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Cardiac role in exercise limitation in asthmatic subjects with special reference to disease severity

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Cardiac role in exercise limitation in asthmatic subjects with special reference to disease severity. A. Varray, J. Mercier, A-M. Savy-Pacaux, C. Préfaut. ©ERS Journals Ltd 1993.

ABSTRACT: We wanted to assess limitations in cardiorespiratory fitness of asthmatic subjects, acclimatized to 1,300 m altitude and in a clinically stable state.

We therefore studied 16 young asthmatic and 8 normal young subjects during an incremental bicycle exercise test. The asthmatics were divided into two groups, according to the Aas classification: a moderate asthma group (degree 2 and 3, no pulmonary impairment during symptom-free intervals), and a severe asthma group (degree 4 and 5, with persistent airway obstruction).

The results showed that cardiorespiratory fitness is limited in severe asthmatic subjects acclimatized to an altitude of 1,300 m, due to decreased cardiac output and stroke volume. At submaximal exercise, the lower stroke volume is compensated by an increased arteriovenous oxygen content difference, but this compensation no longer exists at maximal exercise, which explains the lower maximal oxygen uptake in the severe asthma group. The hypothesis that the high tidal volume in the severe asthma group could lead to a decrease in left ventricular performance is considered.

In conclusion, with respect to cardiorespiratory response to exercise, asthmatics should not be considered as a homogeneous group. Furthermore, relationship between ventilatory requirement and its consequences upon cardiac stroke volume provides a strong argument for the physical rehabilitation of asthmatics. Indeed, aerobic training can decrease the ventilation level for a given workload, and thus reduce inappropriate adaptations to exercise.

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There are few data in the literature concerning the circulatory, ventilatory, and metabolic adaptations to exercise in persons with asthma [1]. Most investigators have indicated that asthmatic subjects present either minor or no alterations in these adaptations. These studies, however, were carried out on asthmatic subjects without severe airway obstruction and, generally, during submaximal exercise. Other studies have indicated that with a sufficient level of pre-exercise obstruction, alterations in response may occur [2]. The need to take bronchial obstruction into account was acknowledged in a recent study by HEDLIN *et al.* [3], which noted a tendency for children with more severe asthma to achieve lower maximum workloads. In addition, previous work carried out in our laboratory showed a slight cardiorespiratory limitation in mild to moderate asthmatics [4], whilst it was marked in more severe asthmatics [5]. We advanced the hypothesis that airway obstruction, during symptom-free intervals, is a limiting factor to exercise in asthma [5], but were unable to ascertain whether the cardiovascular system limits exercise, because cardiac output was not measured.

This study was carried out to determine whether cardiac adaptation to exercise in asthmatics acclimatized to moderate altitude and in a clinical steady state, is similar to that observed in healthy subjects, and, if not, what is the effect of bronchial obstruction on these adjustments to exercise.

Material and methods

Subjects

Eight normal and 16 asthmatic young subjects were studied in Osseja (altitude: 1,300 m). Their anthropometric and spirometric characteristics are given in table 1. All of the asthmatic patients were known to have had recurrent reversible wheezing episodes, and were required to fulfil at least three of the four following criteria: 1) Clinical - family history of asthma and/or personal history of eczema, conjunctivitis or rhinitis caused by a known allergen; 2) Allergic - cutaneous hypersensitivity to one or several allergens; 3) Immunological - blood immunoglobulin E (IgE) levels above 150 $UI \cdot ml^{-1}$. The blood IgE values were determined by the paper

radio-immunosorbent test (PRIST); 4) Functional - an improvement of at least 15% in forced expiratory volume in one second (FEV_1) by inhaling a bronchodilator.

