

Methacholine inhalation challenge: a shorter, cheaper and safe approach

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ABSTRACT: Increased nonspecific bronchial hyperresponsiveness to pharmacological agents such as histamine or methacholine (MCh) is a hallmark of asthma. The measurement of airway reactivity is quite sensitive but testing is tedious, and time and money consuming. The present aim was, therefore, to design the shortest possible, yet safe inhalation challenge protocol applicable for a lung function referral centre.

All records of studies performed in our institution during 1996 were analyzed retrospectively with a baseline ratio (bl) of forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) ≥ 0.7 (n=449). It was questioned what the initial dose should be, and whether some inhalation steps could have been skipped without losing pertinent information and/or causing an adverse response (a fall in FEV₁ >40%). When unavailable, provocative dose causing a 20% fall in FEV₁ (PD₂₀) values were obtained by linear inter- or extrapolation of the existing data.

The present study showed that three-fold concentration steps could have been employed with minimal change in outcome. Only 15/449 patients (3.3%) would have experienced a severe response. Five subjects (of 169, 3.0%) with FEV₁/FVC_{bl} 0.7–0.8 reacted to inhalation up to 0.073 μmol . Four subjects (of 280, 1.4%) with FEV₁/FVC_{bl} ≥ 0.8 reacted to inhalation up to 0.219 μmol .

The authors suggest that: 1) an initial dose of 0.219 μmol (initial concentration=0.21 $\text{mg}\cdot\text{mL}^{-1}$) may be used when the baseline ratio of forced expiratory volume in one second to forced vital capacity ≥ 0.8 and 0.073 μmol (initial concentration=0.07 $\text{mg}\cdot\text{mL}^{-1}$) when the baseline ratio is <0.8; 2) a tripling dose protocol is easier to perform, cheaper and 30.2% faster, yet just as safe; and 3) other abbreviated protocols used in epidemiologic settings may not be applicable in a referral centre setting.

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Methacholine (MCh) or histamine inhalation challenge tests are often used to generate dose-response curves and measure nonspecific bronchial hyperresponsiveness. The method is quite sensitive [1], but is tedious, and time and money consuming. In Hadassah University hospital, MCh challenge tests are performed according to a modified method of CHAI *et al.* [2] and COCKCROFT *et al.* [3]. They often take over one hour to complete and cost over \$100 in Israel.

Several short protocols for bronchial provocation testing have been proposed in the past 20 yrs [4–12]. The biggest disadvantage of any proposed protocol is the risk of developing marked airways obstruction *i.e.* a fall >40% in forced expiratory volume in one second (FEV₁) [4, 8–10, 12]. For example, in the protocol suggested by CHATHAM *et al.* [10], as many as 38.5% of subjects actually developed such a marked obstruction. In addition, abbreviated protocols may be safe when applied in random populations, but may not be as safe for a referral pulmonary function centre.

Furthermore, any comparison of results obtained from a pair of challenges needed in a prospective design, is prone to errors since between-test variability is in the order of magnitude of one doubling

concentration [11]. In contrast, a retrospective analysis is a better approach for the question at hand since each subject serves as their own control within the same challenge. Additionally, any abbreviated protocol can be tested on as many records as possible and without affecting the subjects. Thus, the present analysis allowed the authors to calculate the added risks involved in simulated protocols starting at a higher initial dose, and in shortening the protocol by widening the steps between inhalations, without putting the subject at risk.

To the best of the authors' knowledge, there is no study based on a retrospective analysis which tests the feasibility and safety of a short MCh provocation test in a referral pulmonary function centre. The purpose of this study was to design the shortest possible, yet safe methacholine challenge test (MCT) protocol to measure nonspecific airways reactivity.

Subjects and methods

A retrospective analysis of all 487 records of patients who underwent an MCT in the authors' institution, was performed during 1996. Anthropometric data of the

Table 1. – Patient anthropometric data and baseline values

	FEV ₁ /FVC _{bl}		Total
	≥0.8	<0.8	
Subjects n	280	169	449
Male	153 (55)	94 (56)	247 (55)
Age yrs	19 (6–72)	26 (7–84)	19 (6–84)
FEV ₁ % pred	94.3±11.3	88.9±12.7	92.2±11.9
FEF ₅₀ % pred	94.3±18.4	66.2±12.9	83.7±21.3
Positive responders	155 (55.4)	113 (66.7)	268 (59.7)
PD ₂₀ µmol*	1.50 (0.14–17.05)	0.94 (0.05–17.31)	1.24 (0.08–17.82)

