Eur Respir J 2004; 23: 300–303
DOI: 10.1183/09031936.03.00055003
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European Respiratory Journal
ISSN 0903-1936

Exaggerated bronchoconstriction due to inhalation challenges with occupational agents

J-L. Malo*, A. Cartier*, C. Lemière*, A. Desjardins*, M. Labrecque*, J. L'Archevêque*, G. Perrault#, J. Lesage#, Y. Cloutier#

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ABSTRACT: Inhalation challenges with occupational agents are used to confirm the aetiology of occupational asthma. It has been proposed that using closed-circuit equipment rather than the realistic challenge method would improve the methodology of these tests.

Changes in forced expiratory volume in one second (FEV_1) were examined in 496 subjects with "positive specific inhalation challenges", *i.e.* changes in FEV_1 of $\geqslant 20\%$ after exposure to an occupational agent, including 357 subjects exposed by the realistic method, 108 using the closed-circuit method and 31 by both methods.

For immediate reactions, 18 of 95 (19%) showed changes in FEV_1 of $\geqslant 30\%$ with the closed-circuit method, whereas a significantly larger proportion, *i.e.* 77 of 200 (38.5%), showed such changes using the realistic method. As regards nonimmediate reactions, changes in FEV_1 of $\geqslant 30\%$ occurred in 16 of 43 (37%) cases with the closed-circuit method as compared to a larger proportion, *i.e.* 87 of 180 (48%) cases, using the realistic method. This favourable effect was significantly more pronounced in workers with higher levels of bronchial hyperresponsiveness to methacholine.

It is concluded that, for agents that can be generated using the closed-circuit method, use of such apparatus results in a smaller proportion of exaggerated bronchoconstriction than does the realistic method, this being particularly true for low-molecular weight agents. *Eur Respir J 2004; 23: 300–303.*

*Dept of Chest Medicine, Sacré-Cœur Hospital, and #Institut de recherche Robert-Sauvé en santé et sécurité du travail du Québec, Montreal, Canada.

Correspondence: J-L. Malo
Dept of Chest Medicine
Sacré-Cœur Hospital
5400 West Gouin Blvd
Montréal
H4J 1C5
Canada
Fax: 1 514 3383123
E-mail: malojl@meddir.umontreal.ca

Keywords: Asthma
bronchial provocation tests
occupational asthma

Received: May 15 2003
Accepted after revision: September 2 2003

Several steps have been proposed for the investigation of occupational asthma (OA) [1]. One of these consists of exposing workers to the possible offending agent, either in a laboratory hospital or at work under the supervision of a technician [2]. PEPYS and HUTCHCROFT [3] were the first to suggest exposing workers in a "realistic way", by asking them to reproduce their usual work in a cubicle. It has been proposed that closed-circuit equipment will yield lower and more stable concentrations of the agent. Using such equipment, it is possible to generate dry aerosols (particles) [4–6], vapour [7] and aerosols of isocyanates, as well as vapours of some chemical agents, including formaldehyde [8] and glutaraldehyde. The goal of using this equipment is to generate low and stable concentrations of occupational agents in order to minimise the risk of exaggerated bronchoconstriction, mainly in the first minutes following exposure, at which time changes in airway calibre occur more rapidly than those found in so-called late reactions [3, 9]. As an added benefit, it places the personnel performing the tests at lower risk of developing sensitisation and asthma due to exposure to occupational agents.

Although it has been shown that the concentrations observed are lower and more stable using closed-circuit equipment, there is no evidence, to date, that using this method diminishes the risk of inducing exaggerated bronchoconstriction as compared with a more "realistic" approach.

Therefore, in the present study, the magnitude of bronchoconstriction induced by exposure to various occupational agents using either the closed-circuit or realistic method was compared.

Subjects and methods

Design

In this retrospective study, the maximum percentage falls in forced expiratory volume in one second (FEV_1) after exposure to occupational agents were examined in all subjects with a positive test result, defined as a fall in FEV_1 of $\geqslant 20\%$, in Sacré-Cœur Hospital (Montreal, Canada) during the period October 1985–October 2002 (17 yrs). Although specific inhalation challenges with occupational agents started in 1977 in Sacré-Cœur Hospital, the rationale for selecting 1985 was that closed-circuit equipment became available at this time. It was, therefore, possible to examine reactions using the two methods over the same time period. The only reason for selecting one method over the other as the initial procedure was the possibility or otherwise of generating the agent using closed-circuit equipment. It was possible to generate agents in dry particle form (flour, wood dust, pharmaceutical powders, *etc.*) from 1985 and, for isocyanates, formaldehyde and glutaraldehyde, in vapour form from 1990. In all instances of negative test results using the closed-circuit method, exposure was subsequently carried out using the realistic method.

