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Assessment of Spirometry and Impulse Oscillometry in Relation to Asthma Control

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Abstract
Introduction Guidelines advocate the use of spirometry to assess pulmonary function in asthmatic patients. Commonly used measures include forced expiratory volume in 1 s (FEV_1), forced expiratory ratio (FEV_1/FVC), and forced mid-expiratory flow between 25 and 75 % of forced vital capacity ($FEF_{25–75}$). Impulse oscillometry (IOS) is an effort-independent test performed during tidal breathing. IOS may be used to assess the total and central airway resistance at 5 Hz (R5) and 20 Hz (R20), respectively, and hence derive the peripheral airway resistance from the difference (R5–R20). We compared spirometry and IOS as tests of global airway function (i.e., FEV_1, FEV_1/FVC, R5) and putative measures of small airways function (i.e., $FEF_{25–75}$, R5–R20) and their relationship to oral steroid and short-acting beta-agonist (SABA) use as surrogates for long-term asthma control.
Methods Spirometry and IOS measurements from physician-diagnosed asthmatics were linked to a health informatics database for oral steroid and SABA use 1 year prior to the index measurements.
Results Four hundred forty-two patients had both spirometry and IOS, mean $FEV_1 = 86$ % predicted, 94 % on ICS, median dose 800 μg/day. IOS and spirometry measures were equally predictive of impaired asthma control for both oral steroid and SABA use. For oral steroid use, the adjusted odds ratio, OR (95 % CI) is as follows: $FEV_1 < 80$ %: 1.56(0.99–2.47), $p = 0.056$; FEV_1/FVC < 0.70: 1.67(1.03–2.69), $p = 0.037$; $FEF_{25–75} < 60$ %: 1.84(1.18–2.86), $p = 0.007$; R5 > 150 %: 1.91(1.25–2.95), $p = 0.003$; and R5–R20 > 0.1 kPa L^{-1} s 1.73(1.12–2.66), $p = 0.013$. For SABA use, the adjusted OR (95 % CI) is as follows: $FEV_1 < 80$ %: 2.22(1.43–3.44), $p < 0.001$; FEV_1/FVC < 0.70: 2.26(1.44–3.57), $p < 0.001$; $FEF_{25–75} < 60$ %: 2.51(1.65–3.82), $p < 0.001$; R5 > 150 %: 1.76(1.18–2.63), $p = 0.006$; and R5–R20 > 0.1 kPa L^{-1} s: 2.94(1.94–4.46), $p < 0.001$.
Conclusion Spirometry or IOS measurements were equally useful as potential markers of asthma control in persistent asthmatic patients.

Keywords Small airways · Spirometry · Impulse oscillometry · Asthma, corticosteroid · Short-acting beta-agonist

Introduction

Current management guidelines advocate the use of spirometry to assess pulmonary function in asthmatic patients [1]. Commonly used measures include forced expiratory volume in 1 s (FEV_1), forced expiratory ratio (FEV_1/FVC), and forced mid-expiratory flow between 25 and 75 % of forced vital capacity ($FEF_{25–75}$). The forced expiratory manoeuver is somewhat artificial in that it tends to exaggerate volume-dependent small airway closure. Furthermore, there is an inherent degree of variability involved with the $FEF_{25–75}$ as a putative measure of small airways function as it is dependent on patients performing full effort-dependent expiration from total lung capacity to residual volume. Impulse oscillometry (IOS) is an effort-independent test performed during normal quiet tidal breathing and is therefore considered as being more

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physiological and requires less patient cooperation than spirometry. IOS may be used to assess the total and central airway resistance at 5 Hz (R5) and 20 Hz (R20), respectively, and hence derive the peripheral airway resistance from the difference (R5–R20) [2].

The purpose of the present study was twofold, first to compare spirometry and IOS as tests of global airway function (i.e., FEV_1, FEV_1/FVC, R5), and second to assess putative measures of small airways function (i.e., $FEF_{25–75}$, R5–R20), in terms of their relationships to long-term asthma control.

We have therefore evaluated spirometry and IOS measurements from an unselected sample of physician-diagnosed asthmatic patients referred from primary care to our research unit for potential screening into clinical trials.

Methods

Study Design and Population

Spirometry and IOS measurements from an unselected sample of physician-diagnosed asthmatic patients who attended our research unit for potential screening into various clinical trials were linked to prescription data. Prescription data were obtained from the Health Informatics Centre. The Health Informatics Centre collects all community-dispensed prescriptions using a person's unique identifier, the Community Health Index (CHI).

