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Immediate and late asthmatic responses induced by exercise in patients with reversible airflow limitation

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ABSTRACT: The existence and prevalence of late asthmatic responses to exercise in patients is uncertain. We investigated whether the late falls of peak expiratory flow rate (PEFR) after exercise challenge were still significant after comparison with the corresponding clocktime PEFR on a control day. We examined 86 patients with reversible airflow limitation, 79 with asthma and 7 with chronic obstructive pulmonary disease (COPD), all under regular treatment with bronchodilators and/or anti-inflammatory agents. Patients were randomized for a control day and an exercise day and PEFR was recorded hourly. On the exercise day, each patient underwent an 8 minute bicycle ride at 90% of predicted heart-rate. An early and a late asthmatic response to exercise were considered to occur when PEFR decreased by 10% or more on the exercise day compared to the corresponding clocktime PEFR on the control day. Thirty-three patients (38%) had a 10% or greater fall of PEFR at 4 to 13 hours after exercise when PEFR was compared with the corresponding clocktime on a control day. Seven (8%) had an isolated late asthmatic response, and 26 (30%) had a dual asthmatic response. We conclude that true late asthmatic responses develop after exercise in a significant number of patients with well controlled reversible airflow limitation.

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Exercise-induced asthma was first described in the 17th century by Sir JOHN FLOYER [1]. At that time this phenomenon was regarded as a distinct clinical entity. Views began to change in 1962, when JONES *et al.* [2] had established for the first time that exercise-induced asthma could be a normal symptom of asthma. Now, exercise is considered as a common and potent trigger of bronchoconstriction in asthmatic patients [3]. According to ANDERSON [3], exercise-induced asthma is proved by a 10% or greater fall of peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV_1) after exercise when compared to pre-exercise values. Patients with exercise-induced asthma may develop an early and/or a late asthmatic response [4, 5]. The early fall in PEFR or in FEV_1 develops within ten minutes after exercise, reaches a maximum after 20–30 min and normally disappears within 1–3 h. The late response can occur after recovery from the early response and starts 4–12 h after the exercise, decreases in severity 12 hours after challenge and has usually disappeared within 24 hours after challenge.

The prevalence of late asthmatic responses to exercise is uncertain [6, 7]. RUBINSTEIN *et al.* [8] observed the same delayed asthmatic response in most of their subjects during an exercise day and during a control day on which the FEV_1 was measured serially but no exercise was performed, demonstrating the lack of specificity of late responses to exercise; however, one of the patients examined had a true late asthmatic response, as shown by a delayed decrease of FEV_1 on the exercise but not on the control day [8]. Unfortunately in most previous studies, FEV_1 after exercise was compared with FEV_1 before exercise [5, 7, 9, 10] raising the suspicion that observed late asthmatic responses may represent a decrease of pulmonary function related to withdrawal from therapy [8].

In the present study we examined the bronchoconstrictor response to exercise in a group of patients with reversible airflow limitation, and we calculated the number of late asthmatic responses obtained by comparing the percent fall of PEFR after exercise either with the corresponding clock time PEFR on a control day, or with PEFR before exercise on the exercise day.

Patients and methods

We examined 115 patients hospitalized in the Dutch Asthma Centre Davos, Switzerland, and included in the study the 86 patients with a PEFR greater than 65% of the predicted value [11]. Seventy-nine suffered from asthma, 7 had COPD (table 1). All patients with bronchial asthma as defined by the American Thoracic Society, had a documented bronchial hyperresponsiveness to histamine below 8 $mg \cdot ml^{-1}$ as measured

according to COCKCROFT *et al.* [12, 13]. Asthmatic patients showed an FEV_1 reversibility greater than 20% of predicted value after 4 puffs of salbutamol. Also the patients with COPD had a documented bronchial hyperresponsiveness to histamine below 8 $mg \cdot ml^{-1}$. In these cases FEV_1 reversibility was less than 20% of predicted value after 4 puffs of salbutamol, and the PEFR was greater than 65% of predicted value.