Bronchial provocation tests

The protocol used has already been described in detail elsewhere [10]. Briefly, on the first day, spirometry was performed every 10 min for 1 h, every 30 min for 2 h and then hourly for a total of 7–8 h. Bronchial responsiveness to methacholine was then assessed. On the second day, the worker was exposed, for 30–120 min, to a control agent (lactose in the case of flour, a wood dust other than the one suspected of causing OA for wood dust, and control chemical product in the case of isocyanates and other chemical agents causing OA). If the FEV1 was stable (within 10% of baseline during the day of monitoring), the worker started being exposed to the suspected agent in a progressive manner on the third day, *i.e.* one breath, 10, 20 and 30 s, and 2, 5 and 30 min for a total of 2 h. In 1985, the occurrence of a severe though reversible immediate reaction as a result of exposing a subject to psyllium for 1 min prompted separation of the first minute of exposure into shorter intervals [11]. In the case of high-molecular-weight agents, exposure was carried out on a single day. For low-molecular-weight agents, which often cause nonimmediate reactions, the cumulative duration of exposure was progressively increased from day to day (1–5 min on the first day, depending on the level of bronchial responsiveness to methacholine; 5 min when the duration was 1 min on the previous day; 30 min and 2 h). FEV1 was assessed immediately and then 5–10 min after stopping the exposure. If the FEV1 was stable (within 5% of baseline), the exposure was prolonged. If changes in FEV1 reached $\geqslant$20%, the exposure was stopped. If changes in FEV1 were 5–19%, monitoring of FEV1 was repeated every 5 min on two or three occasions, and, if the fall in FEV1 did not reach 20%, the exposure was prolonged. FEV1 was followed thereafter as on the control day and responsiveness to methacholine was assessed, either after 7–8 h on the same day or on the following morning (provided that the FEV1 was within 10% of the control day baseline).

In the case of tests performed in the workplace, after a first control day in the hospital laboratory, the worker was exposed initially for 5–30 min. If there was no significant change in FEV1 (<20%), the worker was asked to continue their usual work for periods of 30–60 min with serial assessment of FEV1. In the case of isocyanates, continuous monitoring with instruments that assess the concentration on line was carried out to maintain concentrations at <20 parts per billion; reaching this target proved to be more difficult using the realistic method [7].

In the case of tests carried out in the hospital laboratory, the same steps, in terms of duration of exposure and timing of spirometry, were followed regardless of the methodology used (closed-circuit or realistic method).The principles behind the use of the closed-circuit method are simple: the occupational agent is generated, monitored on line (*via* high-performance liquid chromatography for vapours and isocyanates) using an optical reader previously calibrated with a standard and directed to an exposure chamber from which the subject inhales through a port.

Asthma medication was kept unchanged during the tests, except for stopping the following medications for specific times: 1) short-acting β_2 adrenergic agents for 12 h; and 2) long-acting β_2 adrenergic agents for 3 days. The total daily dose of inhaled steroids was unchanged but was taken in one dose in the evening.

Analysis of results

The numbers of exaggerated bronchoconstrictive reactions, defined as a change in FEV1 of $\geqslant$30% [12], and nonexaggerated reactions were compared for the two procedures (closed-circuit and realistic methods) using the Chi-squared test. A paired t-test was used for comparing changes in FEV1 with the two methods in a subgroup of 31 subjects.

Results

Between October 1985 and October 2002, 1,712 different subjects underwent specific inhalation challenges at Sacré-Coeur Hospital, with the result considered positive (change in FEV1 of $\geqslant$20%) in 496 (29%) subjects. Table 1 provides information on the nature of the product according to the method of challenge for subjects with positive results. Isocyanates and flour were the most common agents.