The asthmatics were divided into two groups (n=8), following the Aas criteria [6] in order to distinguish a moderate asthma group (degree 2 and 3 of the classification), and a severe asthma group (degree 4 and 5 of the same classification). The Aas classification was chosen because it includes both attack frequency and airway functional states in symptom-free intervals. All subjects gave informed consent and had been acclimatized to moderate altitude (1,300 m) for four months before the study began.

analyser (OM 11, Sensor Medics Corp., California, USA), and for CO_2 with an infra-red analyser (Diamant 6000, Cosma, France). Each analyser was calibrated before and after every test with standard gases. The inspiratory airflows and the fractions of expired O_2 and CO_2 (F_{EO_2} and F_{ECO_2}) were calculated by a computer over 10 breath cycles. Averages were then established for minute ventilation ($\dot{V}_E$; $ml \cdot min^{-1}$ body temperature pressure and saturation (BTPS)), O_2 uptake ($\dot{V}_{O_2}$; $l \cdot min^{-1}$ standard temperature and pressure dry (STPD)), CO_2 production ($\dot{V}_{CO_2}$; $l \cdot min^{-1}$ STPD), respiratory ratio (R), ventilatory equivalents for O_2 and CO_2 (minute ventilation/oxygen uptate ($\dot{V}_E/\dot{V}_{O_2}$ and minute ventilation/carbon dioxide production $\dot{V}_E/\dot{V}_{CO_2}$),

Table 1. – Anthropometric and spirometric characteristics of control and asthmatic groups

	Control			Moderate asthma			Severe asthma		
	Mean	SEM	Range	Mean	SEM	Range	Mean	SEM	Range
Age yrs	16	0.6	13–17	16	0.6	13–17	16	0.5	12–17
Height cm	167	2.7	151–173	167	3.1	150–182	165	4.1	146–185
Body mass kg	54.1	3.7	42–75	54.1	3.2	38–59	51.8	4.1	35–73
FVC % pred	113	3.7	103–130	113	2.9	101–124	104	2.9	93–118
FEV_1 % pred	109	4.3	97–130	108	3.6	99–132	78	2.7	67–89*
FEV_1/FVC	82	2	75–93	83	2	76–92	64	2	59–77*
MEF_{50} % pred	97	5.6	73–144	97	7.4	82–147	46	3.8	38–69*
$FEF_{25-75\%}$ % pred	96	5.4	76–122	99	8.1	84–153	48	4.1	35–66*
$FEF_{25-75\%}$/FVC	81	4	74–94	84	6	68–119	44	4	28–66*
RV/TLC	23	4	19–40	25	2	20–39	29	1	25–35

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $MEF_{50\%}$: maximal expiratory flow at 50% of FVC; $FEF_{25-75\%}$: forced expiratory flow between 25 and 75% of FVC; RV/TLC: residual volume/total lung capacity ratio; *: significant difference from control ($p<0.001$); % pred: percentage predicted.

Measurements

Lung function studies included lung volumes, capacities and flows (residual volume (RV), forced vital capacity (FVC), total lung capacity (TLC), FEV_1, maximal expiratory flow at 50% of FVC ($MEF_{50\%FVC}$), and forced mid-expiratory flow ($FEF_{25-75\%}$)). The measurements were made in a whole body plethysmograph (Transmural Bodybox 2800, SensorMedics, California, USA). FEV_1/FVC, $FEF_{25-75\%}$/FVC, and RV/TLC ratios were then calculated. The predicted values were those of CRAPO and co-workers for airway flows [7], capacities, and volumes [8].

The exercise tests were performed on a cycle ergometer (EPC 990 Bodyguard, Jonas Ogland AS, Norway). The subjects breathed through a low-resistance valve (Warren E. Collins Inc., Mass., USA, dead space 90 ml). Inspiratory airflow was measured during exercise with a Fleisch No.3 pneumotachograph (Godard Statham, Holland), and a pressure transducer (Validyne MP 45, Engineering Corp., California, USA), with a measuring range of ± 2 cmH_2O. The pneumotachograph was placed on the inspiratory tubing in order to avoid problems due to water vapour. The calibration of the flow module was made by introducing a calibrated volume of air at several flows. Expired gases were sampled in a mixing chamber (5 *l*), and analysed for O_2 with a polarographic

breathing frequency (*f*b; bpm), tidal volume (V_T; ml BTPS), mean inspiratory flow (V_T/T_I; $ml \cdot s^{-1}$), and inspiratory duty cycle (T_I/T_{tot}). Breathing pattern data ($\dot{V}_E$, V_T and V_T/T_I) were normalized for body weight [9].

