Dose omission to shorten methacholine challenge testing: clinical consequences of the use of a 10% fall in FEV\textsubscript{1} threshold

Valérie Lévesque\textsuperscript{1}, Claude Poirier\textsuperscript{1} and Bruno-Pierre Dubé\textsuperscript{1,2*}

Abstract

Introduction: In methacholine challenge testing (MCT), skipping a methacholine dose is suggested if FEV\textsubscript{1} falls by < 5%. Using a larger threshold may further shorten test duration, but data supporting this hypothesis is lacking. We evaluated the safety and consequences of using a 10% FEV\textsubscript{1} fall as threshold to skip the next dose of methacholine in patients undergoing MCT.

Methods: We reviewed MCTs performed in our center in 2017–2018. A \( \leq 10\% \) FEV\textsubscript{1} fall allowed the omission of the next methacholine dose. Patients of interest were those in which a dose was skipped after a previous FEV\textsubscript{1} fall outside the usual range (5–10%, termed “skip\textsubscript{5–10\%}”). Adverse events (AE; mild: > 1 nebulized salbutamol dose (2.5 mg) to reach basal FEV\textsubscript{1}, palpitations; severe: hypoxemia and/or need for medical attention or intervention) were compared in the skip\textsubscript{5–10\%} group and others. Regression analysis was used to identify predictors of AE.

Results: 208 MCTs were analysed (135 males, age 52 ± 15 years). Skip\textsubscript{5–10\%} occurred 111 times in 90 tests. Prevalence of AE was 5% and all were mild. Patients who developed AEs had lower FEV\textsubscript{1}, FVC and FEV\textsubscript{1}/FVC ratio, and higher lung volume values (all \( p < 0.05 \)), but similar prevalence of skip\textsubscript{5–10\%} (36 vs. 44%, \( p = 0.64 \)). Overall, MCTs in which at least one skip\textsubscript{5–10\%} occurred had a lower mean number of doses (3.1 ± 0.6 vs. 3.5 ± 1.3 doses, \( p = 0.007 \)). Baseline residual volume was independently related to the development of AEs (OR 1.05, 95% CI 1.01–1.10, \( p = 0.01 \)), but not the presence of a skip\textsubscript{5–10\%}, even when the skipped dose directly led to the reaching of PC\textsubscript{20} (OR 5.40, 95% CI 0.73–39.22, \( p = 0.10 \)).

Conclusion: Omitting a methacholine dose based on a \( \leq 10\% \) fall in FEV\textsubscript{1} occurs frequently and has the potential to shorten test duration. AE are rare, but patients with worse baseline lung function and gas trapping are at increased risk of mild side effects.

Keywords: Asthma, Methacholine challenge testing, Respiratory physiology

Introduction

Bronchoprovocation challenge is a critical tool in the diagnosis and monitoring of asthma. One of the first standardized methacholine challenge testing (MCT) protocol proposed a five-breath dosimeter protocol with a fixed initial methacholine dose followed by doubling increments in methacholine concentration until the provocation concentration causing a 20% decline (PC\textsubscript{20}) in forced expiratory volume in 1 s (FEV\textsubscript{1}) was reached or until the test was over \[1\]. Although safe and accurate, this protocol could be exhausting for patients and time-consuming for both patients and technicians. In the last decades, many protocol variations aiming at simplifying and shortening MCTs were proposed, such as the 2-min tidal breathing dosing method, the optional use of a higher initial dose of methacholine and the skipping of the next methacholine dose when FEV\textsubscript{1} fell by < 5% of its
baseline level [2]. These variations were shown to be safe, while maintaining diagnostic precision [2–5].

In order to further simplify and shorten MCTs, other methods have also been described in more recent years, such as using threefold skips in methacholine concentration [6], the use of 2-tiered protocols [7] or the early stopping of the test when PC_{10} rather than PC_{20} was reached at a methacholine dose of \(\leq 1\) mg/ml [8]. These changes made to the traditional MCT protocol offer the advantage of potentially decreasing test duration, while maintaining diagnostic precision and safety.

Current guidelines suggest the omission of the next methacholine dose if FEV\(_1\) falls by less than 5% of its previous value [2]. The use of a higher threshold for dose omission may further allow the test to be shortened and simplified. In our own center, we implemented the use of a <10% threshold to allow the skipping of a methacholine dose in an attempt to decrease the overall duration of the test, but the safety and efficacy of this measure has not been formally studied yet. We therefore designed the following study to assess the safety and feasibility of using a 10% fall in FEV\(_1\) (as opposed to 5%) as a threshold to skip the next dose of methacholine in patients undergoing MCT.