There were no significant differences in the functional features that reflect severity of asthma between subjects who underwent challenges using the realistic and closed-circuit methods in terms of baseline FEV1 (99.2±18.7% and 102.0± 19.5% of the predicted value, respectively) and provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) (10.2 and 9.5% with greatly enhanced bronchial hyperresponsiveness, *i.e.* PC20 <0.25 mg·mL^{-1}). As shown in figure 1, a significantly smaller proportion of subjects showed changes in FEV1 of $\geqslant$30% using the closed-circuit as compared to the realistic method at the time of immediate reactions (X^2= 8.1, p<0.01); this proportion was also smaller, using the closed-circuit method, for nonimmediate reactions, although not significantly so. Among subjects with greatly enhanced bronchial responsiveness to methacholine (PC20 $\leqslant$0.25 mg·mL^{-1}), only four of 22 (18%) subjects showed falls in FEV1 of $\geqslant$30% when tested using closed-circuit equipment, whereas 27 of 45 (60%) subjects who underwent realistic exposure showed exaggerated bronchoconstriction (X^2=10.4, p<0.01). Of the 99 tests performed in the workplace, 39 (39.4%) resulted in changes in FEV1 of $\geqslant$30%, a percentage not significantly different from that found in tests carried out in the laboratory using the realistic method (44%). As regards tests performed by exposing subjects to low-molecular-weight agents, 20 of 73 (27%) showed changes in FEV1 of $\geqslant$30% using the closed-circuit method in comparison with 122 of 253 (48%) with the realistic method (X^2=10.5, p<0.01). For tests carried out by exposing subjects to high-molecular-weight agents, 14 of 58 (24%) showed changes in FEV1 of $\geqslant$30% using the closed-circuit method as compared to 39 of 123 (31%) with the realistic method.

Table 1. – Agents causing significant reactions using the closed-circuit and realistic methods

	Method			Total n (%)
	Closed-circuit	Realistic	Both	
Isocyanates	29	91	15	135 (27)
Flour	45	34	7	86 (17)
Various chemical	3	49	4	56 (11)
Wood dusts	13	35	1	49 (10)
Drugs	11	25	3	39 (8)
Animal-derived allergens	2	37	0	39 (8)
Various proteins	4	17	0	21 (4)
Metals	0	15	0	15 (3)
Resins/glues	0	15	0	15 (3)
Latex	0	15	0	15 (3)
Cereals/grains	1	12	1	14 (3)
Unknown	0	12	0	12 (2)
Total	108	357	31	496 (100)

Data are presented as absolute numbers.

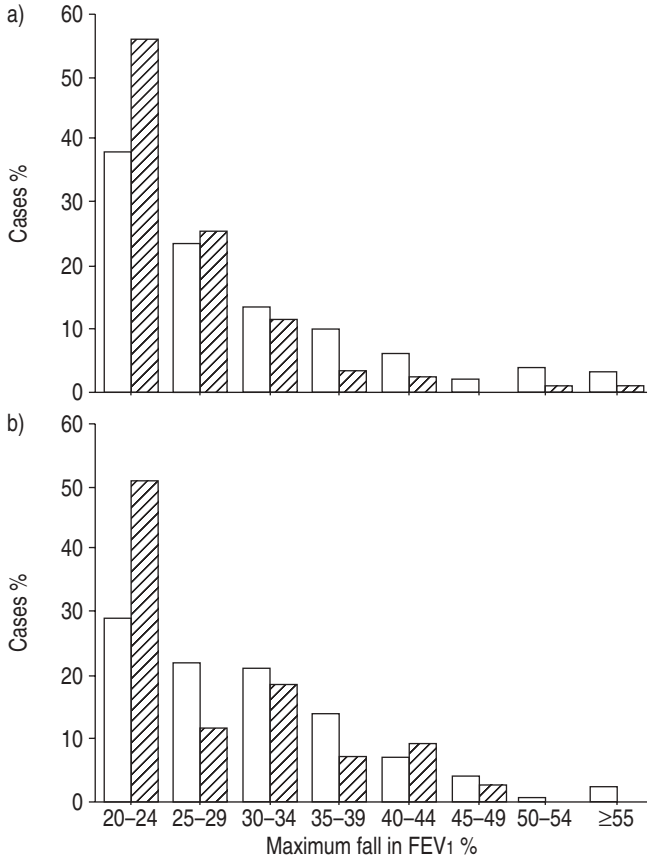

Fig. 1. – Falls in forced expiratory volume in one second (FEV_1) at the time of: a) immediate; and b) nonimmediate reactions using the realistic (□ n=200 for immediate, n=180 for nonimmediate) and closed-circuit (▨ n=95 for immediate, n=43 for nonimmediate) methods. Fewer instances of exaggerated bronchoconstriction, in both immediate and nonimmediate reactions, occurred with the closed-circuit method.

Challenges carried out with isocyanates and flour, the two most common agents causing OA, were examined separately. Whereas, with flour, the proportion of subjects with falls in FEV_1 of $\geqslant 30\%$ were similar using the closed-circuit (10 of 45 (22%)) and realistic methods (eight of 34 (24%)), the respective proportions in the case of isocyanates were almost significantly different (nine of 29 (31%) *versus* 45 of 91 (49%) for the closed-circuit and realistic methods, respectively ($X^2=3.0$, $0.05<p<0.1$)).