Exercise challenges were performed on a bicycle ergometer (Erich Jager, Wurzburg, Germany). The work load in Watts was 80% of the predicted maximum work load. The predicted maximum work load was calculated according to WASSERMAN [14]. Exercise had been performed for 8 minutes during which a heart rate of 90% of the predicted maximum was reached [15, 16]. During the exercise challenge the heart rate was measured by Siemens Sirecust 341 monitor (Siemens, Germany).

Table 1. – Patient characteristics

	Total group with reversible airway obstruction	Children with reversible airway obstruction	Adults with reversible airway obstruction
Age yrs	27.1±14.1	15.2±1.4	34.2±13.5
Sex	46 male, 40 female	23 male, 9 female	23 male, 31 female
Children/Adults	32/54	–	–
Clinical diagnosis	79 asthma, 7 COPD	32 asthma, 0 COPD	47 asthma, 7 COPD
Atopic status	71 atopic, 15 non-atopic	31 atopic, 1 non-atopic	40 atopic, 14 non-atopic
Smokers	10 smokers, 76 non-smokers	1 smoker, 31 non-smokers	9 smokers, 45 non-smokers
Steroids none/oral/inhaled/both	9/7/41/29	3/3/24/2	6/4/17/27
Histamine PC_{20} $mg \cdot ml^{-1}$	1.1±1.6	1.0±1.2	1.1±1.8
Baseline FEV_1 *l*, and %pred	2.85±0.83; 86.7±23.9	2.67±0.75; 86.8±23.5	2.95±0.86; 86.6±24.4
FVC *l*, and %pred	4.05±1.00; 101.9±18.6	3.77±0.89; 101.8±17.2	4.21±1.03; 101.2±19.5

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease. PC_{20}: concentration of histamine that gives a 20% decrease in FEV_1.

Throughout the study period all patients had to submit to concomitant medication rules: the patients had to stop inhaling bronchodilators 8 hours before the exercise challenge, and during the control day; sodium cromoglycate had to be stopped 24 hours before the test and during the control day; any type of oral bronchodilator had to be stopped at least 48 hours before the start of the exercise challenge and during the control day. The dose of oral and inhaled steroids was kept constant. All patients on steroids were using this treatment for at least 3 months. Patients did not stop smoking during the study.

The control and exercise days were chosen at random. They were separated by a minimum of 72 hours and a maximum of 6 days in order to minimize the changes in the clinical situation of the patient. Consent was obtained from each of the adult patients and from the parents of the underage children. The protocol was approved by the Ethical Committee of the clinic.

The degree of airway hyperresponsiveness was measured as the concentration of inhaled histamine which resulted in a 20% decrease of FEV_1, and expressed as $PC_{20}FEV_1$ ($mg \cdot ml^{-1}$) [12].

The relative humidity of the ambient air was 20–40%, the room temperature was 20–23°C, both on the control and the exercise day and both were measured with the Hygrotest 6200 (Quartz AG, Zurich, Switzerland). The humidity and room temperature were allowed to oscillate about 10% during control and exercise day for each patient.

PEFR was measured with the mini-Wright peak flow meter. The best of three measurements was recorded. PEFR was recorded on the control day at t=0 and during the first 13 h after t=0 at hourly intervals; on the exercise day PEFR was recorded at t=0 (pre-exercise PEFR) and 1, 3, 5, 7, 10, 15 and 30 minutes, and then hourly during the 13 h after the end of the exercise challenge.

The existence of exercise-induced asthma was inferred from the calculation of the formula reported in table 2. The early fall after exercise was calculated with the pre-exercise value as a reference.

The late fall in PEFR after exercise was calculated using four methods.

1. The lowest PEFR 4–13 h after exercise in relation with the pre-exercise PEFR.

Table 2. – Formulae used to calculate the early and the late reaction after an exercise challenge

$$\text{Fall early, \%} = \frac{\left[\begin{array}{l}\text{PEFR immediately}\\ \text{before exercise}\end{array}\right] - \left[\begin{array}{l}\text{Lowest PEFR}\\ \text{after exercise 1–30 min}\end{array}\right]}{\text{PEFR immediately before exercise}} \times 100\%$$

