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Determinants of asthma control and quality of life in stable asthma: Evaluation of two new cough provocation tests.

Minna Purokivi, MD,[*] Heikki Koskela, MD, [*] Kirsi Kontra, Pharm. Lic. [**]

E-mail addresses: minna.purokivi@kuh.fi, heikki.koskela@kuh.fi, kirsi.kontra@kuh.fi

[*]Center for Medicine and Clinical Research, Division of Respiratory Medicine, Kuopio University Hospital and [**]Department of Pharmacy, Kuopio University Hospital, P.O.Box 1777, 70211 Kuopio, Finland

Corresponding author:

Minna Purokivi, Center for Medicine and Clinical Research, Division of Respiratory Medicine, Kuopio University Hospital, P.O.Box 1777, 70211 Kuopio, FINLAND e-mail: minna.purokivi@kuh.fi

tel: +358 44 717 4795

fax: +358 17 17 2683

Minna Purokivi designed the study, recruited the subjects, and collected and analysed the data. She had the main responsibility of writing the manuscript.

Heikki Koskela took part in the study planning, recruited the subjects, and took part in the writing process.

Kirsi Kontra took part in the study planning, was responsible for production of hypertonic saline solutions and quality control, and took part in the writing process

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ABSTRACT

Introduction: Asthma control and quality of life are poorly associated with traditional asthma biomarkers.

Objectives: In the present study we evaluated two new cough provocation tests in this respect.

Methods: Asthma Control Questionnaire and Leicester Cough Questionnaire were completed by thirty-six stable asthmatics. Cough provocation tests with hypertonic saline and isocapnic hyperpnoea of dry air were performed, as well as spirometry, ambulatory peak expiratory flow (PEF) monitoring, and exhaled nitric oxide measurement (eNO).

Results: Leicester Cough Questionnaire score correlated closely with cough responsiveness to hypertonic saline and isocapnic hyperpnoea ($R = -0.66$, $p<0.001$ and $R = -0.49$, $p = 0.002$, respectively). Asthma Control Questionnaire score also correlated with the cough responsiveness to these tests ($R = 0.52$, $p = 0.001$ and $R = 0.43$, $p = 0.008$, respectively). FEV_1 (%predicted), diurnal PEF variation and eNO did not correlate with cough-related quality of life but showed some association with asthma control. There was a significant correlation between Leicester Cough Questionnaire and Asthma Control Questionnaire ($R = -0.54$, $p = 0.001$).

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*Conclusion*s: Asthma control and cough-related quality of life are more closely associated with cough responsiveness to the investigated cough provocation tests than to eNO and traditional indices of bronchial obstruction. Cough is a major contributor to poor asthma control.

Keywords: asthma, asthma control, quality of life, cough, eucapnic hyperpnoea of dry air, hypertonic saline

The present study has been reviewed by the Research Ethic Committee, Hospital District of Northern Savo and it has been performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

INTRODUCTION

Poorly controlled asthma is a common problem in western societies. (1) Despite of availability of modern asthma medication, at least 40 % of adult patients are known to remain symptomatic due to asthma. (2) In general practise, up to 59% of asthmatic patients still have uncontrolled disease. (3) It is not surprising that the recently updated GINA guidelines emphasise the good control of asthma as the key target of asthma treatment. (4)

The doctors tend to overestimate asthma control (3), and the opinion of patients and doctors often differ significantly. (5) Therefore, objective measures are needed in assessing the asthma control. Unfortunately, the presently utilised biomarkers for asthma management such as bronchial hyperresponsiveness, spirometry and exhaled nitric oxide (eNO), correlate poorly with asthma control and quality of life. (6, 7)

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Cough is the most common symptom of asthma (8) and probably the most common and neglected symptom in uncontrolled asthma. (9) Despite of asthma treatment, cough is known to remain as a prominent symptom that lessens the quality of life of asthma patients. (10) It has been shown previously that cough-related quality of life does not correlate with lung function (11) or with cough responsiveness assessed with capsaicin. (12)

