Evidence of ventilatory constraints in healthy exercising prepubescent children.

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Evidence of ventilatory constraints during graded exercise in healthy prepubescent children

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ABSTRACT

We assessed if expiratory airflow limitation (expFL) were achieved and how this may modulate the regulation of tidal volume (V_T) during exercise in eighteen healthy prepubescent children (6 girls and 12 boys; 10.1 ± 0.3 years old). They performed a graded exercise to exhaustion on cycle ergometer preceded and followed by pulmonary function tests. Throughout exercise, breathing flow-volume loops were plotted into the maximal flow-volume loop (MFVL) measured at rest. End-expiratory lung volume was determined by measuring inspiratory capacity (IC) relative to the forced vital capacity (IC/FVC) and end-inspiratory lung volume by measuring V_T relative to IC (V_T/IC). The expFL, expressed in percentage of V_T, was defined as the part of the tidal breath that meets the boundary of the MFVL. Eight children did not present expFL (NFL) and ten children presented an expFL (FL) at peak exercise (range: 16 % - 78 % of V_T). At peak exercise, FL present lower V_T/IC and higher IC/FVC ($P<0.01$) than NFL group evidencing two different exercise breathing strategies in children. Significant relationships were reported between expFL and IC/FVC ($P<0.01$; $r = 0.72$; $n = 18$) or V_T/IC ($P<0.05$; $r = 0.51$; $n = 18$). The NFL group regulated regulate V_T to higher lung volume than FL likely to avoid expFL while FL subjects breathed at low lung volume leading to expFL. Nevertheless, oxygen arterial saturation and dyspnea were similar in the two groups. In conclusion, expiratory airflow limitation may occur in healthy prepubescent children and was related to breathing strategy during exercise.

KEY WORDS: Expiratory flow limitation, mechanical ventilatory constraints, breathing reserve, breathing pattern, breathing strategy

INTRODUCTION

In healthy young adults, pulmonary function is not generally a limiting factor during exercise. Indeed, despite the reach of the maximal metabolic level, the breathing reserve remains considerable which allow to cover the oxygen demand even at high intensity exercise (9, 20).

However, children ventilate out of proportion to the metabolic demands of exercise as compared to adults (2, 7, 11, 22). Significant lower PCO_2 and higher $\dot{V}_E/\dot{V}O_2$ have been found in children than in adults and are the result of a higher breathing frequency (*f*) in children (11, 22). A hypothesis to explain the higher ventilation level in children has been evidenced by Gratas-Delamarche et al. (11). These authors have suggested that the relatively rapid and shallow breathing could not allow the children to wash out alveolar air as efficiently as in adult, but more particularly, could also induce an increase in ventilatory work because of an increase in viscous and turbulent work (11). Consequently, owing to this specific ventilatory response to exercise, it could not be surprising that children would have a specific breathing strategy and that they would ventilate more closely to their mechanical limit at high exercise intensity than normal adult. However few studies which dealt with breathing reserve (BR) in children, reported lower values of breathing reserve at maximal exercise in children than adults (20).

Traditionally, ventilatory constraint during exercise has been determined by measuring the BR. This parameter is generally determined from the comparison between the ventilation reached during exercise and the maximal voluntary ventilation measured (MVV) at rest. The MVV could whether be estimated indirectly by multiplying the forced expiratory volume in one second (FEV_1) by 35 or 40, whether be measured directly by asking the subject to breathing the most rapidly and the deepest as possible during about 20 s. But, the MVV is strongly dependent of the subject motivation and, as emphasized by Johnson et al. (15), do not represent the ventilatory pattern typically observed in spontaneous reflex-mediated ventilation. Indeed, a study have shown that the work of breathing with the MVV maneuver greatly exceeded that achieved when the hyperpnea was reflexly mediated (16). In addition, the BR does not provide accurate information about the source or type of ventilatory constraint. Recently, it has been shown that measuring the tidal exercise flow-volume (F-V) loop during exercise and plotting them within the maximal F-V loop (MFVL) provide more specific information on the source or type of ventilatory constraint (15).

The aim of this study was to measure the breathing pattern and the flow-volume loop during a graded exercise test aiming to analyse the ventilatory constraint which could occur during exercise in normal prepubescent children.