$$\begin{array}{l}\text{Fall}\\ \text{late}\\ \text{\% pre-exercise}\end{array} = \frac{\left[\begin{array}{l}\text{PEFR immediately}\\ \text{before exercise}\end{array}\right] - \left[\begin{array}{l}\text{Lowest PEFR}\\ \text{after exercise 4–13 h}\end{array}\right]}{\text{PEFR immediately before exercise}} \times 100\%$$

$$\begin{array}{l}\text{Fall}\\ \text{late}\\ \text{\% of control day}\end{array} = \frac{\left[\begin{array}{l}\text{PEFR on corresponding}\\ \text{clocktime on control day}\end{array}\right] - \left[\begin{array}{l}\text{Lowest PEFR}\\ \text{after exercise 4–13 h}\end{array}\right]}{\text{PEFR on corresponding clock day}} \times 100\%$$

$$\begin{array}{l}\text{Fall}\\ \text{late}\\ \text{\% predicted}\end{array} = \frac{\left[\begin{array}{l}\text{PEFR immediately}\\ \text{before exercise}\end{array}\right] - \left[\begin{array}{l}\text{Lowest PEFR}\\ \text{after exercise 4–13 h}\end{array}\right]}{\text{PEFR predicted}} \times 100\%$$

$$\begin{array}{l}\text{Fall}\\ \text{late}\\ \text{\% mean control}\end{array} = \frac{\left[\text{Mean PEFR on control day}\right] - \left[\begin{array}{l}\text{Lowest PEFR}\\ \text{after exercise 4–13 h}\end{array}\right]}{\text{Mean PEFR on control day}} \times 100\%$$

2. The lowest PEFR 4–13 h after exercise in relation with the PEFR at the same time on the control day.
3. Because of the broad range of PEFR values in different patients (age, FEV_1), we corrected for the differences in baseline PEFRs among subjects by including the predicted PEFR values in the formula.
4. We calculated the mean PEFR on the control day for each patient and related it to the lowest PEFR 4–13 h after exercise.

A fall in PEFR greater than 10% was considered positive for the existence of the early and/or late asthmatic response after exercise [3]. We separately registered PEFR falls of 10–20% and falls greater than 20%, because we wondered whether PEFR fall of greater than 10% was sufficient enough to establish a late response after exercise.

Table 3. – Number of patients with an early and a late reaction after exercise

Defined subgroups	Maximal fall in PEFR compared to pre-exercise level on same day (exercise)			Maximal fall in PEFR compared to same time-level on control day (no exercise)		
	Children	Adults	All	Children	Adults	All
EAR <10%, LAR <10%	10	14	24	9	18	27
EAR 10–20%, LAR <10%	9	6	15	9	5	14
EAR >20%, LAR <10%	6	6	12	5	7	12
EAR <10%, LAR 10–20%	1	4	5	1	4	5
EAR 10–20%, LAR 10–20%	1	1	2	1	4	5
EAR >20%, LAR 10–20%	4	2	6	3	4	7
EAR <10%, LAR >20%	0	4	4	1	1	2
EAR 10–20%, LAR >20%	0	3	3	0	1	1
EAR >20%, LAR >20%	1	14	15	3	10	13
Total	32	54	86	32	54	86

In one column PEFR fall is compared to pre-exercise PEFR. In the other column PEFR fall is compared to the corresponding clock time on a control day. Patients are separately registered as children (<17 yrs) and adults (>17 yrs). EIA: exercise induced asthma; EAR: early asthmatic response; LAR: late asthmatic response.