**Methods**

This is a retrospective observational analysis of MCTs performed in our center (Centre Hospitalier de l’Université de Montréal, Montréal, Canada) between October 2017 and May 2018. The study protocol was accepted by the local ethics board.

**Subjects**

All adult subjects being referred to the pulmonary physiology laboratory for MCT testing during the study period were considered for inclusion in the study. They were referred by their attending physician (either local respiratory medicine specialist, allergist, internist or out-of-hospital general practitioner) for an elective MCT in order to evaluate respiratory symptoms and/or suspected asthma. Patients were excluded if they were unable to complete spirometry and MCT according to current guidelines [2].

**Protocol**

All MCTs were performed according to the American Thoracic Society guidelines using the 2-min tidal breathing dosing protocol [2], with the exception of allowing the omission of the next methacholine dose up to a FEV\(_1\) fall of 10% from its previous value, rather than 5%. The initial methacholine dose which was chosen by the laboratory technician performing the test, based on each patient's pre-test probability for asthma, FEV\(_1\) change after diluent inhalation and basal FEV\(_1\) value. Each MCT was followed by inhalation of nebulized salbutamol (2.5 mg). A second salbutamol dose was administered if FEV\(_1\) did not return to >90% of FEV\(_1\) baseline value 10 min after the first dose. Medical files were reviewed to extract demographic data, presence of a history of asthma or atopy, use of inhaled medication and complete lung function test results. As per current guidelines, each step of the MCT lasted 5 min [2].

Patients of interest were those in which a dose was skipped after a previous FEV\(_1\) fall that was outside the usual range of 5% ("skip\(_{5-10\%}\)"). Bronchial hyperresponsiveness (BHR) was considered present when CP\(_{20}\) was \(\leq 8\) mg/ml.

**Outcomes**

Outcomes of interest were the overall prevalence of skip\(_{5-10\%}\), the prevalence of subjects in which a skip\(_{5-10\%}\) directly led to the reaching of PC\(_{20}\) and adverse effects (AE). AE were categorized as mild: >1 nebulized salbutamol dose (2.5 mg) to reach basal FEV\(_1\), coughing, palpitations; or severe: hypoxemia and/or any need for immediate medical attention or intervention.

**Statistical analysis**

Data are presented as means (standard deviation), median (interquartile range) or n (percent), where appropriate. Comparison of variable between groups were performed using unpaired t-tests for continuous variables or Chi-squared tests for categorical variables. A multiple binary regression model was performed to identify independent predictors of the presence of AE. Sensitivity and specificity analyses of each variable of the regression model that showed an independent relationship to the presence of AE was performed, as well as receiver operating curve (ROC) analyses.

In all cases, a p-value \(\leq 0.05\) was used to identify statistical significance. Analyses were performed using SPSS v21 (IBM corporation).

**Results**

**Population**

A total of 212 MCT were reviewed, of which 208 were included for analysis. Four tests had to be excluded from the study because of the inability of the patients to adequately perform spirometry maneuvers. Baseline complete lung function tests were available for 186 patients (89%).

Table 1 describes the baseline characteristics of the study population, and the comparison between demographic and lung function testing values among
patients with (n = 61) and without BHR (n = 147). Patients with BHR frequently used short-acting beta-agonist medication and had significantly lower values of FEV1/FVC, FEV1 and FVC, and higher values of RV (all \( p \leq 0.05 \)), suggesting more frequent airway obstruction and gas trapping in that group.

Prevalence of skipped doses after FEV1 decrease by 5–10% (skip5–10%)

Overall, there were 90 MCTs in which at least one skip5–10% was performed (43%). Of these, 17 tests included 2 occurrences of skip5–10% and 2 tests included 3 occurrences of skip5–10%, for a total of 111 skipped doses (Fig. 1). Overall, MCTs in which at least one skip5–10% occurred had a lower mean number of doses (3.1 ± 0.6 vs. 3.5 ± 1.3 doses, \( p = 0.007 \)). When considering the 131 subjects in which PC20 was not reached, this difference increased to 3.0 ± 0.1 vs. 4.0 ± 1.1 doses, \( p < 0.001 \).