During the recent years we have investigated cough provocation tests with hypertonic aerosols like mannitol (13), hypertonic histamine (14), hypertonic saline (15) and hyperpnoea. (16) Hyperpnoea may be regarded as a form of hypertonic challenge since it is postulated to increase airway lining fluid tonicity via evaporation of the airway ling fluid water. (17) In contrast to traditional cough provocation tests such as capsaicin (18) and citric acid (19), responsiveness to hypertonic aerosol cough provocation tests can clearly differentiate asthmatic from healthy subjects. Furthermore, asthma symptom improvement during treatment with inhaled corticosteroids is closely mirrored by a decrease in cough responsiveness to inhaled mannitol. (13) All this supports a view that cough responsiveness to hypertonic aerosols is associated with asthma and its severity. Therefore, we hypothesised that cough responsiveness to hypertonic aerosols might also reflect asthma control and cough-related quality of life. The present study was performed to test this hypothesis.

METHODS

Thirty-eight unselected, consecutive patients from Kuopio University Hospital out patient clinic of respiratory diseases entered this study. The diagnosis of asthma was based on patient's history and clinical examination suggestive of asthma, together with objective evidence of reversible airway obstruction in ambulatory peak expiratory flow (PEF) measurement or spirometry, according to the

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GINA guidelines. (4) The exclusion criteria were febrile respiratory tract infection within six weeks, post-salbutamol forced expiratory volume in one second (FEV_1) less than 60%, excessive spontaneous cough (>10 coughs in response to 0.9% saline inhalation) and fall of FEV_1>10% during either of cough provocation tests. Thirty-six subjects completed the study. The Research Ethics Committee, Hospital District of Northern Savo, Finland approved this study (31.10.2008 117//2008) and all subjects provided their written informed consent for participation. Subjects' characteristics are showed in table 1.

Protocol

All subjects were observed over one-week run-in period, during which they recorded PEF values twice daily. On the first study day Asthma Control Questionnaire (ACQ) (20) and Leicester Cough Questionnaire (LCQ) (21) were filled in. Exhaled nitric oxide (eNO) (Sievers Model 280 NOA; Sievers Instruments Inc., Boulder, CO, USA) was measured according to international recommendations. (22) Skin prick tests for common aeroallergens (Soluprick SQ®; ALK-Abello, Hörsholm, Denmark) were performed. Cough provocation tests with hypertonic saline and isocapnic hyperpnoea of dry air were performed on separate days with at least 48 hours between them within one week, during the same time of the day. (16) Inhaled corticosteroids and long-acting β-2 agonists were withdrawn on test days and short-acting β-2 agonists were withdrawn for at least 8 hours before the tests.

Asthma Control

Juniper's ACQ is a validated, widely utilised questionnaire. It consists of seven items including specific symptoms, timing of symptoms, activity limitation, use of rescue medication and lung

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function, which are scored from 0 (=no impairment) to 6 (maximum impairment). The items are equally weighted and the ACQ score is the mean of the seven items varying from 0 (totally controlled) to 6 (severely uncontrolled). (20) The subjects were divided into two groups according to their asthma control determined with ACQ (well-controlled asthma ACQ score ≤0.75, and borderline or uncontrolled asthma ACQ score >0.75). (23)

Cough-related quality of life

The LCQ is a 19-item validated, repeatable and responsive questionnaire consisting of physical, psychological and social domains. Answers are graded on 7-point Likert scale which gives a total score ranging from 3 to 21. A small LCQ score indicates poor cough-related quality of life. (21)