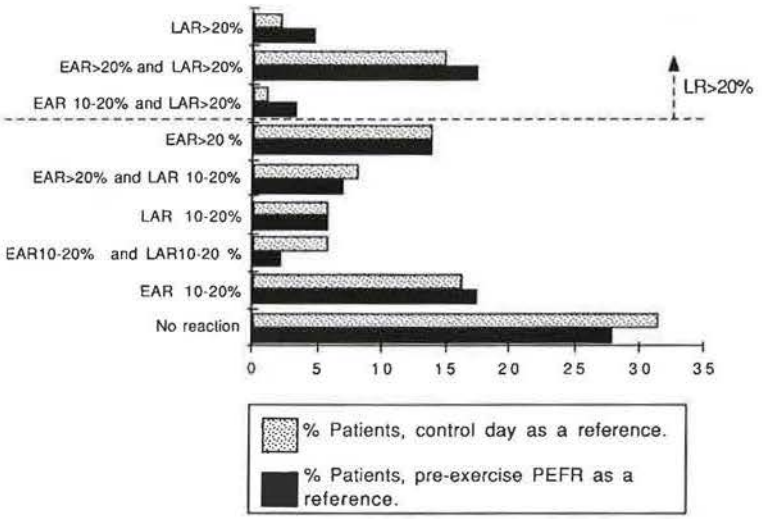

Fig. 1. – The percentage of patients with a PEFR fall after exercise. The patients are registered separately, according to whether the pre-exercise PEFR, or the corresponding clocktime on a control day was taken as a reference. Above the dotted line all late respondents with a PEFR fall greater than 20% are registered. ▨: % patients, control day as a reference; ■: % patients, pre-exercise PEFR as a reference.

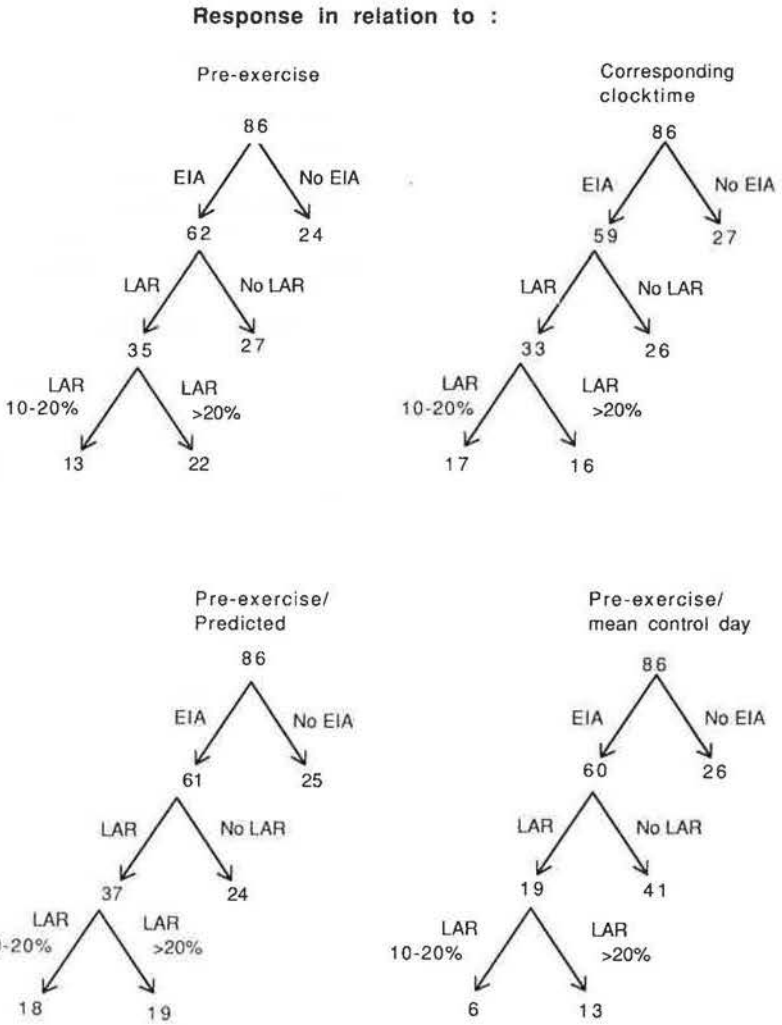

Fig. 2. – Number of patients with EIA and late falls in PEFR after an exercise challenge. The fall in PEFR is expressed only for the LAR in 10–20% and >20%. For the calculation of the number of patients with an EAR and LAR see table 2.

Results

The results of this study are presented in table 3 and in figures 1 and 2. The baseline PEFR values on the control and exercise day were not comparable, the baseline PEFR on the exercise day being higher than PEFR on the control day (control day baseline value 333±88, exercise baseline value 367±65; $p<0.01$).