Oral steroid and SABA use 1 year prior to the index measurements were determined. Oral corticosteroid use was measured as a binary variable i.e., whether or not patients had an oral corticosteroid prescription for an acute asthma exacerbation during the study period. SABA use was also measured as a binary variable and defined as >4 inhalers or ≤4 inhalers prescribed during the study period. For each measurement, we evaluated SABA and oral steroid use according to pre-defined cut-off values as follows: $FEV_1 < 80$ % versus $FEV_1 > 80$ %; $FEF_{25–75} < 60$ % versus $FEF_{25–75} > 60$ %; FEV_1/FVC < 0.70 versus FEV_1/FVC > 0.70; R5 > 150 % versus R5 < 150 %; and R5–R20 > 0.1 kPa L^{-1} s versus R5–R20 < 0.1 kPa L^{-1} s. All patients gave written informed consent for their data to be stored electronically, and ethical approval from the East of Scotland Research Ethics Service was obtained for all the studies the patients were being screened into.

Measurements

IOS (Masterscreen IOS, Hochberg, Germany) was performed in triplicate in accordance with manufacturer's guidelines. A SuperSpiro spirometer (Micro Medical Ltd., Chatham, Kent, United Kingdom) was used to perform spirometry in triplicate in accordance with European Society guidelines [3].

Statistical Analysis

Unpaired Student's *t* tests were used to compare normally distributed baseline data. Non-normally distributed baseline data were summarized as medians with interquartile ranges and were compared using the non-parametric Mann–Whitney *U* test. Categorical baseline data were compared using χ^2 tests. Logistic regression analysis was applied to calculate the odds ratios (OR) for steroid and salbutamol use in the different groups. Age, gender, inhaled corticosteroid (ICS), long-acting beta-agonist (LABA), and leukotriene receptor antagonist (LTRA) use were all included as covariates to calculate the adjusted OR and 95 % CI. Statistical significance for all analyses was set at $P < 0.05$ (two tailed). SPSS version 21 (SPSS Inc., Chicago, Illinois) was used for all analyses.

Results

We retrieved validated data for 442 patients with physician-diagnosed asthma who had measurements of both spirometry and IOS, mean $FEV_1 = 86$ % predicted, mean $FEF_{25–75} = 60$ % predicted, FEV_1/FVC = 0.74, median R5 % = 136 % predicted, median R5–R20 = 0.07 kPa L^{-1} s. (i.e., 0.7 cm H_2O L^{-1} s), mean age 42 years, 36 % males, 94 %

Table 1 Demographics for all patients ($n = 442$)

Age (years)	42 (15)
Gender M:F	157:285
FEV_1 (% predicted)	86 (20)
$FEF_{25–75}$ (% predicted)	60 (27)
FEV_1/FVC	0.74 (0.12)
R5(% predicted)	136 (107–184)
R5–R20 (kPa L^{-1} s)	0.07 (0.03–0.17)
ICS (%)	94
ICS dose (BDP equivalent, μg)	800 (400–1,000)
LABA (%)	44
LTRA (%)	23
Theophylline (%)	7

Data presented as mean (standard deviation) or percentage except for impulse oscillometry indices and ICS dose, which are presented as median (interquartile range)

BDP beclomethasone dipropionate, *$FEF_{25–75}$* forced expiratory flow between 25 and 75 % of vital capacity, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *FEV_1/FVC* forced expiratory ratio, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonist, *LTRA* leukotriene receptor antagonist, *R5* total airway resistance at 5 Hz, *R20* central airway resistance, *R5–R20* difference between total and central airway resistance at 5 and 20 Hz (peripheral airway resistance)