Cough provocation test with hypertonic saline

In the beginning of the test, spirometry was performed three times (Model M9449, Medikro Ltd, Kuopio, Finland) and the largest FEV_1 was recorded. The spirometry was performed according to international guidelines (24) but the between-manoeuvre repeatability criteria were not utilised during the provocation tests to keep the number of blows acceptable for the subject. The spirometer was volume calibrated at least once daily utilising a 3 litre syringe. Then the subject inhaled four inhalations of 100mcg salbutamol (Ventoline Evohaler, GlaxoSmithKline Ltd, Stockley Park West, Uxbridge, Middlesex, UK) using a Volumatic chamber. The spirometry was repeated 15 minutes later, three blows. An ultrasonic nebuliser (De Vilbiss Ultraneb 3000, Sunrise Medical Ltd, Leicester, UK) with a one-way valve (Douglas Bag One-Way Air Valve, Harvard Apparatus, Holliston, MA, USA) was used to deliver the saline solutions. First the subject inhaled isotonic phosphate-buffered saline for 2 minutes using tidal breathing, and wearing a nose clip. The coughs

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occurring during the inhalation and two minutes after it were manually recorded by the investigation nurse. The number of these "spontaneous" coughs was subtracted from the coughs provoked by each hypertonic solution. Subsequently, the subject similarly inhaled solutions with osmolalities of 600, 900, 1200, 1500, 1800, and 2100 mOsm/kg. The test was stopped if the subject asked for it, 15 or more cumulative coughs had been recorded, or the final solution was administered. Finally, the spirometry was repeated, three blows. (25)

Cough provocation test with isocapnic hyperpnoea of dry air

The apparatus is identical to that described by Anderson (26) but without gas meter at the end of the line. The subject inhaled dry compressed air (Woikoski, Varkaus, Finland) containing 5 % CO_2. Next to the air container there was a decompression valve and after that, an on-off valve. The low-resistance tubing and the valves allowed over 300 l/min airflow. The air was directed to two parallel rotameters, together capable to measure up to 300 l/min airflow (Rotameter, Aalborg Instruments, Kytölä, Muurame, Finland). A flow adjuster connected to the rotameters was utilised in the setting of the airflow. After the rotameters the airflow was directed to a target balloon (Direct Fill single Bag Set, Harvard Apparatus Ltd, Edenbridge, Kent, UK) and after that, to a mouthpiece (Douglas Bag One-Way Air Valve and Mouthpiece, Harvard Apparatus Ltd, Edenbridge, Kent, UK). The subject was encouraged to ventilate at a level which is high enough to keep the volume of the balloon constant. By this means, the patient's ventilation level was assumed to be the same as the gas flow into the balloon, after BTPS correction.

The challenge has been described in detail previously. (16) The test began with measurement spirometry, as described earlier, three blows. Salbutamol pre-treatment and control of FEV_1 was performed as described in the previous chapter. The best post-salbutamol FEV_1 was used to

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calculate the maximal voluntary ventilation (MVV), taken as 35 x post-salbutamol FEV_1. The test commenced breathing at 30% MVV for three minutes. Coughs were counted manually by the investigation nurse during the test and up to 10 minutes after it. (25) Then two FEV_1 measurements were performed. The test continued with ventilation at 60% MVV for three minutes, and succeeded with cough counting and two FEV_1 measurements. Finally the subject ventilated at 100% MVV for three minutes, and cough counting and two FEV_1 measurements were repeated. The test was stopped if the subject asked for it, 30 or more cumulative coughs were recorded, or the fall in FEV_1 was 10% or more compared to the post-salbutamol value.

Statistical analysis

Cough responsiveness was expressed as coughs-to-dose ratio (CDR) which was calculated as cumulative coughs/final osmolality (coughs/mOsm/kg) in hypertonic saline test, and as cumulative coughs/ final MVV% (coughs/MVV%) in isocapnic hyperpnoea of dry air test.

Between-groups differences were analysed utilising Student's unpaired t-tests. Correlations were assessed with the Pearson correlation coefficient (R). The data was further analysed with multivariate analysis of variance with backward selection procedure utilising ACQ and LCQ as the dependent variables. The considered independent variables were age, body mass index, gender, smoking, use of inhaled corticosteroids, atopy, improvement of FEV_1 after salbutamol, mean daily PEF variability, eNO, CDRsaline, and CDRhyperpnoea. Baseline FEV_1 (%predicted) was included in models with ACQ 6 questions (i.e. ACQ without FEV_1 (%predicted) result in questionnaire). Due to the correlation between CDRsaline and CDRhyperpnoea (16), their effects were estimated in separate models. All analyses were carried out using SPSS for Windows 15.0 (SPSS Inc.™, Chicago, USA).