The electrocardiograph was monitored continuously using a V5 lead (Diascope, Simonsen and Weel, Denmark).

Cardiac output was estimated by using the exponential rebreathing method. Expired CO_2 was continuously sampled at the mouth for analysis of CO_2, using a rapid response infra-red analyser (Rubis 3000, Cosma, France). The end-tidal carbon dioxide tension (P_{ETCO_2} mmHg) was calculated from the average of the last 10 breath cycles prior to the rebreathing manoeuvre. Immediately following this, subjects performed a 10–12 s CO_2 rebreathing manoeuvre, as described by JONES and CAMPBELL [10], and modified by MCKELVIE *et al.* [11] (exponential technique) with a 7% CO_2 in O_2 gas mixture, in order to compute a bag equilibrium carbon dioxide tension (Pb_{CO_2} mmHg). Arterial carbon dioxide tension (Pa_{CO_2} mmHg) was estimated from corrected end-tidal concentration [10]:

$$Pa_{CO_2}=5.5+0.9\ P_{ETCO_2} - 0.0021\ V_T$$

Mixed venous carbon dioxide tension ($P\bar{v}_{CO_2}$) was estimated from the rebreathing equilibrium plateau, with a downstream correction [10]:

$$P\bar{v}_{CO_2}=Pb_{CO_2} - (0.24\ Pb_{CO_2} - 11)$$

The partial pressures were converted into contents (C), (C_{CO} (ml·dl^{-1})=11.02 $P_{CO_2}^{0.396}$) [10], and cardiac output ($\dot{Q}$) was then calculated according to the Fick formula:

$$\dot{Q}\ (l \cdot min^{-1}) = \dot{V}_{CO_2}\ (cl \cdot min^{-1}) / C(\bar{v}\text{-}a)_{CO_2}\ (ml \cdot dl^{-1})$$

Where $C(\bar{v}\text{-}a)_{CO_2}$ is the venous-arterial content difference for CO_2. Dead space volume (V_D) was calculated according to Bohr's equation:

$$V_D\ (ml\ BTPS) = V_T\ (ml\ BTPS) \times (P_{aCO_2}\text{-}P_{ECO_2}/P_{aCO_2}) - \text{valve box dead space (ml)}.$$

Dead space ventilation ($\dot{V}_D$) was obtained by multiplying V_D by breathing frequency (fb). Alveolar ventilation ($\dot{V}_A$) was then computed ($\dot{V}_A=\dot{V}_E-\dot{V}_D$). In addition exercise arteriovenous oxygen content difference (Ca_{O_2}-$C\bar{v}_{O_2}=\dot{V}_{O_2}/\dot{Q}$), stroke volume (SV), and $\dot{V}_A/\dot{V}_E$ were calculated. All of the calculations (for $\dot{Q}$ and $\dot{V}_A$) were performed by using a software program, which took into account the above formula [12].

The reliability of the rebreathing method, which was chosen for ethical reasons, has been well-documented [11, 13–17]. To avoid bias related to this technique in asthmatics, we verified within the three groups that the arterial to end-tidal CO_2 differences ($P(a\text{-}ET)_{CO_2}$) at rest were normal, and removed from the study all subjects who had at least a 10% fall in FEV_1 after exercise (either immediately or within 10 min after the end of exercise). The arterial P_{CO_2} was measured by a blood analyser (Instrumentation Laboratory IL 1306, Milan, Italy) from arterialized blood samples (earlobe).

Protocol

The incremental exercise test started with a 3 min 30 W warm-up, followed by an increasing workload of 30 W every 2 min (20 W for females), until at least three of the following exhaustion criteria were observed: 1) plateau of $\dot{V}_{O_2}$ in spite of the increasing workload; 2) maximal heart rate = predicted maximal heart rate ±5%; 3) respiratory ratio ≥1.10; and 4) inability to maintain the speed at 50 rpm. The ventilatory variables and the P_{ETCO_2} (for $\dot{V}_A$ calculation) were recorded during the last 10 respiratory cycles at each exercise level; the rebreathing manoeuvre (for $\dot{Q}$ calculation) was only performed every other workload, just after P_{ETCO_2} measurement.