MATERIALS AND METHODS

Subjects

Twenty-four non-athlete prepubescent children participated to this study. Six subjects were removed because of non exploitable data attributable to the ventilatory noise. Eighteen 10.1 ± 0.2 year-old subjects (6 girls and 12 boys) were included in the data analysis. A complete clinical check up was carried out by a physician to prevent a possible contra-indication to exercise. All subjects were free of cardio-respiratory disease including post-exercise asthma. The subjects were weighted, measured and the fat mass percentage was estimated by the skinfold method (10). The same physician makes sure that each subject was at the first stage of maturation according to Tanner's method (24). A physical activity questionnaire validated for French children (8) was distributed to the parents to assess the physical activity of each child. The experimental protocol was approved by the local Ethics Committee. Conformably to the Journal of Applied Physiology policy statement all subjects and their parents received a verbal description of the experiment and completed a written, informed consent form.

Lung function tests

Children equipped with a nose clip performed two lung function tests, one before and one ten minutes after the end of the graded exercise test described below (Ergocard, Medi-soft, Dinant, Belgium). All lung function tests were carried out by the same technician and followed the guidelines of the American Thoracic Society (1). At each time, three MFVL were taken and only the best one was retained to calculate forced vital capacity (FVC), FEV_1, peak expiratory flow (PEF), maximal expiratory flow at 75% ($MEF_{75\%}$), 50% ($MEF_{50\%}$) and 25% ($MEF_{25\%}$) of FVC. We made sure that values were normal.

Graded exhaustive exercise test

The subjects performed a graded exercise test to exhaustion on a magnetic-brake bicycle ergometer (800 S, Ergoline, Bitz, Germany). Graded exercise test began with a resting period of 5 min and pursued itself with 3 min of warmed up at 10 W. Afterwards, the exercise intensity was increased by steps of 10 W each minute until exhaustion so that exercise lasted between 8 min and 10 min. Subjects had to maintain a pedaling rate of 60 rpm and were verbally encouraged until exercise was exhaustive (21).

Gas exchanges and cardio-respiratory measurements

Throughout exercise, a breath by breath gas analyzer calibrated before each test with references gases (Ergocard, Medi-soft, Dinant, Belgium) allowed the measurements of: oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), end-tidal carbon dioxide pressure ($PetCO_2$) and end-tidal oxygen pressure ($PetO_2$), ventilatory flow ($\dot{V}_E$), tidal volume (V_T), breathing frequency (*f*), expiration time (Te), inspiration time (Ti), total breathing time (Ttot), duty cycle (Ti/Ttot), breathing peak expiratory flow (Pef), breathing peak inspiratory flow (Pif). All values were averaged during 30 s. Breathing reserve (BR) was estimated from FEV_1 and $\dot{V}_E$ reached at maximal exercise, according to the following equation (15):

$$BR\ (\%) = [((FEV_1 \times 40) - \dot{V}_E) / (FEV_1 \times 40)] \times 100$$

Expired volume was measured at mouth with a pneumotachograph which was calibrated with a 3-liter calibration syringe. Subjects breathed through a pediatric mouthpiece maintained with a helmet.

During the graded exercise, a 12-lead electrocardiogram (Ergocard, Medi-soft, Dinant, Belgium) recorded the heart rate and an ear pulse oximeter (3800 S, Datex Ohmeda, Madison, USA) measured the SaO_2. Before exercise, the ear was warmed with a vasodilator ointment and the probe was kept in place on the ear by means of adhesive tape to avoid potential problems in signal recording. Moreover, the pulse oximeter evaluated waveform signal quality pulse-by-pulse indicating when problems associated with blood flow to the ear might influence SaO_2. The values of SaO_2 were recorded during the last 10 s of each minute only when the accuracy of the signal was optimal. At each minute during exercise, dyspnea rating scale (5) was showed to the subjects who had to point out a score with their finger

Blood measurements

Immediately after the end of the graded exercise test a finger-tip blood sample of 10 µL was collected to measure blood lactic acid concentration [La] using spectro-photometrical method (Miniphotometer LP 20, Dr Lange, Düsseldorf, Germany).