Table 2 Demographics for the patients based on small airway indices

	$FEF_{25-75} < 60$ % predicted $n = 238$	$FEF_{25-75} > 60$ % predicted $n = 204$	*P* value	R5–R20 > 0.10 kPa L^{-1} s $n = 185$	R5–R20 < 0.10 kPa L^{-1} s $n = 257$	*P* value
Age (years)	45 (14)	39 (15)	<0.001	45 (15)	40 (14)	<0.001
Gender, M:F	96:142	61:143	0.02	63:122	94:163	0.59
FEV_1 (% predicted)	75 (18)	100 (11)	<0.001	77 (21)	93 (16)	<0.001
FEF_{25-75} (% predicted)	40 (14)	83 (17)	<0.001	48 (24)	68 (25)	<0.001
FEV_1/FVC	0.67 (0.11)	0.83 (0.06)	<0.001	0.70 (0.13)	0.77 (0.10)	<0.001
R5 (% predicted)	154 (120–206)	122 (102–158)	<0.001	188 (150–225)	113 (96–136)	<0.001
R5–R20 (kPa L^{-1} s)	0.11 (0.05–0.21)	0.05 (0.02–0.10)	<0.001	0.18 (0.14–0.28)	0.04 (0.01–0.06)	<0.001
ICS (%)	95	94	0.69	94	95	0.65
ICS dose (BDP equivalent, μg)	800 (400–1,000)	800 (400–1,000)	0.16	800 (400–1,000)	800 (400–1,000)	0.01
LABA (%)	45	43	0.63	47	42	0.35
LTRA (%)	25	20	0.24	23	22	0.79
Theophylline (%)	9	5	0.11	10	5	0.06

Data presented as mean (standard deviation) or percentage except for impulse oscillometry indices and ICS dose, which are presented as median (interquartile range)

BDP beclometasone dipropionate, FEF_{25-75} forced expiratory flow between 25 and 75 % of vital capacity, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, FEV_1/FVC forced expiratory ratio, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonist, *LTRA* leukotriene receptor antagonist, *R5* total airway resistance at 5 Hz, *R20* central airway resistance, *R5–R20* difference between total and central airway resistance at 5 and 20 Hz (peripheral airway resistance)

on ICS median dose 800 μg/day; 44 % on LABA, 23 % on LTRA, and 7 % on theophylline. Demographics for all patients and based on small airway indices are presented in Tables 1 and 2, respectively.

The main results are summarized in Fig. 1. For the adjusted OR, aside from FEV_1, there was a significant increase in the propensity for oral steroid usage for all other spirometry and IOS measures: $FEV_1 < 80$ %: 1.56(0.99–2.47) $p = 0.056$, $FEV_1/FVC < 0.70$: 1.67(1.03–2.69) $p = 0.037$, $FEF_{25-75} <$ 60 %: 1.84(1.18–2.86) $p = 0.007$, R5 > 150 %: 1.91(1.25–2.95) $p = 0.003$, and R5–R20 > 0.1 kPa L^{-1} s (i.e., >1.0 cm H_20 L^{-1} s): 1.73(1.12–2.66) $p = 0.013$. Likewise, there was a significant increased propensity for SABA usage according to adjusted OR for all measures: $FEV_1 < 80$ %: 2.22(1.43–3.44) $p < 0.001$, $FEV_1/FVC < 0.70$: 2.26(1.44–3.57) $p <$ 0.001, $FEF_{25-75} < 60$ %: 2.51(1.65–3.82) $p < 0.001$, R5 > 150 %: 1.76(1.18–2.63) $p = 0.006$, and R5–R20 > 0.1 kPa L^{-1} s (i.e., >1.0 cm H_20 L^{-1} s): 2.94(1.94–4.46) $p < 0.001$. Resonant frequency, however, did not have a significant impact in determining asthma control. There were insufficient evaluable data to analyze reactance area (AX).

The cohort was also divided according to British Thoracic Society (BTS) treatment steps [4]. The numbers of patients at each step were as follows: Step 1 (SABA alone), $n = 30$ (7 %); Step 2 (ICS), $n = 169$ (38 %); Step 3 (ICS + LABA/LTRA/theophylline), $n = 111$ (25 %); and Step 4 (high dose ICS and/or 2 second line controllers), $n = 132$ (30 %). The proportion of patients at various cut-off thresholds for FEF_{25-75} and R5–R20 are displayed in Fig. 2. This showed that the relative proportion of patients at a given cut-off threshold is similar across all BTS treatment steps for either spirometry or IOS.

Discussion

Our results have revealed two key findings. First, IOS and spirometry measures were equally predictive in terms of their propensity to be associated with impaired long-term asthma control for both oral steroid and SABA usage over the 1 year prior to the index measurements. Second, putative small airway measures (i.e., FEF_{25-75} and R5–R20) were not different to global measures of pulmonary function (i.e., FEV_1, FEV_1/FVC, R5) in relation to asthma control outcomes. The highest adjusted OR was observed with FEF_{25-75} and R5–R20 for SABA use at 2.51 and 2.94, respectively, although pointedly the 95 % CI overlapped with other global measures. The adjusted OR tended to be lower for steroid use than for SABA use for all measures.