With the pre-exercise PEFR as a reference, 24 patients showed neither an early nor a late response after exercise. A late asthmatic response to exercise with a fall of PEFR greater than 20% compared to pre-exercise value occurred in 22 (26%) of the 86 patients who completed the exercise challenge. Five patients had an isolated late response with a peak flow fall of 10–20%. Four patients had an isolated late response with a peak flow fall greater than 20%. The percent changes of PEFR from baseline on the control and exercise days of 2 patients who developed a late asthmatic response after exercise are illustrated fig. 3. In these patients, the maximum decrease of PEFR from pre-exercise PEFR was 33±21% and 36±14% during the early and late asthmatic response, respectively.

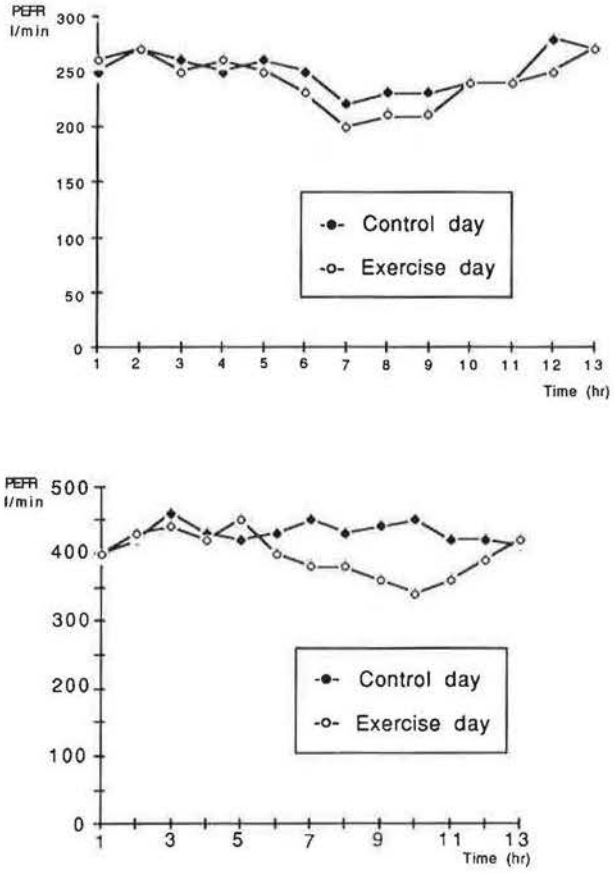

Fig. 3. – PEFR data for 2 patients with a LAR to exercise. The upper curve demonstrates a patient with a late response in relation to the pre-exercise value. PEFR immediately before exercise is 260. The late fall after exercise calculated according to table 2 is 23%. The lower curve demonstrates a patient with a late response in relation to corresponding clocktime on a control day. The calculated late fall after exercise according to table 2 is 16%.

If PEFR 4–13 h after exercise was compared with the same time on the control day, 27 patients showed no response after exercise. A late asthmatic response to exercise with a fall in PEFR greater than 20% compared to control day occurred in 16 (19%) of the 86 patients who completed the exercise challenge. Five showed an isolated late reaction with a peak flow PEFR fall of 10–20. Two patients had an isolated late response with a PEFR fall greater than 20%. Thirteen patients had an early response as well as a late response with a peak flow fall both greater than 20%.

Children developed an isolated early asthmatic response to exercise more frequently than adults, both if PEFR after exercise was compared with PEFR before exercise (children 46.9% adults 22.2%) and with the corresponding clocktime PEFR (children 43.7%, adults 22.3%). By contrast adults developed a late asthmatic response to exercise more frequently than children. Twenty-one adults had a fall of PEFR greater than 20% after exercise when PEFR fall was compared to pre-exercise value and 12 when PEFR was compared with the corresponding clocktime PEFR on a control day. When the lowest PEFR value 4–13 h after exercise was compared with the corresponding clocktime on the control day, 33 patients (38%) had a fall of PEFR greater than 10% and 16 (19%) greater than 20% on the exercise day.