Statistical analysis

The data are expressed as mean±SEM (standard error of mean). The groups were studied at maximal exercise, and at the same metabolic level ($\dot{V}_{O_2}$=1.5 $l \cdot min^{-1}$). This $\dot{V}_{O_2}$ was chosen because it represents a submaximal exercise level which was achieved by all the subjects. Group differences were evaluated by a one-way analysis of variance. $\dot{Q}$ and Ca_{O_2}-$C\bar{v}_{O_2}$ were also studied as a function of percentage of maximum oxygen uptake ($\dot{V}_{O_2}max$) by using a two-way analysis of variance (ANOVA) (group×% $\dot{V}_{O_2}max$). When the ANOVA F ratios were significant, the means were compared by using the contrast method. Multiple stepwise regression analyses were performed within the three groups, to determine the relationships between $\dot{V}_{O_2}max$ and the cardiorespiratory variables SV, HR and Ca_{O_2}-$C\bar{v}_{O_2}$ [18]. The same analysis was also performed to assess the relationships between V_{O_2} at a HR of 150 beats·min^{-1} and both SV and Ca_{O_2}-$C\bar{v}_{O_2}$. For each subject, these "standardized" data were derived by application of the best regression model among polynominal (order 1 and 2), power, and exponential models from individual measured data. In addition, the model was considered reliable if r was ≥0.96.

Results

Spirographic data

Table 1 shows that the moderate asthma group, which corresponds to the Aas [6] classes 2 and 3, did not have different pulmonary function values from the control group. However, significant differences were found between the moderate and severe asthma groups for all values except FVC and the RV/TLC ratio ($p<0.001$).

Maximal exercise

The maximal oxygen uptake and $\dot{Q}max$ were lower in the severe asthma group, which had a very low stroke volume (SVmax) (table 2). In contrast, no differences were found in these variables between the control and moderate asthma groups. The values of Ca_{O_2}-$C\bar{v}_{O_2}max$ were comparable in all of the groups. To avoid bias in the estimation of cardiac output in the asthmatic groups, we compared the resting $P(a\text{-}ET)_{CO_2}$ within the three

Table 2. – Cardiac and respiratory variables during maximal exercise in the 3 groups

	Control	Moderate asthma	Severe asthma
$\dot{V}_{O_2}max$ $l \cdot min^{-1}$	2.5±0.1	2.5±0.1	2.1±0.2*
$\dot{Q}max$ $l \cdot min^{-1}$	24.5±1.1	25.4±1.4	20.1±1.5**
SVmax ml·beat^{-1}	136±7	135±7	108±4**
$V_T max$ ml·kg^{-1}	32.2±1.3	38.7±1.7	41.3±1.3*

$\dot{V}_{O_2}$: oxygen uptake; $\dot{Q}max$: maximal cardiac output; SVmax: maximal stroke volume; $V_T max$: maximal tidal volume. *: $p<0.02$; **: $p<0.01$ compared to other groups.

groups; no significant differences were found (control moderate asthma comparison: 1.6±0.8 *versus* 0.9±1, t=0.5, p>0.6; control-severe asthma comparison: 1.6±0.8 *versus* 1.8±0.7 t=-0.2, p>0.8; moderate asthma-severe asthma comparison: 0.9±1 *versus* 1.8±0.7, t=-0.7, p>0.5). In addition, none of the subjects showed falls in their post-exercise flow-volume curves.

No differences were found either in maximum expiratory flow ($\dot{V}E$max) or in the $\dot{V}A/\dot{V}E$ ratio within the three groups. However, a significantly higher maximum tidal volume (Vtmax) was found in the severe asthma group p<0.05 (table 2).

Stepwise regression analysis showed that, in the asthmatic groups, SV consistently accounted for a larger portion of the variability in $\dot{V}o_2$max than did Cao_2-$C\bar{v}o_2$ (table 3). This phenomenon was linked to the severity of asthma, since SV accounted for 87% of the variability of $\dot{V}o_2$max in the severe asthma group, and only 60% in the moderate asthma group.

