Lung function variability in children and adolescents (LUV study): protocol for a prospective interventional trial in healthy individuals and patients with asthma

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Study protocol

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Abstract

Background Variability analysis of peak expiratory flow (PEF) and forced expiratory volume at 1 s (FEV1) has been used in research to predict exacerbations in adult individuals with asthma. However, there is a paucity of data regarding PEF and FEV 1 variability in healthy or asthmatic children and adolescents. The objective of the present study is the assessment of PEF and FEV 1 variability in: a) healthy children and adolescents, to define the normal daily fluctuation of PEF and FEV 1 and the parameters that may influence it, and b) children and adolescents with asthma, to explore the differences from healthy subjects and reveal any specific variability changes prior to exacerbation.

Methods The study will include 100 healthy children and adolescents aged 6 to 18 years (assessment of normal PEF and FEV 1 variability) and 100 children and adolescents of the same age with diagnosed asthma (assessment of PEF and FEV 1 variability in asthmatics). PEF and FEV1 measurements will be performed using an ultra-portable spirometer (MIR Spirobank Smart) capable to smartphone connection. Measurements will be performed twice a day between 07:00-09:00 and 19:00-21:00 hours and will be dispatched via email to a central database for a period of 3 months. PEF and FEV1 variability will be assessed by detrended fluctuation and sample entropy analysis, aiming to define the normal pattern (healthy controls) and to detect and quantify any deviations (asthmatics). The anticipated duration of the study is 24 months.

Discussion Healthy children and adolescents may present normal short- and long-term fluctuations in lung function; the pattern of this variability may be influenced by age, sex and environmental conditions. Significant lung function variability may also be present in children and adolescents with asthma, but the patterns may differ from those observed in healthy children and adolescents. Such data would improve our understanding regarding the chronobiology of asthma and permit the development of integrated tools for assessing the level of control and risk of future exacerbations.

Trial registration ClinicalTrials.gov, NCT04163146. Registered on 14 November 2019

Background

Asthma is the most common chronic disease of childhood and represents an important cause of morbidity worldwide (1). The disease is characterized by episodes of reversible airway obstruction (exacerbations), with specific symptoms (wheeze, dyspnea, cough, chest tightness) and decrease in peak expiratory flow (PEF) and forced expiratory volume at 1 sec (FEV1) (2). However, lung function changes occur in parallel with clinical deterioration, thus presenting limited ability to predict the exacerbation of the disease (3).

Both PEF and FEV1 demonstrate significant daily variability, i.e., circadian and/or day-by-day fluctuation of measured values (4,5). In healthy individuals the pattern of these fluctuations remains constant over long time periods (weeks, months), as opposed to asthmatic patients where PEF and FEV1 variability increases with loss of disease control, especially prior to exacerbations (5,6) Thus, lung function

variability analysis has been used in research to recognize high-risk patients, predict asthma exacerbations and evaluate the effectiveness of treatment (6–10).

In clinical practice, however, the evaluation of lung function variability requires at least daily measurements with portable devices, recording of PEF and FEV1 values in specialized diaries and periodic evaluation of the data by the attending physicians (2). The whole process may be proven both complicated and time consuming, thus reducing patients' adherence especially in the case of children and adolescents (11, 12). In addition, the periodic post-hoc review of measurements may hamper the prediction of exacerbations, as the time of evaluation may not coincide with changes in the variability of lung function that characterize the loss of asthma control (12).

Over the last years, technological advancements in the field of biosensors and microprocessors have permitted the development of reliable, low-cost, ultra-portable spirometers, able to connect with cutting-edge mobile phones (smartphones) and monitor lung function parameters in real time and from a distance (13). The introduction of such devices in clinical practice may overcome most of the aforementioned barriers in following-up lung function parameters in the long term (13).

Currently, there is a paucity of data regarding long-term PEF and FEV1 variability in children and adolescents; this holds particularly true for children and adolescents with asthma. Such data would improve our understanding regarding the chronobiological aspects of the disease and might permit the development of integrated tools for assessing the level of asthma control and the risk of future exacerbations.

Methods

Study objectives and hypotheses

The first objective of the study is the assessment of lung function variability in healthy children and adolescents, focusing on the range and pattern of short- and long-term fluctuations of PEF and FEV1 and the parameters that may influence them (objective #1). The second objective is the assessment of lung function variability in children and adolescents with asthma; the pattern of short- and long-term PEF and FEV₁ variability will be established and the differences from healthy subjects will be defined (objective #2). Specific changes of the variability pattern prior to exacerbation will be also sought and described (objective #3).