Determination of flow limitation and breathing strategy

To determine how close children came to an expiratory airflow limitation (expFL), tidal F-V loops recorded from a flow-sensing pneumotachograph coupled to the gas analyzer (Ergocard, Medi-soft, Dinant, Belgium). The tidal F-V loops were plotted during exercise within maximal expiratory F-V curve (MFVL) based measured before exercise (figure 1). The expiratory airflow limitation was defined as the part of the F-V loops that met the boundary of the expiratory portion of the MFVL measured before exercise. Expiratory airflow limitation was expressed in percentage of the V_T from the exercise. The breathing strategy is evidenced by the regulation of the end-expiratory lung volume (EELV) and the end-inspiratory lung volume (EILV). End-expiratory lung volume was determined by the inspiratory capacity (IC) relative to FVC (IC/FVC) and EILV by V_T relative to IC (V_T/IC) (15). Exercise tidal breaths were obtained over the last 20 s of each stage of exercise. A mean of 10 - 20 tidal breaths was average by a computer averaging program to provide a representative tidal F-V loop for that workload. Maximal IC maneuvers were carried out after the collect of the tidal breath at each work load in order to correct the drift problem in F-V sensing devices (15). Two groups were constituted based on the occurrence of expFL at peak exercise. The subjects were considered as flow limited (FL) when an expFL of at least 5 % was detected during exercise and persevere up to maximal exercise (6). Then, subjects with transient expFL during sub-maximal exercise were considered as non-flow limited (NFL).

Statistical analysis

All values are given as means ± SE. The statistical analysis was made using statistical software (SigmaStat 2.03, SPSS Science, Chicago, USA). Normality was controlled before each treatment. When normality passed, a t test was used to compare the values of each parameter between flow limited subjects and non flow limited. When the normality failed, a Mann-Whitney rank sum test was used for analysis. Linear regression test was used to search for correlations between the different parameters. The level of significance was set at $P<0.05$.

RESULTS

Data analysis identified two groups formed by subjects who presented an expFL and those who did not as defined in method part. Ten subjects presenting expFL (6 boys and 4 girls) comprised the flow limited group (FL). The non-flow limited group (NFL) was made up of the 8 remaining subjects (6 boys and 2 girls).

Anthropometrical and spirometrical data

The weekly physical activity was similar in FL than in NFL. No difference was found concerning age, size, weight, fat mass percentage, body mass index (BMI) and body surface area (BSA) between FL and NFL (table 1).

No significant difference was found in spirometrical data between both groups before exercise. No significant change was found concerning all the spirometrical data between before and after exercise (table 2).

Comparison of resting and sub-maximal exercise parameters between FL and NFL groups

At rest as during sub-maximal exercise, ,no significant difference was reported in $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $PetO_2$, $PetCO_2$ and SaO_2 between FL and NFL (table 3).

No difference was reported at rest concerning ventilatory and timing parameters between both groups (table 4). From 30 W up to 70 W, no significant difference was reported in Ti, Te, Ti/Ttot, Pif, BR, V_T/FVC and dyspnea between both groups (table 4). Lower Pef and $\dot{V}_E$ were measured at 30 W and 50 W respectively, in FL than NFL ($P<0.05$) (table 4) but no significant difference in $\dot{V}E$ relative to body mass was found between the groups (figure 2). From 30 W up to 50 W, significant lower *f* was reported in FL than NFL ($P<0.05$) associated with higher V_T relative to body mass ($P<0.05$) (figure 2).

As shown in figure 3A, transient expFL (i.e., values of expFL higher than zero) were observed in 3 children of the NFL group during sub-maximal exercise more particularly at 70 W (2 children), but these expFL did not persevere up to peak exercise. No significant difference in expFL was reported between both groups throughout sub-maximal exercise (figure 3A). At 50 W and 70 W, IC/FVC was higher in FL than in NFL ($P<0.01$) (figure 3B). Throughout submaximal exercise, no significant difference was reported in V_T/IC between both groups (figure 3C).

Comparison between FL and NFL groups at peak exercise

At peak exercise, a significant lower peak oxygen uptake ($\dot{V}O_{2peak}$) was reported in FL than NFL ($P<0.05$). As during submaximal exercise, no significant difference was found in $\dot{V}CO_2$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $PetO_2$, $PetCO_2$ and SaO_2 between both groups (table 3).

Significant lower $\dot{V}_E$ and Pif were observed in FL than in NFL at peak exercise and significant higher BR was reported in FL than NFL ($P<0.05$). No significant difference was found in Ti, Te and Ti/Ttot, Pef, V_T/FVC and dyspnea between both groups (table 4). No significant difference was reported for $\dot{V}_E$ relative to body mass, V_T, V_T relative to body mass and *f* between both groups (figure 2).