Same metabolic level, $\dot{V}o_2$ 1.5 l·min^{-1}

At a $\dot{V}o_2$ of 1.5 l·min^{-1}, the severe asthma group presented lower SV (108±10 *versus* 134±9 ml in the moderate asthma group, and 142±10 ml in the controls; p<0.01), and $\dot{Q}$ (17.6±0.7 *versus* 19.7±0.7 and 19.4±0.5 l·min^{-1}, respectively; p<0.05). In order to reach the same $\dot{V}o_2$, the decrease in $\dot{Q}$ was compensated for by an increase in Cao_2-$C\bar{v}o_2$ (86.4±3.7 *versus* 76.7±2.2 and 77.8±2.2 ml·l^{-1}, respectively; p<0.01). No differences were found between the control and moderate asthma groups. When the results were expressed as percentage of $\dot{V}o_2$max, a systematic and significant lower $\dot{Q}$ was observed in the severe asthma group (fig. 1) (p<0.001). In addition, a significantly higher arteriovenous O_2 content difference was observed in the severe asthma group, but only at very low intensities (fig. 2) (p<0.01).

Table 3. – Relationship between $\dot{V}o_2$max as the dependent variable and SV, HR and Cao_2-$C\bar{v}o_2$ at $\dot{V}o_2$max in the 3 groups

	Explanatory variables			
	SVmax variation explained %	HRmax variation explained %	Cao_2-$C\bar{v}o_2$max variation explained %	Total % explained variation r^2
Control	42	16	42	100
Moderate asthma	60	9	31	100
Severe asthma	86	1	12	100

$\dot{V}o_2$max: maximal O_2 uptake; SVmax: maximal stroke volume; HRmax: maximal heart rate; Cao_2-$C\bar{v}o_2$max: arteriovenous O_2 content difference at $\dot{V}o_2$max.

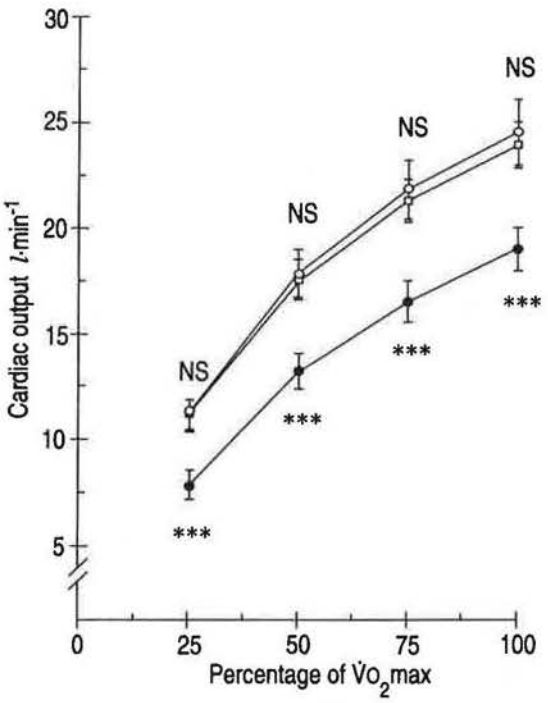

Fig. 1. – Cardiac output as a function of percentage of $\dot{V}o_2$max. Data are given as mean±SEM. NS: no statistical differences between control and moderate asthma groups. ***: p<0.001 between control and severe asthma groups; □: controls; ○: moderate asthma; ●: severe asthma; $\dot{V}o_2$max: maximal O_2 uptake.