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RESULTS

Differences between controlled and uncontrolled asthmatic patients

Cough responsiveness to hypertonic saline and hyperpnoea (figure 1), FEV_1, and scores of ACQ and LCQ differed statistically significantly between controlled and uncontrolled asthma (table 1).

Bivariate correlations of ACQ and LCQ with the investigated biomarkers

Both ACQ and LCQ correlated well with CDRsaline and CDRhyperpnoea (table 2). The three domains of LCQ also correlated with these cough indices (table 3). Of the other investigated biomarkers, only eNO showed a statistically significant correlation with LCQ. Analysis with non-smoking subjects alone had paralleling results (data not shown). Finally, a clear correlation could be shown between ACQ and LCQ (R= -0.54, p=0.001).

Determinants of ACQ and LCQ in multivariate analysis

Multivariate models including CDRsaline

Fifty-two percent of the variation in asthma control was explained by model including CDRsaline, smoking, and improvement of FEV_1 after salbutamol (ACQ 7 questions, table 4). In the model with ACQ 6 questions as the dependent variable, CDRsaline, eNO, FEV_1(%predicted), smoking, and mean daily PEF variation together explained 61 % of the variation in asthma control. In both models CDRsaline was far the most significant determinant of asthma control. In the model with

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LCQ as the dependent variable only CDRhyperpnoea showed a statistically significant association explaining 43% of the variation in the cough-related quality of life. The data was also analysed without smokers, but it did not have an impact on the results (data not shown).

Multivariate models including CDRhyperpnoea

In the model with ACQ 7 questions as the dependent variable (table 5), CDRhyperpnoea and improvement in FEV_1 after salbutamol together explained 34 % of the variation in asthma control. In the model with ACQ 6 questions, CDRhyperpnoea, FEV_1(%predicted), and eNO together explained 52% of the variation in asthma control. In both models CDRhyperpnoea was the most significant determinant of asthma control. In the model with LCQ as the dependent variable only CDRhyperpnoea showed a statistically significant association.

DISCUSSION

The present results indicate that asthma control is more closely related to the cough responsiveness to hypertonic saline and hyperpnoea than to traditional asthma biomarkers such as spirometric indices, ambulatory PEF monitoring, and eNO. Cough-related quality of life was also closely associated with the cough provocation test results but did not show any associations with the traditional asthma biomarkers. Furthermore, the strong correlation between LCQ and ACQ corroborates that cough is the major symptom contributing to poor asthma control. (10)

Cough-related quality of life correlated unexpectedly well with the cough responsiveness to both tested agents. This is of interest when compared to results of Birring et al. (12) who did not find any statistically significant correlation between cough responsiveness to capsaicin and LCQ assessed

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quality of life in chronic coughers. This may be explained by the differences in the mechanisms of action. Cough response to capsaicin is mediated via type I vanilloid receptor (TRPV 1) while hypertonic saline activates airway sensory nerves independently of TRPV 1. (27, 28) Also, the determinants of cough-related quality of life may differ between subjects with chronic cough and asthma.

It has been stated before that lung function does not predict cough related quality of life in asthmatic patients. (11) Our results underline this statement; none of the traditional indices of bronchial obstruction associated with LCQ score. Cough is a common symptom among asthma patients (8) and may affect the quality of life even after successful management of lung function indices. (10)

The demonstrated positive correlation between eNO and LCQ in the bivariate analysis is surprising since it indicates that high eNO is associated with high LCQ score (i.e., high quality of life). This finding is difficult to explain. Perhaps high eNO indicates good responsiveness to inhaled corticosteroids and therefore, less cough in asthmatic patients. However, the multivariate analysis with the cough indices included suggested that eNO may not be an independent determinant of LCQ. Smoking is known to affect eNO values. (29) However, in the present study the exclusion of the smoking patients did not affect the results.