At peak exercise, expFL was only present in FL because the two groups were constituted according this parameter. Consequently, the mean value of expFL in NFL was zero and was statistically lower than in FL ($P<0.01$) (figure 3A). This difference in expFL between both groups at peak exercise was associated with higher IC/FVC ($P<0.01$) (figure 3B) and lower V_T/IC ($P<0.01$) (figure 3C) in FL than in NFL.

Relationships between respiratory parameters

In all subjects, significant relationships were reported between peak exercise values of expFL and IC/FVC ($P<0.01$; $r = 0.72$; $n = 18$) or V_T/IC ($P<0.05$; $r = 0.51$; $n = 18$) (figure 4A and 4B respectively). In FL, a significant relationship was found between peak exercise values of expFL and BR ($P<0.05$; $r = 0.69$; $n = 10$) (figure 4C). In this group, V_T/IC at peak exercise was significantly related to FEV_1 ($P<0.05$; $r = 0.76$; $n = 10$), PEF ($P<0.05$; $r = 0.77$; $n = 10$) and $MEF_{75\%}$ ($P<0.05$; $r = 0.77$; $n = 10$) (figure 5A, 5B and 5C respectively).

DISCUSSION

Our results showed that exercise expiratory flow limitation may occur in healthy prepubescent children (10 out of 18 subjects, ~ 55 %) when they performed a graded exercise test to exhaustion. The development of this expiratory flow limitation was associated with dissimilar breathing strategies between flow limited subjects and non-flow limited subjects. These different breathing strategies were reflected by significant higher IC/FVC and lower V_T/IC in flow limited subjects than in non-flow limited at peak exercise.

Exercise expiratory flow limitation in prepubescent children

We found that 10 subjects from 18 presented an expFL ranging from 16 % up to 78 % of V_T. In comparison, normal adult with average fitness may present expiratory flow limitations but generally near peak exercise and below 20 % of tidal breath (15). In this study, eight children of the ten FL subjects presented an expFL higher than 20 % although normal level of physical fitness and weekly physical activity. The prevalence of expFL in children in comparison with adults could be related to the fact that children are known to ventilate out of proportion to the metabolic demands of exercise (2, 7, 21). Therefore, the relative high ventilation level in children seemed to reach more easily the limit of the ventilatory function. This is in agreement with literature which reports lower values of breathing reserve in children than adults (20).

However, all the children did not present expiratory flow ventilation (8 from 18 subjects). This difference in children can not be explained by anthropometric difference between both groups because age, height, weight, fat mass percentage, BMI, BSA and FVC were not statistically different.

One explanation could be attributable to any differences in breathing pattern between the two groups of children. At 30 W and 50 W workloads, $\dot{V}_E$ and $\dot{V}_E$ relative to body mass were similar in both groups but significant lower *f* was observed in FL subjects than NFL. The lower *f* was compensated in FL by a higher tidal volume which explained that no difference was found for $\dot{V}_E$ or $\dot{V}_E$/kg during sub-maximal exercise. This difference in breathing pattern was associated with lower Pef at 30 W which support a slower and deeper breathing in FL than NFL at the sub-maximal of exercise. In contrast, at peak exercise, $\dot{V}_E$ was lower in FL subjects compared to NFL. This finding could be in opposition to what we would expected (i.e., FL should present the highest $\dot{V}_E$ achieving the pulmonary mechanical limits at peak exercise). The lower $\dot{V}_E$ in FL group could be due to the lower $\dot{V}O_{2peak}$ achieved by this group than NFL or by the fact that pulmonary function in FL children was mechanically limited and did not allow them to reach such high ventilatory levels than NFL.

Another explanation of the expiratory limitation occurrence could be the achievement of high ventilation levels and consequently of low BR at peak exercise in FL group. Surprisingly and in disagreement with this hypothesis, FL group presented lower BR than NFL. This result seems to emphasize the insufficiency of the breathing reserve measurement in order to estimate mechanical flow limitation in children. Nevertheless, we found even so a relationship in FL group only. This suggests that whether children were flow-limited, those who presented the lowest BR were also those who showed the greatest expiratory flow limitation. Therefore, as reported in literature (15), the BR seems not to be the most appropriate index to determine flow limitation in children but it could be related to the severity of expiratory flow limitation when it exits.

Finally, the last explanation for the expiratory flow limitation in prepubescent children could be a difference in breathing strategy, i.e., differences in the regulation of end-expiratory or inspiratory lung volume during exercise.