We hypothesize that healthy children and adolescents present normal short- and long-term variability of PEF and FEV1, and that the pattern of variability is influenced by age, sex and environmental stimuli (season, weather conditions, viral infections, etc.). Significant lung function variability is also expected for children and adolescents with asthma; the patterns of variability in asthmatics may differ from those observed in healthy children and adolescents, being also influenced by environmental conditions and treatment modalities (controller therapy) in a distinguishable way. Finally, we hypothesize that changes in

the pattern of lung function variability occur prior to the loss of asthma control and, thus, may be used to predict the exacerbations of the disease.

Study design

The study was designed as a non-randomized, open-label, interventional clinical trial, with single group assignment (2 study groups).

Study population

The study will include a cohort of healthy children and adolescents (N=100) for the assessment of normal PEF and FEV₁ variability (objective #1) and a cohort of children and adolescents with asthma (N=100) (2) for the assessment of PEF and FEV₁ variability in asthmatics (objective #2) and investigation of its potential clinical relevance (objective #3). Participants will be recruited at the Pediatric Respiratory Unit and the Department of Pediatrics of the University Hospital of Patras and at private pediatric offices in the city of Thessaloniki, Korinth and Trikala, Greece. Each participant will receive a unique study number (8 digits; 2 letters-8 numbers in random order).

Sample size estimation

Data regarding long-term PEF and FEV₁ variability in children and adolescents (with or without asthma) are lacking. Based on lung function variability data from asthmatic adults (15) and assuming a maximum dropout rate of 10%, we estimated that a sample size of 200 children and adolescents (100 in each group) would allow to detect a difference of at least 1% in PEF or FEV₁ coefficient of variation (CV) between healthy and asthmatic participants, with 90% power at the 0.05 level. Sample size estimation was performed using the G*Power software (16), after assuming a non-parametric distribution of lung function parameters (Wilcoxon rank-sum test).

Inclusion criteria

General (both cohorts)

- Age 6 - 18 years
- Availability of smartphone (parents or participants) with internet connection (Wi-Fi or mobile data)
- Informed written consent to participate (parents or parents and participants for adolescents >12 years old)

Healthy children and adolescents

- No asthma diagnosis or prescription of relevant medication (beta-2 agonists, anticholinergics, inhaled corticosteroids or montelukast) in the last 2 years, and
- normal baseline spirometry, defined as FEV₁ and FEV₁/FVC > 80% of predicted (Global Lung Initiative - GLI normative data (14)), without significant reversibility (FEV₁ change < 10%) after

administration of 300 mcg salbutamol inhaler.

Children and adolescents with asthma

- Doctor-diagnosed mild/moderate asthma (2) in the last two years, and
- administration of controller therapy for at least 6 months in the previous year, and
- at least one spirometry, with FEV1 and FEV1/FVC < 80% of predicted (GLI normative data (14)) in the previous year

Exclusion criteria

- Major disabilities (e.g., chromosome abnormalities, neurological or muscular disorders, neuro-developmental delay) that may hamper the proper performance of lung function measurements or
- respiratory conditions (e.g., severe respiratory infection, chest trauma) or other health-related events (e.g., surgery, trauma) in the month prior to enrollment or during the 3-month period of observation or
- failure to complete the run-in period successfully (i.e., to perform acceptable spirometries at the predetermined time frames - see below) or
- inability to perform three consecutive measurements or 6 measurements in total (3.3% of the anticipated 180 measurements) within the 3-month period of observation.

Lung function measurements

Device

PEF and FEV1 measurements will be performed using an FDA-approved ultra-portable spirometer (*Spirobank Smart*, MIR, Rome, Italy), with a bi-directional digital turbine (flow range ± 16 L/s, volume accuracy $\pm 3\%$ or 50 mL, flow accuracy: $\pm 5\%$ or 200 mL/s, dynamic resistance < 0.5 cm H₂O/L/s), capable to connect to smartphone via Bluetooth® using a dedicated freeware application (*iSpirometry*, MIR, Rome, Italy). Apart from PEF and FEV1, the device provides data on the forced expiratory capacity (FVC) and forced expiratory flow between 25 and 75% of FVC (FEF₂₅₋₇₅). The application includes graphic incentives to assist in performing technically acceptable tests; it also includes a quality grading system that generates messages to inform whether the measurement was technically correct or, if not, what was the exact mistake (e.g., “good blow” for an acceptable test or “blow faster”, “blow longer”, etc. for non-acceptable maneuvers). Each participant will receive his personal spirometer which will be paired to one or more smartphones (personal or/and parents’ device). In case of two or more participants within the same family, each spirometer will be paired to a separate smartphone. Detailed information regarding use and maintenance of the device will be provided (printed brochure and online resources available at the study web-site www.luvstudy.gr).