Asthma control was also mirrored by the responsiveness to the investigated cough provocation tests even though the study groups were rather small for this kind of analysis. It must be admitted that there was a rather large inter-individual variation in cough responsiveness both in controlled and uncontrolled asthma groups which should be taken into account if these tests would be utilised in an individual basis. However, the cough provocation tests associated with asthma control more closely

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than FEV_1, mean daily PEF variation and eNO, all biomarkers that are commonly utilised in everyday clinical practice. This is in line with previous studies with both adults and children. (30, 31)

Smoking was included into the multivariate analysis because it is thought to be related both to cough-related quality of life and asthma control. (32) However, in this study smoking explained only a minor portion of asthma control while showing no association with cough-related quality of life. This is probably due to low number of pack-years. Importantly, the ability of cough provocation tests to explain both asthma control and quality of life was independent of smoking.

In this patient population cough responsiveness to hypertonic saline explained asthma control better than cough responsiveness to isocapnic hyperpnoea. In theory, both of these provocative agents are thought to increase the osmolality of the airway lining fluid, stimulating airway sensory nerves and causing cough. (16, 27) However, there are methodological features that may explain the superiority of hypertonic saline. In the hypertonic saline test, osmolality is raised in seven steps. A nebuliser with calibrated output is used in delivering the solutions into the airways, and the changes in osmolality are thought to happen gradually. The repeatability of the test is high. (15) In the hyperpnoea test, the ventilation is raised in just three steps. The conditions affecting the osmolality of airway lining fluid, for instance maintaining of ventilation and thermal conditions in the airways, can not be controlled in detail. (33) Also, the authors' way to approximate the patients' minute ventilation by rotameters may not be as accurate as that by a gas meter. (26) Furthermore, a recent report has demonstrated that hyperpnoea can actually down regulate the sensitivity of the cough reflex in healthy subjects. (34) The use of isocapnic hyperpnoea cough provocation test needs further evaluation.

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Inadequacy of asthma control is widely acknowledged. (1-3) It has been stated before that the perspective provided by ACQ on asthma control may be limited (35), and additional information is needed to construct the full picture for optimal management of asthma. (30) From the biomarkers utilised in this study, cough responsiveness to the investigated tests were independent markers of both asthma control and cough-related quality of life. The combination of ACQ and measures of cough responsiveness would extend the view of asthma control. At this point, hypertonic saline cough provocation test is safe, reproducible and valid method for this purpose. (15)

In conclusion, the present study suggests that both asthma control and cough-related quality of life are closely related to cough responsiveness to hypertonic saline and hyperpnoea. Traditional asthma biomarkers such as spirometry, ambulatory PEF monitoring, and eNO explained minor proportions of the variation in asthma control while showing no associations with the quality of life. Furthermore, the demonstrated strong association between asthma control and cough-related quality of life highlights the importance of cough as the main symptom contributing to poor asthma control. (10) These findings suggest that correction of indices of bronchial obstruction or eNO does not guarantee sufficient asthma control or quality of life in asthma patients. Monitoring of cough responsiveness to hypertonic aerosols or hyperpnoea may be useful in the management of asthma.

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FIGURE LEGENDS

Figure 1. Coughs-to-dose ratios (CDR) of hypertonic saline (a) and isocapnic hyperpnoea of dry air (b) tests. The patients were divided to two groups according to the Juniper's Asthma Control Questionnaire (ACQ) score with $\leq$ 0.75 representing controlled and > 0.75 borderline or uncontrolled asthma. Horizontal bars represent the mean values.

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Table 1. Demographic and functional patient characteristics.