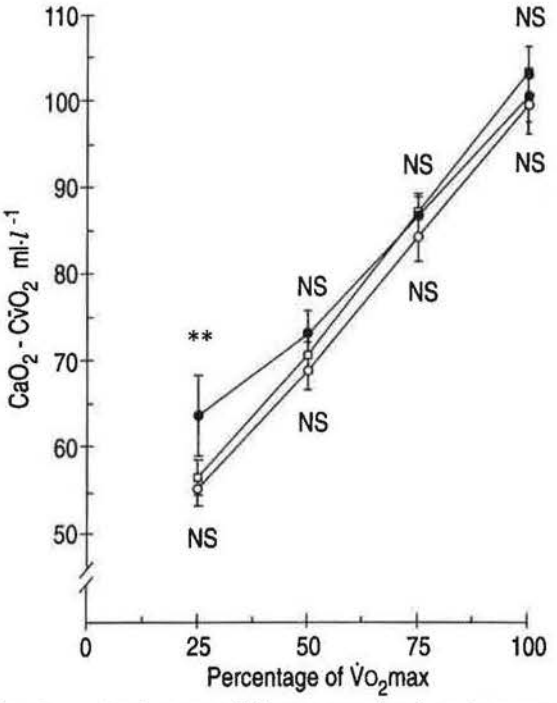

Fig. 2. – Arteriovenous difference as a function of percentage of $\dot{V}o_2$max. Data are given as mean±SEM. Upper "p values" relate to control *vs* severe asthma groups. Lower "p values" refer to control *vs* moderate asthma groups. NS: no statistical difference; **: p<0.01. Cao_2 - $C\bar{v}o_2$: arteriovenous O_2 content difference; $\dot{V}o_2$max maximal O_2 uptake. □: controls; ○: moderate asthma; ●: severe asthma.

Breathing pattern in the severe asthma group was characterized by an exaggerated ventilatory requirement to reach the same $\dot{V}O_2$ as the others (1186±121 *versus* 961±121 ml·min^{-1}·kg^{-1} in the moderate asthma group and 806±82 ml·min^{-1}·kg^{-1} in controls; $p<0.001$). In addition, we found a significantly higher VT (33.8±2.1 *versus* 29.1±2.5 and 23.5±1.5 ml·kg^{-1}, respectively; $p<0.001$) and VT/TI (42.6±4.3 *versus* 34.1±3.6 and 27.9±3.1 ml·kg^{-1}·s^{-1}; $p<0.01$) in this group.

A multiple regression analysis was performed to assess the contribution of the independent variables, SV and Cao_2-$C\bar{v}o_2$, to the variation in the dependent variable, $\dot{V}O_2$, at a HR of 150 beats·min^{-1} (table 4). The results showed that the more severe the asthma, SV accounted for a larger portion of the variability in $\dot{V}O_2$ than did Cao_2-$C\bar{v}o_2$.

Table 4. – Relationship between $\dot{V}O_2$ at HR of 150 beats·min^{-1} as the dependent variable and SV and Cao_2-$C\bar{v}o_2$ at HR of 150 beats·min^{-1} in the 3 groups

	Explanatory variables		
	SV var exp %	Cao_2-$C\bar{v}o_2$ var exp %	Total % exp var r^2
Control	84	15	99
Moderate asthma	82	10	92
Severe asthma	94	6	100

$\dot{V}O_2$: O_2 uptake; SV: stroke volume; Cao_2-$C\bar{v}o_2$; arteriovenous O_2 difference; HR: heart rate; var: variation; exp: explained.

Discussion

When investigating whether asthmatic subjects, acclimatized to moderate altitude, had normal adaptation to exercise and the part played by bronchial obstruction in these adaptations, we found that the limitation of $\dot{V}O_2$max was linked to lower values of cardiac output and stroke volume in the severe asthma group. This was observed even at submaximal exercise intensities. The moderate asthma group did not have abnormal exercise adaptation, and the values of $\dot{V}O_2$max were normal or greater than those of control subjects. This result does not seem to be due to moderate altitude. Indeed, contrary to a previous study carried out at sea level on asthmatics with less airways obstruction than our severe asthma group [5], we found, in the present study, a lower reduction of $\dot{V}O_2$max. Thus, it seems that moderate altitude does not impair exercise adaptation, and may even improve it.

One is reminded of the classic well-being linked with altitude exposure in asthmatics [19]. Beyond the effects of allergen avoidance, which is generally suggested [20], the lower density of inspired air may also play a role, by minimizing the consequences of obstruction, particularly turbulence during breathing. Indeed, at 1,300 m altitude, the decrease in air density is approximately 17%, and in normal subjects $\dot{V}O_2$max shows an average decrease of 3–5%, as compared to sea level, during the first days following the arrival at altitude [21]. Moreover, after acclimatization, it is practically impossible to detect any difference in maximal exercise performance. Thus, it can be hypothesized that there is an advantage for asthmatics in breathing air at lower pressure, and that there is no harmful effect on physical fitness.