Data presented as mean±SD, n (%) or mean (range), except where stated. FEV₁: forced expiratory volume in one second; FEV₁/FVC_{bl}: baseline ratio of FEV₁ to forced vital capacity; % pred: percentage of the predicted value; FEF₅₀: forced expiratory flow at 50% of vital capacity; PD₂₀: provocative dose causing a 20% fall in FEV₁; *: data presented as geometric mean (95% confidence interval).

population studied are presented in table 1. Most were referred as part of routine investigation of suspected asthmatics, based on clinical signs such as wheezing, dyspnoea, prolonged cough, and atopy, or for re-evaluation of known asthmatics. Thirty-eight of the patients underwent the challenge test despite the fact that they had a baseline ratio of forced expiratory volume to forced vital capacity (FEV₁/FVC_{bl}) ≤0.7. Normally, this condition precludes routine testing and, therefore, these patients were omitted from further analysis.

Routine methacholine challenge test protocol

MCTs have been routinely carried out in the Hadassah University Hospital using the modified method of CHAI *et al.* [2] and COCKCROFT *et al.* [3] *i.e.* the 2 min tidal breathing [3] and the doubling concentrations step-up [2]. Starting concentration is 0.03 mg·mL⁻¹ for all the patients. FVC manoeuvres are performed using an electronic spirometer (Compact, Vitalograph Ltd, Buckingham, UK). The MCT was performed provided that baseline FEV₁ ≥60% predicted and FEV₁/FVC_{bl} >0.7. A complete test consists of inhaling phosphate buffered solution and then doubling concentrations of MCh (Spectrum Quality Products, Inc., CA, USA), starting at 0.031 mg·mL⁻¹ and up to 8.0 mg·mL⁻¹. At each step, the patient breathes tidally for 2 min from a nebulizer (Respigard II nebulizer System, Marquest Medical Products Inc., NJ, USA) having an output of 0.34 mL·min⁻¹. Spirometry is performed in duplicates 1 min after the inhalation, as suggested by YAN *et al.* [4], the best FEV₁ value is recorded, and the percentage change in FEV₁ from baseline (ΔFEV₁) is calculated. If ΔFEV₁ <15%, the test proceeds to the next step. When the response is borderline (ΔFEV₁ 15–20%) the next inhalation given is half the next doubling concentration. The test continues until a positive response (*i.e.* ΔFEV₁ ≥20%) is observed or when the final concentration is reached. The provocative dose causing a ΔFEV₁ of 20% (PD₂₀) is calculated by linear interpolation of the last two responses.

In order for the results to be comparable with other publications, cumulative doses are presented in µmol delivered. Using our nebulizer output (0.34 mL·min⁻¹),

time of inhalation (2 mins), and the duty cycle for tidal breathing (assumed at 0.3), the conversion factor suitable for the centre was calculated based on the following relationship: delivered dose (µmol)=factor (µmol·mg·mL⁻¹)·concentration (mg·mL⁻¹) factor (µmol·mg⁻¹·mL)=molecular weight (µmol·mg⁻¹)·nebulizer output (mL·min⁻¹)·time of inhalation (min) molecular weight of MCh=195.7 (g·mol⁻¹) factor (µmol·mg⁻¹·mL)=5.1098 (µmol·mg⁻¹)·0.34 (mL·min⁻¹)·2 (min)·0.3=1.042.

Hence, the dose given in mg·mL⁻¹ was converted to µmol, delivered by a factor of 1.042. The concentrations used were 0.03–8 mg·mL⁻¹ and the doses actually delivered were 0.032–8.34 µmol.

Study design

All past records were reviewed and cumulative doses at each step were calculated. The authors then simulated various abbreviated protocols (*i.e.* three-fold dose steps, four-fold, and so on) on each record to see what would have been that subject's response had they been exposed to the stipulated design. Values were calculated by linear interpolation or extrapolation of the available data at the nearest two inhalations.