Despite the use of oral steroids, 3 patients developed a late asthmatic response after exercise when PEFR was compared with the pre-exercise value. Ten patients had a late asthmatic response of greater than 20% using both oral and inhaled bronchodilators. The mean starting time of a fall of PEFR greater than 20% was at 6.0±2.1 hours after exercise when PEFR was compared to the control day and 9.0±2.4 hours, when PEFR fall was compared with the corresponding clocktime PEFR on the control day.

All seven patients with COPD developed a late asthmatic response after exercise if the fall of the PEFR was calculated on the pre-exercise PEFR, and 6 of them if the fall of PEFR was calculated on the corresponding clocktime PEFR on a control day.

Discussion

In our study we compared the post-exercise decrease in PEFR to the corresponding clocktime PEFR on a control day. We found a considerable number of late responses. We demonstrated that the late response can occur without an early response. The late response after exercise can occur as an isolated or as a dual response. A late response was present despite the use of oral and inhaled steroids. These drugs have been shown to play a protective role in the late asthmatic response after allergen provocation [17]. The mechanisms of exercise-induced late responses seem to be quite different from those responsible for the late responses to allergens, because the late response is much less reproducible and shorter lasting [10].

The prevalence of early, exercise induced asthma (EIA) is as stated in literature [18]. Children are relatively more affected with EIA than adults. For the late response, the

contrary is shown. Asthmatic patients older than 17 years are relatively more affected by the late response after exercise than patients younger than 17.

Our results are different from those of Rubinstein *et al.*, who also used a control day in their experiments. Rubinstein *et al.* demonstrated the lack of specificity of late responses to exercise in most subjects, but found one patient having a true late fall in FEV_1, after exercise challenge. The controversy in the literature about the late asthmatic response to exercise is whether or not late responses to exercise do occur, and if so, what is their frequency. The difficulty of analysing this problem is the following: to which value should a fall in PEFR of for instance >20%, 4–13 hours after exercise be related? Is this the pre-exercise value, or the value at corresponding clocktime on a control day, or the pre-exercise/predicted PEFR, or the pre-exercise/mean value on the control day, or perhaps another value? We do not agree with Rubinstein *et al.* that the late asthmatic response to exercise is an epiphenomena (fig. 2) because we demonstrated 16 patients having a late asthmatic response >20% to exercise when the PEFR fall was compared to corresponding clocktime on a control day. We do agree with Rubinstein *et al.* that PEFR fall after an exercise challenge should be related to corresponding clocktime on a control day, also without medication. In this way the diurnal variation of airway calibre can be taken into account. Few investigators have used a control day in the examination of the existence of a late fall in PEFR or FEV_1 after an exercise challenge [8–10, 19].

One should consider the effect of stopping drugs on PEFR or FEV_1. For this reason the control day is particularly important. In studies without a control day the diurnal post-exercise rhythm is not compared with the diurnal rhythm of a day without exercise. We used in our study the PEFR. Other investigators used the FEV_1 [9]. We consider the mini-Wright peak flow meter a good instrument for recording the PEFR after an exercise challenge. We reported our results according to Andersons's definition of EIA [15, 16]. This definition describes a fall in post-exercise PEFR greater than 10%. There is no agreement in the medical literature whether the percentage of a PEFR fall after an exercise challenge should be 10 or 20%. It depends on the spontaneous variability of the parameters for the population studied. If a change in PEFR >10%, spontaneous variability has to be <10%. We considered that a PEFR fall greater than 20% may cause a late asthmatic response.

In contrast to our study BIERMAN [20] stated that it is important to perform a control day before the exercise day instead of after it, because the preceeding late response may have changed the subject's airway responsiveness and subsequent diurnal variation of PEFR.

In our study we came across a considerable number of patients using oral and inhaled steroids who had a late fall after an exercise challenge. Why these efficient drugs given in adequate pharmacological amounts, did not prevent the late fall, is not quite clear to us. It is possible that without steroids the patients would have had a much more severe late response. There may be two reasons for the occurrence of late responses to exercise in corticosteroid-treated patients. First, the dose of corticosteroids may not be sufficient to control symptoms and/or prevent induced inflammatory responses associated with the late responses. Secondly, the late responses to exercise may not be associated with inflammatory responses of the airways. Exercise can induce increased airway responsiveness, with or without late responses as allergen exposure does, but this does not imply that inflammation is involved in the genesis of these phenomena as seen with allergen [10, 21]. Neuropeptide release, mediator release from bronchial mucosa resident cells, or even the reactive hyperaemia in the bronchial mucosa which follows the vascular constriction due to hyperventilation-induced heat loss can cause delayed bronchoconstriction and increased sensitivity of airway smooth muscle [22–24]. BOULET *et al.* [19] showed an unchanged bronchial reactivity to histamine 24 hours after the exercise.