All subjects with negative test results with the closed-circuit equipment subsequently underwent exposure *via* the realistic approach to verify test results (see *Bronchial provocation tests* section). In eight of the 365 (2.2%) subjects who underwent realistic exposure, this exposure resulted in a positive reaction, whereas the test result was considered negative (falls in FEV_1 of 16–19%) using closed-circuit equipment. In 23 other subjects, the test was carried out using both methods even if the results could have been considered positive with the closed-circuit equipment; indeed, the clinician in charge of the test judged that it was relevant to receive further confirmation of results. Examining this total group of 31 subjects, eight of the 31 (26%) experienced changes in FEV_1 of $\geqslant 30\%$ with the closed-circuit method, whereas 16 of the 31 (52%) showed changes in FEV_1 of $\geqslant 30\%$ with the realistic method. In these 31 subjects, the mean$\pm$SD difference in percentage change in FEV_1 with the two methods (5.9$\pm$9.5%) favoured the closed-circuit method (t-test 3.4, p=0.002).

Discussion

The present study shows that, when specific inhalation challenges are performed using closed-circuit equipment, as previously described [4–8], there are fewer occurrences of exaggerated bronchoconstriction, defined as a fall in FEV_1 of $\geqslant 30\%$ [12], than when they are performed using the realistic method, as initially proposed [3].

When performing specific inhalation challenges with occupational agents, the major concern is the magnitude of the potential asthmatic reaction, especially in the minutes immediately following exposure. These reactions can indeed be rapid, whereas late reactions usually develop over a longer period, leaving time to administer the relevant medication. The occurrence of severe immediate reactions when performing specific inhalation challenges in the realistic way [11] prompted the idea of splitting the intervals of exposure during the first minute (one breath, 10 s, *etc.*) and led to the development of closed-circuit equipment, which makes it possible to expose individuals to lower and more stable concentrations of occupational agent. The risk of immediate exaggerated bronchoconstriction with the closed-circuit apparatus is a little greater (19% of cases) than that observed using the pharmacological agent methacholine (10–12% of cases) [12], but only half that with the realistic method.

Although the beneficial effect was observed primarily for immediate reactions, there was a slight (10%), although nonsignificant, reduction in occurrences of exaggerated reduction in airway calibre at the time of the late reaction. This can be explained by the fact that the intended dose (concentration and duration of exposure) is easier to obtain using the closed-circuit generator than with the realistic method since the concentration is more stable and concentrations above the threshold limit value can generally be avoided [4, 7]. Interestingly, it was also found that the individuals who are most likely to benefit from exposure *via* the closed-circuit method are those with severe nonspecific bronchial responsiveness, defined as a PC_{20} of $\leqslant 0.25$ mg·mL^{-1}. This finding is probably explained by a propensity to develop more severe immediate asthmatic reactions as the levels of bronchial hyperresponsiveness and allergen sensitisation increase [13, 14].

The benefit from using closed-circuit equipment was superior, and significantly so, for low- as compared to high-molecular-weight agents. However, comparing the results for the most common causal agents of OA in the present series, *i.e.* flour and isocyanates, it was found that exaggerated bronchoconstriction occurred less frequently with flour than with isocyanates. It is indeed the present authors' experience that subjects with OA to flour show reactions only after rather lengthy exposures. It is rare to find workers "exquisitely" sensitised to flour, as is often the case with other agents, such as isocyanates, for which exposure for just one breath can induce a significant reaction.

It is interesting to note the low frequency of false negative responses using closed-circuit equipment; this test gave negative results while realistic exposure resulted in a positive reaction in only 2.2% of subjects. Although several agents can be generated with the closed-circuit equipment, the methodology still needs to be developed for many agents (those agents in table 1 for which no tests were performed using the closed-circuit method). Obviously, the results found in the present study are specific to the agents generated by the equipment and need to be generalised to all occupational agents. More widespread use of the closed-circuit method could potentially result in fewer instances of exaggerated bronchoconstriction and greater use of specific inhalation challenges in the confirmation of occupational asthma. More

generally, specific inhalations tests are still performed in too few hospital institutions and are included in an insufficient number of residency training programmes [15].

Acknowledgements. The authors are grateful to the personnel of the Pulmonary Physiology Laboratory at Sacré-Cœur Hospital (Montreal, Canada), as well as to the research and clinical fellows who were involved in challenge testing over the period of the study (F. Lagier, B. Perrin, O. Vandenplas, C. Leroyer and L. Perfetti). They also thank L. Schubert for reviewing the manuscript.

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