Adverse events

Across the whole study population, a total of 11 AEs were reported (5%). All AEs were mild and consisted of the need to provide patients with an additional dose of SABA after the completion of the test due to an FEV1 value failing to reach its baseline value, most often

### Table 1 Baseline patient characteristics

|                       | All          | BHR present | BHR absent | \( p \) |
|-----------------------|--------------|-------------|------------|--------|
| n                     | 208          | 61          | 147        |        |
| Age                   | 52 (15)      | 53 (17)     | 51 (14)    | 0.42   |
| Male sex              | 135 (65)     | 41 (67)     | 94 (64)    | 0.65   |
| BMI                   | 28 (6)       | 29.2 (6.0)  | 27.5 (6.0) | 0.07   |
| History of asthma     | 60 (29)      | 22 (37)     | 38 (26)    | 0.11   |
| Atopy                 | 110 (53)     | 34 (62)     | 76 (52)    | 0.23   |

**Pharmacological treatment**

|                      |              |              |            |
|----------------------|--------------|--------------|------------|
| SABA                 | 75 (36)      | 30 (51)      | 45 (31)    | 0.008   |
| LABA                 | 2 (1)        | 0 (0)        | 2 (1)      | 0.37    |
| LAMA                 | 7 (3)        | 4 (7)        | 3 (2)      | 0.09    |
| ICS                  | 51 (25)      | 18 (31)      | 33 (23)    | 0.25    |
| ICS–LABA combination | 34 (16)      | 9 (15)       | 35 (17)    | 0.73    |

**Lung function testing\(^a\)**

|                      |              |              |            |
|----------------------|--------------|--------------|------------|
| FEV1/FVC             | 0.76 (0.07)  | 0.73 (0.09)  | 0.79 (0.06)| < 0.001 |
| FEV1, l              | 2.82 (0.77)  | 2.55 (0.81)  | 2.95 (0.72)| 0.001   |
| FEV1, %              | 95 (14)      | 90 (15)      | 98 (13)    | < 0.001 |
| FVC, l               | 3.66 (0.95)  | 3.45 (98)    | 3.76 (0.92)| 0.04    |
| FVC, %               | 97 (13)      | 96 (14)      | 98 (12)    | 0.24    |
| RV, l                | 1.86 (0.57)  | 2.01 (0.70)  | 1.79 (0.49)| 0.02    |
| RV, %                | 100 (25)     | 111 (33)     | 96 (19)    | < 0.001 |
| FRC, l               | 2.85 (0.68)  | 2.88 (0.75)  | 2.83 (0.65)| 0.66    |
| FRC, %               | 96 (19)      | 100 (23)     | 94 (16)    | 0.07    |
| TLC, l               | 5.61 (1.03)  | 5.56 (1.00)  | 5.63 (1.04)| 0.70    |
| TLC, %               | 102 (13)     | 104 (14)     | 102 (12)   | 0.27    |
| DLCO %               | 94 (19)      | 92 (24)      | 96 (17)    | 0.24    |

**Methacholine challenge**

|                      |              |              |            |
|----------------------|--------------|--------------|------------|
| Starting dose, mg/ml | 1 (0.25–1)   | 1 (0.25–1)   | 1 (1–1)    | 0.001   |
| PC\(_{20}\), mg/ml\(^b\) | 4.2 (1.5–6.8)| 2.2 (1.1–5.3)| 12.3 (10.0–14.1)| < 0.001 |

Data presented as mean (standard deviation), median (interquartile range) or \( n \) (percent), where appropriate

BHR is considered present when CP20 is \( \leq 8 \) mg/ml

BHR: bronchial hyperresponsiveness, BMI: body mass index, SABA: short-acting beta-agonist, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic antagonist, ICS: inhaled corticosteroid, FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity, RV: residual volume, FRC: functional residual capacity, TLC: total lung capacity, DLCO: diffusion capacity of the lung for carbon monoxide

\(^a\) Data available for 186 patients

\(^b\) Mean for the “BHR absent” group based on 16 patients. PC\(_{20}\) was > 16 mg/ml in the remaining 131 patients
accompanied by cough (8/11 cases). No severe AE occurred.

Table 2 reports patient characteristics according to the development of AE. Patients in which AE occurred had significantly lower resting pulmonary function values for FEV1/FVC, FEV1 and FVC and higher values of RV and TLC. However, the mean values of FEV1 and FVC remained in the normal range even in this group. In addition, the presence of an AE was associated with lower PC20, but not with the presence of a skip5–10% that led to the reaching of the PC20. Of those, only RV (percent predicted) was significantly related to the development of an AE (OR 1.05, 95% CI 1.01–1.10, p = 0.01). Of note, the presence of skip5–10% that led to the reaching of the PC20 was not an independent predictor of the presence of AE (OR 5.40, 95% CI 0.73–39.22, p = 0.10).