We acknowledge our data have limitations being retrospective in nature in terms of oral steroid and SABA use with no accompanying patient reported outcomes of symptom control such as diary cards, asthma control test, or

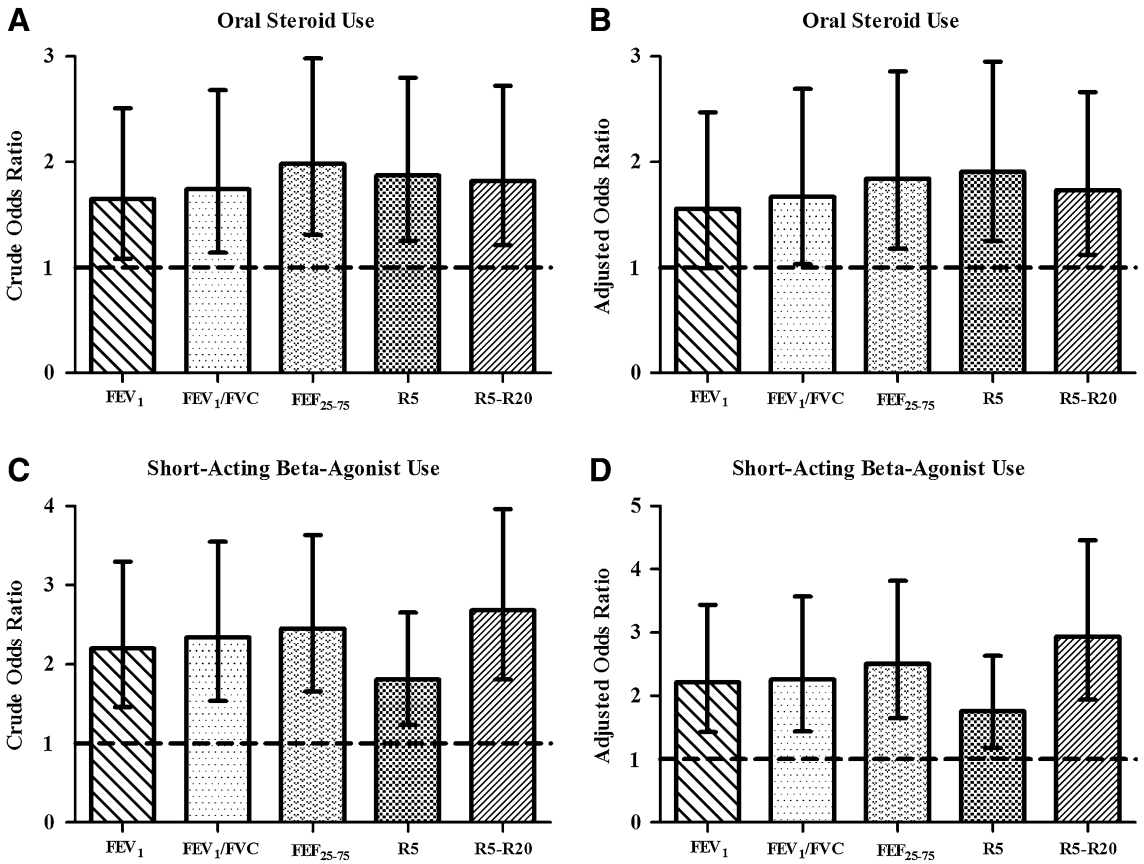

Fig. 1 Crude and adjusted odds ratios (95 % CI) for oral steroid (**a**–**b**) and short-acting beta-agonist use (**c**–**d**) in the year preceding measurements of FEV_1 (<80 % predicted, $n = 140$ vs. >80 % predicted, $n = 302$), FEV_1/FVC (<0.70, $n = 131$ vs. >0.70, $n = 311$), $FEF_{25–75}$ (<60 % predicted, $n = 238$ vs. >60 % predicted, $n = 204$), R5 (>150 % predicted, $n = 183$ vs. <150 % predicted, $n = 259$), and R5–R20 (>0.10 kPa L^{-1} s, $n = 185$ vs. <0.10 kPa L^{-1} s, $n = 257$). The 95 % CIs which exclude unity are defined as being of statistical significance