LEE *et al.* [25] found no fall in FEV_1 after acetylcholine inhalation, in six persons with documented exercise-induced late response, indicating that an exercise-induced late-phase response is more than the non-specific sequel of previous bronchoconstriction or a response to drug withdrawal.

It is of very great importance to clinicians to recognise a late fall after an exercise challenge. Patients can visit their physician with pulmonary discomfort which could be related to performed exercise 4–13 hours before the complaints started [26]. A number of nocturnal dyspnea complaints can also be a late response to exercise. The recognition of a late fall is very easily done with a mini-Wright peak flow meter. The early response can be prevented by inhaling beta-sympathicomimetics, or disodium cromoglycate [27, 28].

We should only speak of a late response after an exercise challenge, when the diurnal post-exercise rhythm has been compared with a diurnal rhythm of a day without exercise. This is demonstrated in fig. 3, in which the upper curve shows a PEFR fall to exercise of 23% and the lower curve of 16%. Although the percentage fall in PEFR after exercise is higher in the upper curve it is not a late asthmatic response to exercise because the variation in the PEFR is due to circadian variation in airway calibre. One can never say that a patient has a late asthmatic response to exercise when a PEFR fall is related only to pre-exercise value. To draw a graph, instead of looking at figures, may be more illustrative for demonstrating a late asthmatic response exercise.

Not all patients who had a late PEFR fall as compared with pre-exercise value, had a late PEFR fall when the peak flow decrease was compared with the corresponding clocktime on a control day. We think a PEFR fall greater than 20% can sufficiently demonstrate a late response after exercise. We demonstrated that the late bronchoconstrictive response after exercise had a prevalence of 38% when PEFR fall greater than 10% was compared with the corresponding clocktime on a control day. The percentage was 19% when PEFR fall of greater than 20% was compared with corresponding clocktime on a control day.

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Réponses asthmatiques immédiates et tardives, induites par l'effort, chez des patients atteints de limitation réversible du débit aérien. B. Speelberg, N.J. van den Berg, C.H.A. Oosthoek, N.P.L.G. Verhoeff, W.T.J. van den Brink.

RÉSUMÉ: L'existence et la prévalence des réponses asthmatiques tardives à l'effort chez les patients sont incertaines. Nous avons investigué si les chutes tardives du débit expiratoire de pointe après une provocation d'effort étaient encore significatives après comparaison avec le débit expiratoire lors d'un jour de contrôle à la même heure. Nous avons examiné 86 patients souffrant d'une diminution réversible des débits gazeux, 79 atteints d'asthme, et 7 de BPCO, tous sous traitement régulier aux bronchodilatateurs et aux agents anti-inflammatoires. Les patients ont été répartis de façon randomisée en un jour de contrôle et un jour d'effort, avec enregistrement horaire du débit expiratoire de pointe. Pendant le jour d'effort, chaque patient a subi une épreuve à la bicyclette pendant 8 minutes à 90% du pouls cardiaque prédit. Une résponse asthmatique précoce et tardive à l'effort a été considérée comme présente si le débit de pointe diminuait de 10% ou davantage le jour de l'effort, par comparaison à la même heure le jour de contrôle. Trente-trois patients (38%) ont montré une chute du VEMS de 10% ou davantage entre 4 et 13 heures après l'effort, lorsque le débit de pointe était comparé avec le débit correspondant à la mème heure le jour contrôle. Sept (8%) n'ont manifesté qu'une réponse tardive isolée, et 26 (30%) ont eu une réaction asthmatique double. Nous concluons que des réactions asthmatiques tardives authentiques se développent aprés l'effort chez un nombre significatif de patients atteints d'une limitation réversible mais bien contrôlée des débits aériens.

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