Statistical analysis

Comparisons were made by paired, unpaired t-tests and by the Chi-squared test, and differences were considered significant at p<0.05 level. As PD₂₀ values are logarithmically distributed, mean values (95% confidence interval (CI)) were calculated after log transformation. The analyses performed in this work stem from the authors' attempt to answer the following three questions. What is an acceptable risk? The authors' *a priori* assumption was that the risk currently acceptable when performing the full protocol should be acceptable for any abbreviated protocol. This risk factor was determined by reviewing all 268 records in which a positive response *i.e.* ΔFEV₁ ≥20%, was observed. Despite all the necessary precautions taken when running the routine (and supposedly safest) protocol, 57 subjects (20.9%) developed a moderate response *i.e.* ΔFEV₁ >30%, and 11 subjects (4.1%)

developed marked airways obstruction *i.e.* $\Delta FEV_1 > 40\%$. Hence, the authors decided to use this latter threshold as an acceptable risk factor of developing a marked airway obstruction for comparison with present results. What should be the initial MCh dose? Reviewing all past records, the number of positive responses at each successive step were counted and the accumulated percentage of occurrence was compared to risk factor. That is, the number of subjects who would have been at risk had the test been started at an MCh dose higher than that at which they had responded, was determined. What is the optimal dose-multiplier? As previously described, the authors ran simulations of various abbreviated protocols and counted the number of positive responses at each higher dose. The optimal step was thus determined when the number of responses (per cent occurrence) reached the level of acceptable risk *i.e.* 4.0%, as previously determined. Once the new step was determined, the results of each subject were interpolated or extrapolated to this inhalation step in order to determine the subject's response had they been studied by the abbreviated protocol.

Results

A total of 487 records were reviewed but only those with an $FEV_1/FVC_{bl} > 0.7$ ($n=449$) were analyzed (table 1). According to American Thoracic Society recommendations, FEV_1/FVC_{bl} is an important parameter to distinguish an obstructive impairment [13]. Therefore, the subjects were divided according to their baseline values, with 169 subjects (37.6%) having $FEV_1/FVC_{bl} < 0.8$ and 280 with $FEV_1/FVC_{bl} \geq 0.8$. Two-hundred and sixty-eight subjects (59.7%) had a positive response to MCh at or before reaching the final dose of $17.73 \mu\text{mol}$ (concentration of $8 \text{ mg}\cdot\text{mL}^{-1}$). Baseline values of FEV_1 were similar but forced expiratory flow rate at 50% vital capacity (FEF₅₀) were significantly lower in the $FEV_1/FVC_{bl} < 0.8$ group ($p < 0.0001$). The per cent of responders in this group was higher (Chi-squared test, $p < 0.05$) and PD₂₀ lower ($p < 0.05$).

What should be the initial dose?

Only five of 169 subjects (3%) with $FEV_1/FVC_{bl} < 0.8$ had a PD₂₀ $< 0.073 \mu\text{mol}$ and only two of them (table 2) had a positive response to a lower inhalation dose *i.e.* $0.033 \mu\text{mol}$. When inter- or extrapolating their data to the suggested initial step of $0.073 \mu\text{mol}$, two of the subjects would have developed a severe response (out of 169, 1.2%) (table 3). Only four of 280 subjects (1.4%) with $FEV_1/FVC_{bl} \geq 0.8$ had a PD₂₀ $< 0.219 \mu\text{mol}$, and only one of them had a positive response to a lower inhalation. None of the subjects would have presented a severe response (table 3). Thus, it is suggested that the initial dose for routine MCh challenges for subjects having $FEV_1/FVC_{bl} \geq 0.8$ (constituting approximately two-thirds of the sample) need not be less than $0.219 \mu\text{mol}$. It is further suggested that subjects having $FEV_1/FVC_{bl} < 0.8$ need not be challenged at a dose $< 0.073 \mu\text{mol}$ (fig. 1).

What is the optimal dose-multiplier?

Having determined a prevalence of 4.1% of severe response (*i.e.* $\Delta FEV_1 > 40\%$) as an acceptable risk, the authors determined the three-fold dose-multiplier to be the optimal protocol (table 2). Eight of the subjects with $FEV_1/FVC_{bl} < 0.8$ had PD₂₀ $0.073\text{--}0.219 \mu\text{mol}$ and one responded at an intermediate step. None of the subjects would have presented with an extrapolated severe response at $0.219 \mu\text{mol}$. Taken together, none of the 13 patients would have presented with a severe response at $0.219 \mu\text{mol}$. Combining severe responses at each step and mid-step, only 15 of the 449 subjects (3.3%) would have presented a severe response of $\Delta FEV_1 > 40\%$ (table 2) in the suggested abbreviated simulation. Compared to the 11 subjects who had actually experienced a severe response, there was virtually no added risk with the suggested abbreviated three-fold protocol.