Difference in breathing strategy throughout the graded exercise between FL and NFL

In order to attenuate the heterogeneity in lung volume in the children population, we investigated breathing strategy by determining V_T/IC and IC/FVC ratios. When V_T/IC was high, it reflects a high EILV whereas a high IC/FVC reflects a low EELV (see methods). At 30 W workload, both children breathed at low lung volume (tendency to increase IC/FVC) as illustrated by the mean time course of F-V loops during exercise in figure 6. Hence, the breathing strategy at the beginning of a graded exercise in healthy children seems close to what is generally observed in the early stage of exercise in adults (3, 12, 15). Indeed, in normal adult, EELV decrease with exercise because of recruitment of expiratory muscles and EILV increases with rise in V_T (3, 12, 15). The partitioning of the increase in V_T over both the expiratory and inspiratory reserve volume in normal adult, also shares out the increase in work of breathing between expiratory and inspiratory muscles (3). But in our population, as the workload rose, V_E rose also and the breathing strategy of FL children (figure 6A) differed from NFL (figure 6B) more particularly at peak exercise.

In NFL, as ventilatory demand increased in parallel to workload, the children tend to decreased IC/FVC (i.e., increase EELV) back to resting value (figure 6B). This decrease in IC/FVC was associated in NFL with an increase in V_T/IC in order to preserve the exercise V_T and corresponded to a dynamic hyperinflation (15). Previous studies have shown that children ventilate out of proportion in comparison with adult (2, 7, 11, 22, 23). Then, it was not surprising that breathing strategy in NFL looked like this of trained adults rather than sedentary (13, 14, 18). Thus, the high level of ventilation at peak exercise could compel the children of the NFL group to breath at high lung volume in order to take advantage of the higher available maximal expiratory airflows, but also likely to avoid expiratory flow limitation (3, 4, 15). Therefore, this dynamic hyperinflation could reflect mechanical ventilatory constraints which could result to a decrease in inspiratory muscle length and induce an increase of the work and oxygen cost of breathing (15, 18).

In FL children, no dynamic hyperinflation occurred with increase exercise load as in NFL and in spite of the increase of expFL. In FL, IC/FVC remained relatively constant from the beginning of exercise up to peak workload explaining the significant difference between FL and NFL from 50 W up maximal exercise. Consequently, because V_T was similar at peak exercise between both groups, V_T/IC was lower in FL than in NFL. This breathing strategy had subsequent effect on expFL i.e., FL breathed closely to the low expiratory flow resulting in the occurrence of an expiratory flow limitation, more particularly at maximal exercise. This conclusion was strengthened by the significant relationships found between expFL and IC/FVC or V_T/IC. Hence, the more V_T shifted to the right (to the low pulmonary volume), the more V_T met the boundary of the maximal flow-volume curve. The failure to increase EELV and consequently EILV in presence of significant expFL could reflect an inspiratory muscles fatigue or co-existent elastic loading due to increased lung recoil or constraints imposed by chest wall (15). This could explain the lower $\dot{V}_E$ measured at maximal exercise in FL subjects than NFL. However, this difference in $\dot{V}_E$ could also be related to the lower $\dot{V}O_{2peak}$ reported in FL children than NFL. This lower $\dot{V}O_{2peak}$ could itself come from the lower $\dot{V}_E$ reached by the FL children and/or from a more economic breathing strategy associated with low EELV at peak exercise (15, 18). Nevertheless, we must interpret this relationship of cause and effect between $\dot{V}O_{2peak}$ and $\dot{V}_E$ very cautiously because $\dot{V}_E/\dot{V}O_2$ was not different between both groups.

Another concern was also why children may present two different breathing strategies. In FL group, the airway calibre reflected by maximal expiratory flows, was significantly related to the breathing strategy because significant relationships were found between V_T/IC and FEV_1 or

PEF or $MEF_{75\%}$. Indeed, children who presented the higher V_T/IC (i.e., the higher EILV) at maximal exercise were those who had the lower resting maximal expiratory flows of large airways (FEV_1, PEF, $MEF_{75\%}$). This suggests that the expiratory flow limitation could be related to the airway calibre. Lanteri et al. (17) reported dysanaptic development of the respiratory system from infancy up to adolescence (i.e., lung volume seemed increase at a greater rate than the increase in airway diameter). Now, the balance between lung compliance and airway resistance seems to strongly influence the work of breathing. Thus, the difference observed between both groups concerning breathing strategy could reflect a difference in maturation speed of the respiratory system between FL and NFL.