The limitation of $\dot{V}O_2$max in the more severe asthmatic group is unlikely to have been due to reduced fitness for three reasons: firstly, the physical activity level was the same in all of the groups for 4 months prior to study; secondly, a deconditioned state would have produced a decreased arteriovenous difference in the less fit group, which was not observed either at maximal exercise or at any exercise level in the severe asthma group; and thirdly, a reduced fitness cannot explain the abnormalities revealed by the multiple stepwise regression analyses, either at sub or maximal exercise. The $\dot{Q}$ values of the control group were comparable to those reported in the literature [22, 23], and the differences observed in cardiovascular response to exercise were still evident after the normalization of exercise intensities, in percentage of $\dot{V}O_2$max. Thus there is a specific problem concerning the adaptation to exercise in the severe asthma group, which cannot be explained by lack of fitness alone. The limitation of the $\dot{V}O_2$max is linked to lower values of SVmax, which lead to a low maximum cardiac output ($\dot{Q}$max).

The rebreathing technique to measure cardiac output indirectly has been well-validated in healthy subjects. In patients with asthma, the accuracy of this method is questionable, in view of the potential for ventilation/perfusion mismatch. DAVIS *et al.* [24] have reported that the CO_2 rebreathing method for measuring cardiac output is reliable in seriously ill patients. According to this work, it is possible to use $PaCO_2$ instead of $PETCO_2$ when the ventilation/perfusion mismatch is known (severe respiratory distress syndrome). In our study, we chose a non-invasive technique for $\dot{Q}$ measurement, but we were careful to avoid major bias due to ventilation/perfusion mismatch. This is why we checked that, under resting conditions, the arterial to end-tidal CO_2 differences were the same in our three groups. In addition, it has been shown that, in the absence of exercise-induced bronchospasm, no alteration in gas exchange occurs [25], even at maximal exercise [26, 27], indicating the absence of ventilation/perfusion mismatch. Moreover, the evolution of the physiological dead space/tidal volume ratio is the same as in healthy subjects. Since, in the absence of exercise-induced bronchospasm, there is no evidence of bias in $\dot{Q}$ measurement, the major problem is to avoid the interpretation of a $\dot{Q}$ measurement in a subject who had a post-exercise reduction in FEV_1. For these reasons, we removed from our study all subjects who had at least a 10% FEV_1 fall after exercise test. Since HAAS *et al.* [28] have shown that pulmonary function is not impaired during exercise one can reasonably assume that an accurate estimate of cardiac output was obtained in all groups. In addition, in our study, we chose the exponential rebreathing method with 7% CO_2, because MCKELVIE *et al* [11] have shown that it is very difficult to obtain a CO_2 equilibrium during unsteady state exercise for two

main reasons: 1) due to an initial high concentration of CO_2 and the large accumulation of CO_2 in the bag, it is difficult for the subject to carry out rebreathing manoeuvre at high power outputs; and 2) the bag concentration of CO_2 has to be carefully chosen, and may require more than one rebreathing to obtain an acceptable record, which leads to technical problems in the realization of the exercise test. Therefore, the major advantage of the exponential method is that it is very well-tolerated at any level of exercise, and the $\dot{V}O_2/\dot{Q}$ relationship was the same when cardiac output was measured in either steady or unsteady state conditions [11].

To our knowledge, no studies including $\dot{Q}$ measurements have been carried out to evaluate the exercise response among asthmatic groups of different severity. The only data available are those of GRAFF-LONNEVIG *et al.* [29], and HEDLIN and FREYSCHUSS [30]. The latter study reported normal values of $\dot{Q}$ in four patients, but without direct comparison to a control group. A particularly interesting observation, made by the authors, was that one subject in this study did not show the increase in $\dot{Q}$ that might have been expected from the O_2 uptake. The authors were unable to explain this finding. The results of our study indicate that it could be due to the severity of asthma. Indeed, we did not observe any abnormalities concerning cardiovascular adaptation in the moderate asthma group, but only in the more severe group.