The mean \pm SD time needed to perform the usual doubling concentration protocol was 42.4 ± 9.6 min. If the new tripling protocol proposed on the same subjects

Table 2. – Outcome of the simulated methacholine three-fold dose protocol

Cumulative dose μmol	Total responders <i>i.e.</i> $\Delta FEV_1 > 20\%$	Moderate responders <i>i.e.</i> $< \Delta FEV_1 30\text{--}40\%$	Severe responders <i>i.e.</i> $\Delta FEV_1 > 40\%$
0.073	5 [§] (3.0)	1 (0.2)	2 (0.4)
0.126*	1 [§] (0.6)*	0*	0*
0.219	12 (2.7)	0	0
0.379*	17 (3.8)*	1 (0.2)*	0*
0.657	18 (4.0)	6 (1.3)	2 (0.4)
1.137*	35 (7.8)*	8 (1.8)*	1 (0.2)*
1.970	34 (7.6)	5 (1.1)	4 (0.8)
3.412*	30 (6.7)*	7 (1.6)*	0*
5.910	42 (9.4)	16 (3.6)	4 (0.8)
10.237*	32 (7.1)*	5 (1.1)*	1 (0.2)*
17.731	42 (9.4)	3 (0.7)	1 (0.2)
Total	268 (59.7)	52 (11.6)	15 (3.3)

Data are presented as number of subjects (percentage of subjects participating at that dose) at each inhalation step, including intermediate steps (indicated by *). [§]: since only 169 subjects would have participated in these steps, percentages are out of 169. ΔFEV_1 : the percentage change in forced expiratory volume in one second from baseline.

Table 3. – Outcomes of the simulated methacholine three-fold dose protocol for separate groups during early protocol steps

Cumulative dose μmol	FEV ₁ /FVC _{bl} <0.8 (n=169)		FEV ₁ /FVC _{bl} \geq 0.8 (n=280)	
	ΔFEV_1 30–40%	ΔFEV_1 >40%	ΔFEV_1 30–40%	ΔFEV_1 >40%
0.073	1 (0.6)	2 (1.2)	ND	ND
0.126*	0*	0*	ND	ND
0.219	0	0	0	0

Data are presented as number of subjects (percentage of subjects participating at that dose) at each inhalation step, including intermediate steps (indicated by *). ΔFEV_1 : the percentage change in forced expiratory volume in one second from baseline; FEV₁/FVC_{bl}: baseline ratio of forced expiratory volume to forced vital capacity; ND: not determined.

had been used, the time to perform these 449 challenge tests could have been significantly reduced to 29.6 (8.0) min ($p < 0.001$) with a time saving of 30.2%.

Discussion

All records of MCh bronchial challenge tests performed in the authors institution during 1996 were analysed retrospectively and it was found that an abbreviated protocol could have been administered to the subjects without increasing the risk of a severe response to any inhalation. According to the new protocol, the initial concentration of MCh can be 0.219 μmol if FEV₁/FVC_{bl} \geq 0.8, and 0.073 μmol if not. Also, it was found that steps between inhalations

could be widened beyond the usual doubling concentration. Thus, a protocol consisting of inhalation of a total of five or six delivered doses (0.073, 0.219, 0.657, 1.97, 5.91 and 17.73 μmol) is as safe as the routine one (these are synonymous to concentrations of 0.07, 0.21, 0.63, 1.89 and 5.67 $\text{mg}\cdot\text{mL}^{-1}$).

Obviously, any protocol for MCT should strive for a zero risk factor *i.e.* no risk for a severe response in any subject. In practice, the authors found that even when taking all the necessary precautions when running the routine and supposedly safest protocol, 57 subjects (20.9%) were found to have $\Delta\text{FEV}_1 > 30\%$ and 11 subjects (4.0%) a marked bronchoconstriction *i.e.* $\Delta\text{FEV}_1 > 40\%$. A review of short inhalation challenge protocols in the literature shows that a severe bronchoconstriction was seen in 3–38% of the patients, depending on the protocol [4, 8–10, 12]. In the protocol of CHATHAM *et al.* [10], as many as 38% of the subjects experienced a severe airway response. At the other end of the range, KREMER *et al.* [8] observed only 3% occurrence of severe response. Their reported percentage may be underestimated though, as 38 tests were rejected from the analysis. Hence, the present suggested protocol, yielding only 3.3% risk of severe response, seems to be one of the safer protocols.