	Well-controlled asthma (N=13) **ACQ ≤ 0.75**	**Borderline or uncontrolled asthma (N=23)** **ACQ > 0.75**	**p**
Age (y)	41(18-68)	41(18-60)	
Gender M/F	3/10	7/16	
Current smoking (mean packyears)	4 (2.4)	5 (3.0)	
Atopy[¶]	10 (77%)	12 (52%)	
Use of inhaled cortocosteroids (ICS)	11 (85%)	13 (57%)	
daily ICS dose (ug)	629 (408-850)	502 (320-684)	
Body mass index (kg/m^2)	25.8 (23.0-28.6)	27.5 (25.3-29.8)	0.31
Mean daily PEF variation (%)	8.20 (3.10-12.4)	7.74 (5.41-10.1)	0.84
FEV_1 (%predicted)	99 (93-106)	84 (79-89)	<0.001
Improvement of FEV_1 after salbutamol (%)	3.50 (2.27-4.73)	4.83 (2.69-6.96)	0.40
CDRsaline[§] (coughs/mOsm/kg)	0.008 (0.003-0.012)	0.016 (0.011-0.020)	0.01
CDRhyperpnoea (coughs/ MVV%)	0.29 (0.07-0.51)	0.57 (0.32-0.81)	0.05
Exhaled nitric oxide (ppb)	24.0 (12.4-37.8)	15.4 (10.8-20.1)	0.12
[#]ACQ total	0.49 (0.36-0.63)	1.76 (1.42-2.10)	<0.001
[##]LCQ total social psychological physiological	17.8 (15.9-19.8) 5.77 (481-6.73) 6.14 (5.54-6.75) 5.86 (5.35-6.38)	13.5 (11.8-15.2) 4.66 (3.97-5.36) 4.54 (3.90-5.18) 4.33 (3.86-4.79)	0.001 0.03 0.001 <0.001

Age, ICS dose, FEV_1 (%predicted) expressed as mean (min-max). The other ones are expressed as mean(95%CI).

[¶] Atopy was assessed as ≥3 mm mean wheal diameter in the skin prick test to at least one common aeroallergen. [§]CDR=coughs to dose ratio. [#]Asthma control questionnaire. [##]Leiscester cough questionnaire. A small LCQ score indicates poor cough-related quality of life.

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Table 2. Bivariate correlations of questionnaire assessed asthma control and cough-related quality of life with cough responsiveness, indices of bronchial obstruction and exhaled nitric oxide.

	ACQ [#] R (p-value)	**LCQ [##] R (p-value)**
CDRsaline[§] (coughs/mOsm/kg)	0.52 (0.001)	-0.66 (<0.001)
CDRhyperpnoea[§] (coughs/ MVV%)	0.43 (0.008)	-0.49 (0.002)
FEV_1 (%predicted)	-	0.12 (0.50)
Exhaled nitric oxide (ppb)	-0.03 (0.84)	0.33 (0.049)
Mean daily PEF variation (%)	0.04 (0.80)	-0.14 (0.44)
Improvement of FEV_1 after salbutamol (%)	0.20 (0.25)	0.16 (0.36)

[§]CDR=coughs to dose ratio. [#]Asthma control questionnaire. [##]Leiscester cough questionnaire. The association between ACQ and FEV_1 was not analysed since FEV_1 is included in the definition of ACQ.

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Table 3. Bivariate correlations of different domains of Leicester cough questionnaire (LCQ) with cough responsiveness, indices of bronchial obstruction and exhaled nitric oxide.

	LCQ[##] social R (p-value)	**LCQ [##] psychological R (p-value)**	**LCQ [##] physical R (p-value)**
CDRsaline[§] (coughs/mOsm/kg)	-0.64 (<0.001)	-0.60 (<0.001)	-0.62 (<0.001)
CDRhyperpnoea[§] (coughs/ MVV%)	-0.43 (0.009)	-0.46 (=0.005)	-0.50 (0.002)
FEV_1 (%predicted)	0.04 (0.82)	0.16 (0.34)	0.13 (0.44)
Exhaled nitric oxide (ppb)	0.39 (0.018)	0.26 (0.12)	0.31 (0.068)
Mean daily PEF variation (%)	-0.16 (0.34)	-0.11 (0.52)	-0.08 (0.66)
Improvement of FEV_1 after salbutamol (%)	0.22 (0.21)	0.11 (0.54)	0.15 (0.40)

[§]CDR=coughs to dose ratio

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Table 4. Multivariate analysis of variance models containing CDRsaline[§].