A receiver operating curve analysis (Fig. 2) revealed that a resting RV (percent predicted) value of > 108% could predict the presence of an AE with a sensitivity and specificity of 90% and 78%, respectively (area under the curve 0.83, 95% CI 0.72–0.95, p < 0.001).

**Discussion**

To our knowledge, this study is the first to evaluate the feasibility and safety of using a threshold higher than 5% in FEV1 fall to allow dose-omission during MCT. Our main results can be summarized as follow: (1) the use of a 10% fall in FEV1 threshold to skip the next methacholine dose allowed shortening the test in a large proportion of our subjects, (2) the use of this threshold was generally safe, with only mild AE being reported and (3) resting lung function values, especially RV, were associated with the occurrence of AEs.

The safety of other time-saving methods, such as increasing the initial dose of methacholine and skipping doses whenever the FEV1 falls by < 5% has been described several times. Troyanov et al. observed an incidence of exaggerated bronchoconstriction, defined as either a fall in FEV1 of > 20% after saline or > 30% after methacholine inhalation, of 10% in a group of 408 subjects, and skipped concentrations accounted for 12% of them (overall prevalence of 1%) [5]. Cockroft et al. showed that, in a population of 380 subjects undergoing MCT, 11 of them had a fall in FEV1 > 20% after a skipped concentration dose, but no cases of exaggerated bronchoconstriction, defined as a fall in FEV1 > 40%, were observed after a skipped concentration [3].

The use of rapid modern nebulizers may also be used to shorten inhalation time, time between the start of each inhalation and, eventually, total MCT time. However, these devices can be expensive, and are associated with lower PC20 values due to the cumulative effect of providing doses at a shorter interval [9–11].

The incidence of AEs in our study was low and comparable to the aforementioned safety data regarding the skipping of methacholine doses based on FEV1 fall, even though we used a larger threshold than the one of 5% usually reported.

Our finding that baseline function was related to the occurrence of AEs during the tests echoes the notion of any inhaled medication, baseline FEV1 (percent predicted), baseline RV (percent predicted) and the presence of a skip5–10% that led to the reaching of the PC20. Of those, only RV (percent predicted) was significantly related to the development of an AE (OR 1.05, 95% CI 1.01–1.10, p = 0.01). Of note, the presence of skip5–10% that led to the reaching of the PC20 was not an independent predictor of the presence of AE (OR 5.40, 95% CI 0.73–39.22, p = 0.10).

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that baseline airway obstruction should help tailor certain MCT parameters (such as the methacholine starting dose) to individual patient's characteristics [2, 12]. Our results suggest that patients with overt baseline gas trapping (as measured with RV) and those with lower FEV1 and FEV1/FVC ratio had higher rates of AEs when using our protocol, although only RV was identified as an independent predictor of the presence of AEs. In clinical practice, the usefulness of these findings may seem limited because measurements

Table 2 Patient characteristics according to the presence of adverse events

|                        | Adverse event | No adverse event | p  |
|------------------------|---------------|------------------|----|
| n                      | 11            | 197              |    |
| Age                    | 55 (14)       | 52 (15)          | 0.49|
| Male sex               | 7 (64)        | 128 (65)         | 0.93|
| BMI                    | 28.3 (4.4)    | 28.0 (6.1)       | 0.87|
| History of asthma      | 5 (45)        | 55 (28)          | 0.14|
| Atopy                  | 5 (45)        | 105 (55)         | 0.74|
| Use of any inhaled medication | 8 (80) | 93 (48) | 0.05|

Lung function testing*

|                        | Adverse event | No adverse event | p  |
|------------------------|---------------|------------------|----|
| FEV1/FVC               | 0.71 (0.41)   | 0.79 (0.35)      | 0.02|
| FEV1, %                 | 84 (14)       | 96 (14)          | 0.005|
| FVC, %                 | 80 (29)       | 96 (13)          | 0.001|
| RV, %                  | 141 (53)      | 98 (20)          | < 0.001|
| FRC, %                 | 116 (28)      | 95 (17)          | < 0.001|
| TLC, %                 | 110 (16)      | 102 (12)         | 0.06|
| Dl, CO, %              | 92 (33)       | 95 (19)          | 0.66|

Methacholine challenge

- Starting dose, mg/ml 1 (0.25–1) 1 (0.25–1) 0.46
- PC20, mg/ml 2.4 (1.7) 5.5 (4.4) 0.03
- Dose skipped after FEV1 decreased 5–10% 4 (36) 86 (44) 0.64
- Dose skipped after FEV1 decreased 5–10% and PC20 reached 3 (27) 16 (8) 0.03
- Number of skipped doses after FEV1 decreased 5–10% 0 (0–1) 0 (0–1) 0.40

Data presented as mean (standard deviation), median (interquartile range) or n (percent), where appropriate.