An inhalation challenge protocol can be abbreviated in three ways: 1) by starting at a higher concentration; 2) by using a higher dose-multiplier than the usual doubling concentration protocol; and 3) by decreasing the time of delivering any dose. Most of the abbreviated protocols do not start at a higher initial dose [4, 8, 9, 12, 14]. Indeed, the authors found that patients with airway obstruction (FEV₁/FVC_{bl} <0.8) could be started with only a slightly greater dose (0.073 instead of 0.032 μmol). In comparison, JUNIPER *et al.* [14] recommend that the initial concentration be only 0.03 $\text{mg}\cdot\text{mL}^{-1}$ in patients treated by corticosteroids (inhaled or ingested). Indeed, the present study found two subjects (out of 169, 1.2%) who responded at the first inhalation and would have responded severely using the suggested protocol. JUNIPER *et al.* [14] further suggested that patients in this group with airway obstruction could be started at an initial concentration of 0.125 $\text{mg}\cdot\text{mL}^{-1}$ if they were not treated with steroids. The present study found five additional patients (3.0%) who had a lower PD₂₀ and would have responded severely at that concentration. Thus, special care needs to be taken when studying these patients in order to avoid a high percentage of severe responses. In addition, since the use of inhaled steroids became the first line of

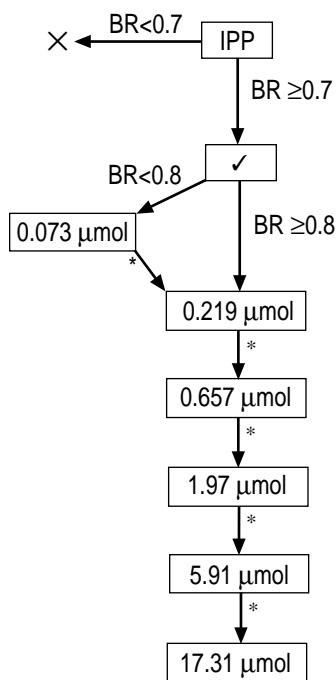


Fig. 1. – Suggested abbreviated protocol. Patients with baseline ratio (BR) \geq 80% of predicted, are separated for the initial inhalation step, beyond which the protocol is identical for both groups. *: the next step can follow if the change from baseline forced expiratory volume in one second (ΔFEV_1) < 10%. X: Methacholine Challenge Test (MCT) not performed; ✓: MCT performed; IPP: Initial patient population; BR: baseline ratio of forced expiratory volume in one second to forced vital capacity (FEV₁/FVC_{bl}).

treatment, the suggestion of JUNIPER *et al.* [14] needs to be revised.

Conversely, subjects with no evidence of airway obstruction ($FEV_1/FVC_{bi} \geq 0.8$) could be safely started at a higher initial dose of $0.219 \mu\text{mol}$. JUNIPER *et al.* [14] suggested that in asthmatic subjects having normal baseline lung function, the initial concentration can be as high as $1 \text{ mg}\cdot\text{mL}^{-1}$ if they are maintained on intermittent bronchodilators and $2 \text{ mg}\cdot\text{mL}^{-1}$ if they take no medication. In the present study, 19 of 280 subjects (6.8%) having an $FEV_1/FVC_{bi} \geq 0.8$, reached the end of the challenge at an inhalation concentration of $0.5 \text{ mg}\cdot\text{mL}^{-1}$, four of them having a $PD_{20} < 0.219 \mu\text{mol}$ (table 2). It is very probable that all 19 would have developed a severe response had they been started at an initial concentration of $1 \text{ mg}\cdot\text{mL}^{-1}$. An additional 40 subjects (14.3%) responded at that concentration. Thus, the authors do not feel that the recommendations of JUNIPER *et al.* [14] are safe enough.

Most of the abbreviated protocols used a four-fold or even higher dose-multiplier. In the protocol used by SEARS *et al.* [15] in an epidemiological setting, the concentration of MCh was increased in ten-fold steps. Simulating the SEARS *et al.* [15] protocol on the records of patients from the present study, rather than random population, it was calculated that 179 of 449 patients (40%) would have reacted with a severe bronchoconstriction (*i.e.* $\Delta FEV_1 > 40\%$). This finding illustrates the importance of tailoring a suitable protocol to the population being studied. Other protocols used four-fold concentration increases [8–10, 12, 14]. Simulating four-fold step increases on the present study's records yielded a 7.5% rate of severe airway response, substantially greater than the 3.3% found by the present protocol. The JUNIPER *et al.* [14] protocol, which was endorsed by the Canadian Thoracic Society and has become quite popular worldwide, is believed to be safe. However, this popular protocol would have yielded a significantly larger number of severe responses than the present suggested protocol (25 *versus* 15; 5.6% *versus* 3.3%). Moreover, since it practices a switch back to doubling concentration steps if the response of ΔFEV_1 is $\geq 5\%$ (compared to $\Delta FEV_1 \geq 10\%$ in the present study), it affords only a 16.5% saving of time compared to the present 30.2%.