The explanation for the observed low cardiac output could be linked to the breathing strategy used to compensate for the additional load represented by airway obstruction. This strategy has been discussed previously [4, 5]. Briefly, it consists of increasing the V_T instead of *f*b, more so than in normal subjects, in order to increase the level of $\dot{V}_E$, which leads to increased ventilation without worsening airway turbulence. We found higher values of V_T, both at maximal exercise and for the same $\dot{V}O_2$, in the severe asthma group. Many studies carried out on heart-lung interactions have shown that inspiration contributes to a decrease in SV [31–35], this phenomenon being especially prevalent during exaggerated inspiratory effort. The main mechanism is an increase in right ventricular afterload, due to exaggerated inspiratory swings in pleural pressure. The right ventricular stroke volume is thus decreased, the right ventricular end-systolic volume is increased, and the left ventricular compliance is lowered. In addition, by an interdependence effect between right and left ventricles, there is a decrease in SV. This analysis supports the finding of MARTIN *et al.* [36], who argued that modifications in breathing pattern may decrease left ventricular output, and the combination of the above could explain the abnormality of SV in the severe asthma group. To confirm the interaction between breathing pattern and SV, we verified the correlation existing between V_T and SV, at least during the linear increase phase of SV. We obtained a close negative correlation ($r=-0.79$), which supports this assumption, especially as BOUTELLIER and FARHI [37] have shown that the rebreathing $\dot{Q}$ measurement is overestimated, if the V_T is high.

This correlation cannot, therefore, be due to a bias linked to the breathing pattern. It is, however, possible that when asthma is severe, the specific ventilatory adaptation during exercise leads to a decrease in left ventricular performance, and subsequently to low SV and $\dot{Q}$. This assumption supports the result of a recent study of BABB *et al.* [38], who showed that patients with mild-to-moderate airflow limitation present an increased end-expiratory lung volume during exercise. It raises the possibility that hyperinflation, and the associated reduced mean pleural pressures, could limit cardiovascular function, for the same reasons as presented above. At submaximal exercise in the severe asthma group, we observed that the decrease of $\dot{Q}$ was compensated for by an increased $Cao_2\text{-}C\bar{v}o_2$, but this compensation disappeared at maximal exercise intensity, with a subsequently lower $\dot{V}O_2max$. The stepwise regression analysis, performed both for the same heart rate and at maximal exercise, provides additional arguments for the hypothesis that a sufficient level of bronchial obstruction leads to marked changes in exercise adaptation. Indeed, in the severe asthma group, $\dot{V}O_2$ is more influenced by SV than in the moderate asthma or control groups. This could explain why the previous studies found no alteration in cardiorespiratory adaptations during exercise, since the degree of bronchial obstruction was not considered as a study variable [29, 30].

The fact that the ventilatory requirement is exaggerated for the same metabolic level in the more severe asthmatic group, with possible effects on cardiac output, is a particularly interesting argument for rehabilitation of asthmatics by physical training. Indeed, as we observed in a previous study [39], there is a decrease of this ventilatory requirement after aerobic training for a given level of $\dot{V}O_2$. Thus, in addition to the common effects of reconditioning, it is possible that, by decreasing hyperventilation, we would induce better cardiovascular adaptations during exercise. This could explain the great magnitude of improvement in $\dot{V}O_2max$ after a reconditioning programme [39].

In conclusion, this study shows that young subjects with moderate asthma who are acclimatized to moderate altitude show no impairment of cardiorespiratory adaptation to exercise compared with normal controls. In contrast, subjects with severe asthma have a lower O_2 uptake than control and moderate asthma groups. The severity of pre-exercise obstruction should be taken into account, in order to improve our understanding of the cardiorespiratory adaptations at maximal and submaximal exercise in asthmatics. Indeed, the more severe the asthma, the greater is the part played by stroke volume in determining oxygen uptake. The effects of exaggerated ventilatory requirement (proportional to the severity of asthma) may explain the lower values of cardiac output. This provides a strong argument for the physical reconditioning of these subjects, in terms of improvement of adaptation to submaximal exercise, because aerobic training leads to a reduction in the level of ventilation required for a given exercise intensity.

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