FEV1, forced expiratory volume in 1 s, FVC forced vital capacity, RV residual volume, FRC functional residual capacity, TLC total lung capacity, DLCO diffusion capacity of the lung for carbon monoxide.

* Data available for X patients.

** Data available for the 77 patients with PC20 < 16 mg/ml.

Table 3 Multiple binary regression model for the identification of predictors of adverse events

|                        | Odds ratio | 95% CI          | p   |
|------------------------|------------|-----------------|-----|
| Any inhaler medication | 0.50       | 0.06–3.81       | 0.50|
| FEV1, percent predicted | 0.97      | 0.90–1.03       | 0.30|
| RV, percent predicted  | 1.05       | 1.01–1.10       | 0.01|
| Dose skipped after FEV1 decreased 5–10% and PC20 reached | 5.40 | 0.73–39.22 | 0.10|

FEV1, forced expiratory volume in 1 s, RV residual volume

Fig. 2 Receiver operating characteristic (ROC) curve evaluating the relationship between residual volume (at the optimal cut-off value of 10% predicted) and the presence of an adverse event during the test.
of lung volumes are not always available before performing MCT. In addition, baseline FEV₁ in our study remained in the normal range even in the group of patients with AEs, making a pre-test risk stratification difficult. Nonetheless, these results highlight the need for clinicians to use, whenever possible, baseline lung function data to decide whether or not to proceed with a skipping protocol such as ours.

Strengths of our study include the relatively large sample size that allowed for the inclusion of a wide spectrum of patients with various pre-test probability of asthma. The majority of our subjects had no history of airway hyperresponsiveness and only half had a history of atopy, which reflects the spectrum of patients being referred to our center both by general practitioners and specialists. Selection bias was attenuated by including all tests performed during the study period, excepted for a small number of cases where patients could not complete the MCT for technical reasons.

Our study also has weaknesses that need to be acknowledged. First, the absence of a control group (one in which a standard threshold of 5% fall in FEV₁ would have been used to skip doses) precludes a direct comparison of the prevalence of AEs between those two protocols, and the direct comparison of our results with others from the literature [5]. It remains, however, that our results support the safety and feasibility of our protocol in clinical practice. Also, the incidence of AEs was low, which may impair the statistical power of certain analyses, especially when aiming at identifying predictors of the occurrence of AEs. This low incidence of AEs may be related to the intrinsic safety of MCTs, but also to the prevalence of BHR in our cohort (29%). This prevalence is similar to some [3], but lower than other [8] studies performed in the clinical setting. Further prospective studies aiming at directly comparing the effects of using the 10% or 5% fall in FEV₁ threshold to skip methacholine doses would help strengthen our results. In addition, studies investigating the effects of the simultaneous use of various time-saving procedures (tailoring of initial dose, threshold for dose-skipping, early termination of test) could eventually lead to an MCT protocol allowing more customization based on individual characteristics of each patient.

Conclusion
During MCT, the prevalence of the omission of the next methacholine dose based on a ≤10% fall in FEV₁ is high, and shortens test duration. When using this protocol, AEs remain rare and mild, but are associated with greater baseline airway obstruction and gas trapping. These results suggest that the use of this threshold is both feasible, useful and safe, but further studies are needed on the effect of combining various time-saving modifications to the MCT protocol.

Authors’ contributions
VL, CP and BPD designed the study, VL and BPD collected and analyzed the study data. VL and BPD drafted the manuscript. All authors provided critical input and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Author details
1 Département de médecine, Service de pneumologie, Centre Hospitalier de l’Université de Montréal (CRHUM), 1051 Sanguinet, Montreal, QC, Canada.
2 Centre de Recherche du Centre Hospitalier de l’Université de Montréal (CRCHUM) – Carrefour de l’Innovation et de l’Évaluation en Santé, Montreal, QC, Canada.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
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