Protocol

Tests will be performed according to ATS/ERS standards (17). The technique will be demonstrated by one of the investigators at enrollment, while detailed information will be also available (online video resources at study web-site www.luvstudy.gr). Measurements will be performed twice a day between 07:00-09:00 and 19:00-21:00 hours. Each participant should perform at least 3 technically acceptable maneuvers. Completed measurements will be dispatched by the participants or their parents to a central database *via* email (encrypted pdf format).

Eligible children and adolescents will be initially asked to complete a run-in period of ten days (20 trials), to assess their ability to perform technically acceptable spirometries (daily and at predetermined time frames), dispatch the measurements to the central database and comply to investigators instructions. Those who will demonstrate satisfactory adherence, will proceed to the main study consisting of daily measurements at predetermined time frames for a period of three months (90 days - 180 trials).

The expected duration of the study is 24 months and it will include two phases:

- Phase I (January - September 2020): assessment of lung function variability in healthy children and adolescents
- Phase II (October 2020 - December 2021): assessment of lung function variability in children and adolescents with asthma

A flow chart of the study is presented in Fig. 1. The protocol is in accordance with SPIRIT guidelines (Fig. 2). The full SPIRIT checklist is presented in Additional File 1.

Data acquisition and monitoring

PDF files will be downloaded and converted to text files using optical character recognition. PEF, FEV1, FVC and FEF25-75 values, as well as quality grading of each measurement will be recognized and introduced in a specific registry. The best PEF, FEV1, FVC and FEF25-75 values among the technically acceptable trials for a given date/time point will be identified and transferred from the registry to a participant-specific file. Additionally, all registry data will be included in a monitoring table presenting the number of acceptable tests per day/time for each participant (Figure 3). PDF downloading and data acquisition will be performed automatically by special scripts implemented in MatLab.

The monitoring table (Figure 3) will be reviewed twice a day (at 11:00 and 23:00 hours) and participants will be notified by direct telephone contact in case of inappropriate technique or missing measurements.

Variability analysis

Participant-specific files will be used for variability analysis, focusing primarily on the variability of PEF and FEV1 and secondary on FEV1/FVC and FEF25-75. All variables will be transformed in % predicted values according to GLI normative data (14). Lung function variability will be assessed by:

- Standard variability indices, such as CV (defined as SD divided by mean). To avoid any bias due to the presence of trends within the timeseries, CV will be also calculated as the average of 24 'moving' windows (length 14 measurements; step 7 measurements).
- Detrended Fluctuation Analysis (DFA), a method that has been widely used for the investigation of intrinsic correlation within time series (18). Initially, the square root of the time series $[F(n)]$ is calculated for segments of different (time) length n . A linear relationship in the logarithmic graph $F(n) - \log(n)$ indicates the existence of fractal architecture in the scaling of the specific data, while the slope a of the line describes the pattern of long-term fluctuations (18). A change in daily variability of PEF or FEV1 results in a simultaneous deviation from the predetermined a value (6). This deviation can easily be detected and quantified. It has been shown that the magnitude of a deviation reflects the likelihood of asthma exacerbation within the next month (6).
- Sample entropy (SampEn), a measure of increased irregularity or complexity, which relies on the identification of recurrent patterns within a nonstationary timeseries (i.e., the probability that a series of points within the signal will repeat themselves at a subsequent time-point) (19). Within a regular and less complex system, the frequency of sequence matches is high, therefore, the entropy is low. SampEn has emerged as a more reliable index of dynamic variability, mainly because it is relatively independent of the length of the timeseries (19).

Variability analysis will be performed in MatLab (MathWorks, Inc., Natick, MA, USA) environment.

Additional data

Patients' characteristics (age, sex, place of residence, baseline lung function, allergy, comorbidities, type of medication, etc) will be recorded. The effect of these parameters on the pattern of lung function variability will be also explored.

Statistics

Normally distributed data will be presented as means $\pm$ SD and compared with Student's t test, while non-parametric data will be presented as medians with ranges and compared with Mann-Whitney U test. Chi-square or Fisher's exact test will be applied to compare different frequencies between the study groups. Multivariable linear regression analyses will be used to explore the effect of various parameters on lung function variability. All analyses will be performed with MatLab and the IBM SPSS software version 25.0 (IBM Corp., Armonk, NY).

Discussion

Increased lung function variability correlates with the frequency of respiratory symptoms in the general population (20) and is indicative of poor asthma control in patients with asthma (7–9, 15).