YAN *et al.* [4] did not clearly describe their abbreviated protocol, only mentioning that they sometimes shortened the test by combining two doses together. Hence, any comparison with this protocol is difficult. Their protocol substantially reduced the time it took to complete the challenge. This was achieved by shortening the time of inhalation by taking one full inspiration lasting $< 10 \text{ s}$ compared with the 2 min of tidal breathing in the CHAI *et al.* [2] protocol. The authors believe that tidal breathing is a more reliable mode of delivery than vital capacity manoeuvres [3, 8–10, 12], because the tidal breathing manoeuvre is independent of patient cooperation. This is especially true for young children and elderly patients, and may also improve the quality of the results.

Another advantage of the present abbreviated protocol is that the choice of starting MCh concentration relies solely on an objective criterion of baseline lung function, *i.e.* FEV_1/FVC , rather than on any subjective

criterion such as a questionnaire. This is in contrast to most of the published abbreviated protocols [5, 6, 8, 9, 14–16] that were applied only to subjects with no indication of airway hyperresponsiveness and/or asthma, and were based on a questionnaire or taking of clinical history. A questionnaire may become objective only if the set of rules that goes with it is well defined (*e.g.* a scoring system). No, or even vague, instruction will inevitably result in a subjective determination by the physician at hand. The authors believe that the use of an objective and simple criterion is an important feature in the daily running of a busy referral laboratory, since it simplifies the routine for all personnel involved.

There is the important question of whether or not MCh inhalations are cumulative and hence, whether PD_{20} should be reported instead of the provocative concentration causing a 20% fall in FEV_1 (PC_{20}). There is no evidence for cumulative effect when histamine aerosol is inhaled tidally at roughly 5 min interval [17]. However, MCh is metabolized at a slower rate and some accumulation is evident even with a 5 min interval [17]. The authors believe that reporting cumulative doses is more appropriate for MCh challenges when inhalations are given 3 min apart.

It is noted that the routine doubling concentration protocol calls for halving the dose multiplier when the response to any inhalation is borderline *i.e.* when ΔFEV_1 is 15–20%. In the present simulation, as in most of the abbreviated protocols [8, 9, 12, 14], a more conservative safety criterion was applied *i.e.* ΔFEV_1 of 10–20%. In the study of KREMER *et al.* [8] and in the Guidelines of the Canadian Thoracic Society [14], this threshold was even lower ($\Delta FEV_1 > 6\%$ and $> 5\%$, respectively). Obviously, such a safety criterion reduces the number of severe responses but also prolongs the test for some patients, thus reducing the overall saving in time. Had the present study used the suggested protocol of JUNIPER *et al.* [14], time saving would have been a mere 16.5%.

A known disadvantage of long protocols is the lack of cooperation of some patients. A complete MCT takes about one hour to complete during which the subject is required to perform a repetitive task at their best effort. This is an uneasy routine to many, especially young children and elderly patients. This may also be a burden for laboratory technicians who need to constantly coach and encourage the subjects throughout the test. Hence, the suggested abbreviated protocol would not only save time and money, but also improve the quality of the results by improving compliance and motivation of both the patients and technicians. The present recommendations are applicable to all referral pulmonary function laboratories, in which all tests are performed on patients with a clinical picture suggestive of reactive airway disease or on known asthmatics. Contrary to large-scale epidemiological studies of random populations, such centres tend to be more conservative and use a safer protocol on patients that are more difficult to control. The authors believe that the suggested protocol incorporates the need for a shorter and cheaper procedure, yet is sufficiently safe for the target referral laboratories population.

In conclusion, the present abbreviated methacholine challenge protocol for assessing airway hyperreactivity is advantageous since it is simpler, faster and cheaper to perform than the usual protocol. These benefits were achieved without increasing the potential adverse response of the subjects tested. The authors have started a prospective study in order to validate this new, abbreviated protocol.

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