals manually for sections of motion or other distortion (such as induced by cough, movement or talking) that were left out of further processing and analysis. The selected sections were then filtered with a specifically developed algorithm [6] to remove the cardiogenic impedance changes while maintaining signal linearity with lung volume changes. The naturally lung volume-oriented IP signal was differentiated using a Savitzky-Golay filter [7] of second order with window length of 50 ms to yield a flow-oriented IP signal.

Measurement analysis

The main outcome measures of the study were two IP-derived parameters, CSR and NL, which were analysed with respect to the three patient groups. In addition the most referenced TB variable, the ratio of time of peak expiratory flow and expiratory time, Tptef:Te [8], was derived.

IP signal analysis approach 1 (Curve shape correlation, CSR)

The IP-derived volume and flow signals were cut into sections of individual breaths using a simple volume signal minima-maxima-algorithm. These individual breaths were averaged in the flow-volume domain using the approach of Sato & Robbins [9] using a window of 20 breaths that was moved in overlapping steps of 5 breaths. After averaging the curves were normalized in flow and volume to range 0-1.

These pre-averaged flow-volume curves were then further averaged in a longer, 2-hour window by taking mean. The following procedure of finding CSR values is illustrated in Article Figures 2 and 3. One window was moved in steps of 10 minutes between 12 am and 4 am (early set), and another one between 2 am and 6 am (late set), both time sections yielding thus 13 averaged flow-volume curves. Pearson linear correlation coefficient was determined between all 13 times 13 averaged curves. Since the latter part of the expiration is less affected by muscle control and thus better reflects the mechanical properties (time constant) of the respiratory system [10, 11], the correlation was calculated using only the 50-100% of expired volume part of the curve (Article Figure 3). The smallest encountered curve correlation, denoting the highest overnight change in the curve shape, is reported as CSR_{min} for each patient. See Article Figure 3 for examples of TBFVCs corresponding to different CSR_{min} values.

The averaging process was split into the two described steps to enable fast experimentation with window lengths as the first step was computationally too intensive for repeated running. The rationale for a rather long averaging window in second step was to overcome the variation in airway resistance potentially caused by changing sleep stages [12] and thus reveal slower changes possibly induced by progressing asthmatic obstruction. Window length of 2 hours was considered to extend over sleep stage interval in children [13].

IP signal analysis approach 2 (Noise limit, NL)

The IP-derived flow signal chaoticity was defined by calculating noise limit (NL) using the Noise Titration method which has been described by Poon et al. in detail [14]. Briefly, the algorithm adds white noise to the signal in incremental steps and between each addition it tests (using Volterra-Wiener-Korenberg series) whether chaotic dynamics can still be detected (hence the name “titration”). NL value of zero denotes non-chaotic signal or that its chaoticity was already masked by intrinsic noise. Values above zero express the strength of chaoticity (i.e. its tolerance to added noise). NL was calculated for each manually defined continuous nondistorted data section lasting at least 5 minutes. Before calculating NL the flow signal was downsampled to 5 Hz as this has been shown to improve the detection of chaoticity with NL [15]. The titration algorithm was run using embedding dimension of 6 and nonlinear degree of 3 as these values have been previously shown beneficial [15]. For each patient the mean NL of all sections is reported as NL_{mean} and the lowest value as NL_{min}. See Article Figure 4 for examples.

SUPPLEMENTAL INFORMATION ON RESULTS

Short moments of movement, coughing, crying etc. interrupted the continuous overnight flow measurements. After manual discarding of such section the overnight recordings were cut into 28.2±6.0 (mean±SD) sections of acceptable IP signal from which NL values were calculated. These sections had durations of 15.2±12.6 minutes. NL values did not correlate with the duration of the sections (Pearson r=-0.07). Neither were there significant differences between groups in the amount or duration of non-distorted signal sections (p>0.7 for all comparisons).

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