questionnaire. However, we feel our data are reflective of a real-life situation with a sample of unselected patients who represent a broad spectrum across steps 1–4 of BTS asthma guidelines. We also appreciate that our chosen cut-off values for abnormal small airways function in asthmatic adults were somewhat arbitrary which was done for pragmatic purposes to try and achieve a reasonable balance of numbers in each group. For example, in asthmatic children, Shi et al. showed a cut-of value for R5–R20 of >0.1 kPa L^{-1} s was able to correctly classify 83 % of patients who became uncontrolled after a 3-month follow-up period on unchanged therapy [5]. In another study, Rao et al. using electronic prescription linkage data over 1 year found that children with an $FEF_{25–75} < 60$ % predicted had significantly increased odds ratio for loss of control [6]. Our prescribing data were only for dispensed oral steroids or SABA inhalers over the year, and as such we are unable to make any inferences with respect to patient adherence in each group. While it might have been informative to have other measures of small airways function from nitrogen washout and plethysmography [7], this is not something which is done in our own routine clinical practice. Our data differ from findings of Gonem et al. who observed that R5–R20 was not associated with asthma control or exacerbations [8].

We did not have sufficient numbers of patients to permit a meaningful subgroup comparison of asthma control in patients exposed to coarse or extra-fine particle ICS formulations. In this regard, several retrospective health informatics-based studies comparing coarse and fine particle ICS formulations in unselected patients have shown a consistent pattern of improved control with fine particle inhalers [9–11].

In summary, our data in a real-life clinic setting would suggest that performing either spirometry or IOS measurements is equally useful as potential markers of asthma control in persistent asthmatic patients. Furthermore, putative measures of small airways function appear to confer no additional benefit.

Further long-term prospective studies may be warranted to assess the relative merits of serial measures of spirometry and IOS, perhaps looking at subjective symptom control in addition to health informatics outcomes.

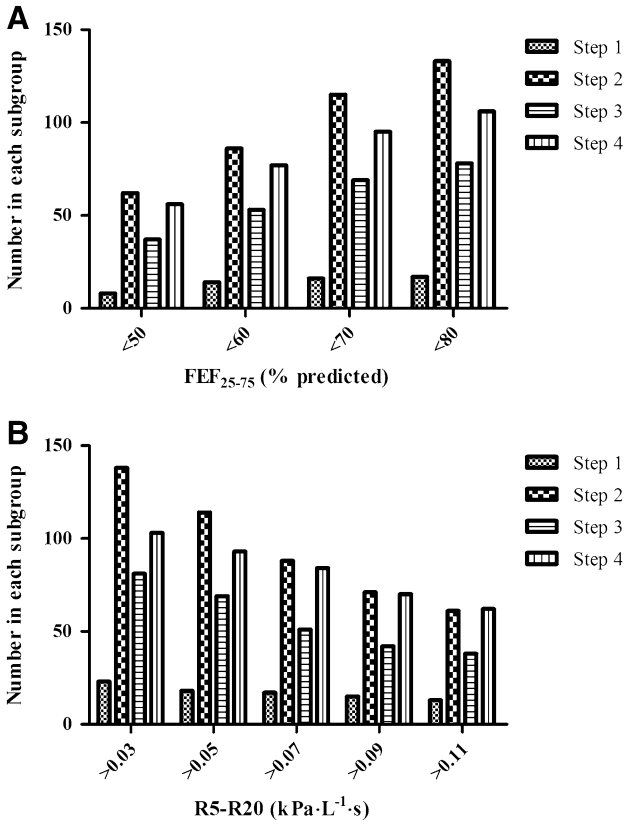

Fig. 2 Number of patients according to British Thoracic Society treatment steps at various thresholds for $FEF_{25–75}$ (**a**) and R5–R20 (**b**)

Conflict of interest AM has received support from Teva to attend the 2013 European Respiratory Society Congress and Chiesi to attend the 2014 meeting. WJA has received support from Chiesi to attend the 2013 European Respiratory Society Congress. BJL is on the Speaker Bureau for Teva and Advisory Board for Chiesi and Teva. JL has no competing interests to declare. The Scottish Centre for Respiratory Research has received unrestricted educational grants from Chiesi and Teva and participated in a multicentre study sponsored by Teva.

Ethical standards This manuscript complies with the current laws of the United Kingdom

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