Frey et al. (6) applied DFA on 300 consecutive PEF values from a cohort of asthmatic adults treated in a crossover manner with regular short-acting beta-2 agonists (SABA), regular long-acting beta-2 agonists (LABA) or placebo. They showed that long-term PEF variability was increased in the SABA phase, meaning that there were several periods of decreased lung function (increased vulnerability - high probability of exacerbation). Conversely, PEF variability was decreased during the LABA phase, signifying that lung function remained persistently within normal limits (decreased vulnerability - low probability of exacerbation). Thamrin et al. (8) showed that the self-similarity of PEF values over time correlates well with loss of asthma control within two weeks following withdrawal of inhaled corticosteroids. Their findings were later corroborated by Kaminsky et al. (15) in a large clinical trial of adult asthmatics under controller therapy. Thamrin et al. have also demonstrated that the probability of asthma exacerbation at the individual level can be estimated by combining the autocorrelation properties of PEF over time with the absolute PEF value at a specific time point, indicating that both are significant for predicting loss of disease control in the near future (21).

Regarding SampEn, Veiga et al. (22) found that the entropy of airflow time series was reduced in asthmatics compared to healthy controls; lower entropy was associated with more severe airflow obstruction (forced oscillations technique) in that study (22). More recently, Dames et al (23) investigated the entropy of airflow in patients with COPD and reported that the SampEn of airflow during resting breathing decreased in proportion to the degree of airway obstruction. Similar data in children and adolescents with or without asthma, are lacking.

To remain stable yet adaptable to change, any physiological system needs to balance between order and chaos (24). Asthma appears to be associated with increased order (reduced complexity) and increased variability of lung function, resulting in wide fluctuations that may lead to periods of increased vulnerability and reduced adaptability to a changing environment (25). From the clinical standpoint, these features translate into more frequent exacerbations and poor control of the disease. Thus, when properly quantified, changes in lung function over time may reflect both past and future control of asthma (25).

Healthy children and adolescents may present normal short- and long-term fluctuations in lung function; the pattern of this variability may be influenced by age, sex and environmental conditions. Significant lung function variability may also be present in children and adolescents with asthma, but the patterns may differ from those observed in healthy children and adolescents. Such data would improve our understanding regarding the chronobiology of asthma and may permit the development of integrated tools for assessing the level of control and risk of future exacerbations.

Trial Status

Protocol version 1.4 (20/1/2020). Recruitment commenced in January 2020 and the trial is scheduled to end in January 2022.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee (decision 218/19-03-2019) and the Scientific Board (decision 329/02-04-2019) of the University Hospital of Patras, Greece. The study was registered with the ClinicalTrials.gov under the number NCT04163146 (registered 14 November 2019, <https://clinicaltrials.gov/ct2/show/NCT04163146?term=NCT04163146&draw=2&rank=1>). Informed consent from parents or parents and participants in case of adolescents aged >12 years will be obtained at inclusion. The informed consent grants access to the participants' measurements and medical file, and permits the transmission of data through internet, given that all conditions of anonymity and data protection are met.

Consent for publication

Not applicable

Availability of data and material

Access to the study dataset will be limited to the investigators. After the analysis and publication of the results, the study database will be made available from the corresponding author on reasonable request. Results will be published in peer-reviewed journals and will be presented in relevant conferences. Authorships will follow the Vancouver declaration.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

SF and MBA designed this protocol and revised the manuscript. ESF and IT drafted the manuscript and participated in the design of the study. DG, NK, GC and PP helped in manuscript drafting and revision. ESF, DG, NK, and GC will enroll participants and assign participants to the interventions. ESF, IT and PP will be involved in data collection and study monitoring. SF and MBA act as study supervisors. All authors read and approved the final version of the manuscript.

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Supplemental Information Note

The full SPIRIT checklist presented in Additional File 1 was omitted by the authors in this version of the paper.

Figures

Figure 1

Study flow chart

	Enrolment	Run-in period	Study period			Close-out
TIMEPOINT	JAN 2020 – SEPT 2021 *	- 10 days	JAN 2020 – DEC 2021			Day 91
			Month 1	Month 2	Month 3	
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation *	X					
INTERVENTIONS:						
<i>Spirometry **</i>		X
ASSESSMENTS:						
<i>Height, weight</i>	X			X		X
<i>History</i>	X					
<i>Symptoms</i>		X
<i>Adherence</i>		X				X

* Phase I (January - September 2020): Healthy children and adolescents; Phase II (October 2020 - December 2021): Children and adolescents with asthma

** Measurements with portable spirometers at home, twice a day between 07:00 - 09:00 and 19:00 - 21:00 hours and dispatching to the central database *via* email.

Figure 2

Trial process (SPIRIT)

	6/1/2020		7/1/2020		8/1/2020		9/1/2020	
ID	pm	am	pm	am	pm	am	pm	am
23s45f31	4	3	3	3	3	3	4	3
x124b451	3	3	2	3	4	3	4	4
3hg45679	3	3	3	4	0	4	3	3

Figure 3

Monitoring table (example) presenting the number of acceptable tests per day/time-point and participant. Green cells signify full adherence, orange cells <3 acceptable measurements and red cells missed measurements.