Nevertheless, even if the children of the present study present two different breathing strategies which evidenced ventilatory constraint and expiratory flow limitation in one group, ventilation was sufficient to supply the high oxygen demand at maximal exercise in all children. Indeed, no arterial desaturation was observed in both groups and $PetO_2$ as well as $PetCO_2$ did not evidenced relative hypoventilation. In addition, no difference was found for dyspnea, which suggests that ventilatory constraints in both groups did not induced specific exercise breathing feelings. However, our findings could open new perspectives in pulmonary investigation in exercising children, e. g., in highly endurance trained children who reach high metabolic demand and may present gas exchange impairment during intense exercise (19).

In conclusion, our study showed that some healthy children may present expiratory airflow limitation near peak exercise. This resulted from ventilatory constraints and different breathing strategies during exercise between flow-limited and non-flow limited children.

ACKNOWLEDGMENTS

We thank the Beuvry hospital which welcomed us for the experimentations, and all the children from the Jean Monnet primary Illies School who participated enthusiastically to this study and the Inpectection d'Académie of Lille (France).

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Table 1. ***Subject characteristics***

	FL	**NFL**
	(n = 10)	**(n = 8)**
Age (years)	9.8 ± 0.5	10.5 ± 0.4
Body mass (kg)	34.4 ± 3.4	41.1 ± 5.3
Height (cm)	135.9 ±2.6	142.5 ± 3.3
Fat mass percentage (%)	16.1 ± 2.8	16.6 ± 3.3
BMI ($kg.m^{-2}$)	18.3 ± 1.2	19.7 ± 1.8
BSA (m^2)	1.13 ± 0.06	1.26 ± 0.09
Physical activity per week (h)	1.9 ± 0.5	2.0 ± 0.8
[La]	5.6 ± 0.4	7.1 ± 0.6

Values are means ± SE. FL, flow limited group; NFL, non flow limited group; BMI, body mass index; BSA, body surface area. [La], blood lactate at peak exercise

Table 2. ***Lung function test data***

	FL (n = 10)		NFL (n = 8)	
	Measured	***% Predicted***	**Measured**	***% Predicted***
		pre-exercise		
FVC (L)	2.00 ± 0.14	*94.7 ± 3.7*	2.30 ± 0.23	*95.6 ± 6.4*
FEV_1 (L)	1.69 ± 0.11	*92.8 ± 3.2*	1.98 ± 0.20	*95.8 ± 7.3*
FEV_1/FVC (%)	87.5 ± 2.6	*102.9 ± 3.0*	86.3 ± 1.6	*101.5 ± 4.5*
PEF ($L.s^{-1}$)	3.35 ± 0.31	*89.0 ± 9.5*	3.71 ± 0.43	*86.5 ± 5.4*
$MEF_{75\%}$ ($L.s^{-1}$)	3.04 ± 0.27	*89.9 ± 8.9*	3.45 ± 0.34	*83.5 ± 6.5*
$MEF_{50\%}$ ($L.s^{-1}$)	2.16 ± 0.19	*87.0 ± 10.4*	2.72 ± 0.22	*90.2 ± 4.7*
$MEF_{25\%}$ ($L.s^{-1}$)	1.10 ± 0.11	*90.5 ± 10.9*	1.34 ± 0.11	*93.5 ± 9.4*
		post-exercise		
FVC (L)	2.01 ± 0.14	*95.9 ± 4.0*	2.29 ± 0.18	*96.8 ± 5.7*
FEV_1 (L)	1.69 ± 0.12	*94.1 ± 2.4*	2.04 ± 0.18	*101.5 ± 8.9*
FEV_1/FVC (%)	85.8 ± 2.4	*101.3 ± 3.1*	87.7 ± 2.2	*103.2 ± 2.6*
PEF ($L.s^{-1}$)	3.20 ± 0.32	*92.0 ± 7.2*	4.00 ± 0.24	*93.1 ± 6.9*
$MEF_{75\%}$ ($L.s^{-1}$)	3.01 ± 0.32	*80.3 ± 5.2*	3.67 ± 0.24	*97.8 ± 7.1*
$MEF_{50\%}$ ($L.s^{-1}$)	2.10 ± 0.21	*83.7 ± 11.4*	2.41 ± 0.24	*83.8 ± 6.6*
$MEF_{25\%}$ ($L.s^{-1}$)	1.16 ± 0.16	*96.1 ± 17.0*	1.43 ± 0.17	*96.5 ± 10.6*

Values are means ± SE. FL, flow limited group; NFL, non flow limited group; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; $MEF_{75\%}$, maximal expiratory flow at 75% of FVC; $MEF_{50\%}$, maximal expiratory flow at 50% of FVC; $MEF_{25\%}$, maximal expiratory flow at 25% of FVC.