Dependent variable	Independent variables	R squared of the model	B	p	95% CI
ACQ[#] 7 questions	CDRsaline		66.7	<0.001	42.3 - 91.1
	Smoking		0.58	0.030	-0.06 - 1.09
	Improvement of FEV_1 after salbutamol		0.09	0.002	0.04 - 0.15
	All three variables	0.52			
ACQ 6 questions	CDRsaline		75.5	<0.001	48.5 - 102
	Smoking		0.58	0.030	0.06 - 1.01
	Exhaled nitric oxide		0.03	0.002	0.01 - 0.05
	Mean daily PEF variation		-0.04	0.049	-0.08 - 0.00
	FEV_1 (% predicted)		-0.03	0.003	-0.05 - -0.01
	All five variables	0.61			
LCQ[##]	CDRsaline	0.43	-278	<0.001	-390 - -167

[§]CDR=coughs to dose ratio. [#]Asthma control questionnaire. [##]Leiscester cough questionnaire. The considered independent variables were age, body mass index, gender, smoking, use of inhaled corticosteroids, atopy, FEV1 (% predicted), improvement of FEV_1 after salbutamol, mean daily PEF variation, exhaled nitric oxide, and CDRsaline.

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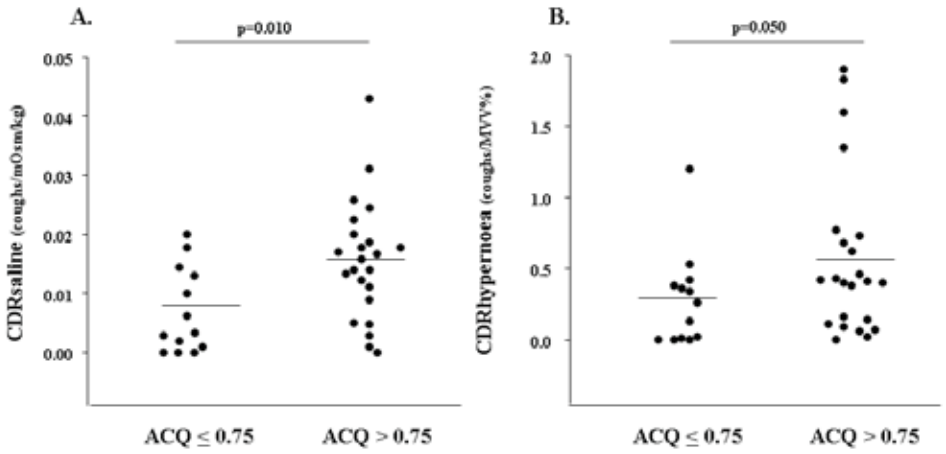
Table 5. Multivariate analysis of variance models containing CDRhyperpnoea[§].

Dependent variable	Independent variables	R squared of the model	B	p	95% CI
ACQ[#] 7 questions	CDRhyperpnoea Improvement of FEV_1 after salbutamol Both two variables	 0.34	0.84 0.08	0.002 0.011	0.34-1.34 0.02-0.14
ACQ 6 questions	CDRhyperpnoea Exhaled nitric oxide FEV_1 (% predicted) All three variables	 0.52	1.10 0.02 -0.04	<0.001 0.012 <0.001	0.64 - 1.57 0.01 - 0.04 -0.01 - -0.02
LCQ[##]	CDRhyperpnoea	0.24	-4.04	0.002	-6.52 - -1.56

[§]CDR=coughs to dose ratio. [#]Asthma control questionnaire. [##]Leiscester cough questionnaire. The considered independent variables were age, body mass index, gender, smoking, use of inhaled corticosteroids, atopy, FEV1 (% predicted), improvement of FEV_1 after salbutamol, mean daily PEF variation, exhaled nitric oxide, and CDRhyperpnoea.

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