Table 3. ***Metabolic variables during exercise***

	Rest	**30 W**	**50 W**	**70 W**	**Pmax**
			FL (n = 10)		
$\dot{V}O_2$ **(mL.min^{-1}.kg^{-1})**	7.1 ± 1.4	18.1 ± 1.2	24.4 ± 1.8	30.5 ± 2.4	36.3 ± 1.7*
$\dot{V}_E/\dot{V}O_2$	31.9 ± 2.5	30.6 ± 1.7	31.4 ± 1.5	36.0 ± 2.1	42.2 ± 2.1
$\dot{V}_E/\dot{V}CO_2$	38.4 ± 1.8	33.9 ± 1.4	32.1 ± 1.0	32.8 ± 1.2	34.6 ± 1.0
$PetO_2$	109.2 ± 2.4	105.8 ± 1.6	107.8 ± 1.6	111.7 ± 2.1	117.6 ± 1.8
$PetCO_2$	35.3 ± 0.9	37.8 ± 1.1	38.3 ± 0.7	36.7 ± 1.2	33.6 ± 1.1
SaO_2 (%)	97.8 ± 0.1	96.8 ± 0.3	96.8 ± 0.1	96.4 ± 0.4	95.7 ± 0.5
			NFL (n = 8)		
$\dot{V}O_2$ **(mL.min^{-1}.kg^{-1})**	7.4 ± 1.5	18.5 ± 1.7	24.4 ± 2.1	30.5 ± 2.6	41.6 ± 1.7
$\dot{V}_E/\dot{V}O_2$	33.3 ± 4.7	30.3 ± 1.6	31.1 ± 1.3	32.9 ± 1.3	39.1 ± 1.8
$\dot{V}_E/\dot{V}CO_2$	38.3 ± 2.9	35.0 ± 1.8	33.0 ± 1.5	32.9 ± 1.0	35.1 ± 1.3
$PetO_2$ (mmHg)	105.6 ± 4.7	103.9 ± 1.7	106.1 ± 1.1	109.3 ± 1.3	117.8 ± 0.8
$PetCO_2$ (mmHg)	34.0 ± 1.2	36.9 ± 1.3	36.9 ± 1.1	36.6 ± 0.7	31.4 ± 1.1
SaO_2 (%)	97.8 ± 0.2	96.8 ± 0.4	96.8 ± 0.2	97.0 ± 0.3	94.9 ± 0.8

Values are means ± SE. FL, flow limited group; NFL, non flow limited group; $\dot{V}O_2$, oxygen uptake; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $PetO_2$, end-tidal partial oxygen pressure; $PetCO_2$, end-tidal partial carbon dioxide pressure; SaO_2, arterial, oxygen saturation. Significant difference between FL and NFL: ***** $P<0.05$

Table 4. V*entilatory and timing variables during exercise*

	Rest	30 W	50 W	70 W	Pmax
			FL (n = 10)		
$\dot{V}_E$ (L.min^{-1})	7.7 ± 1.1	18.8 ± 1.3	25.4 ± 0.6**	35.9 ± 1.8	51.6 ± 3.4*
Ti (s)	1.63 ± 0.17	0.97 ± 0.09	0.83 ± 0.05	0.68 ± 0.06	0.51 ± 0.04
Te (s)	2.11 ± 1.40	1.20 ± 0.07	1.02 ± 0.07	0.76 ± 0.07	0.54 ± 0.04
Ti/Ttot	0.41 ± 0.07	0.44 ± 0.01	0.45 ± 0.01	0.47 ± 0.01	0.48 ± 0.01
Pif (L.s^{-1})	0.51 ± 0.07	1.01 ± 0.08	1.20 ± 0.04	1.54 ± 0.08	1.98 ± 0.14*
Pef (L.s^{-1})	0.53 ± 0.10	0.83 ± 0.08*	1.06 ± 0.16	1.46 ± 0.08	2.02 ± 0.14
V_T/FVC	24.5 ± 2.2	34.5 ± 2.4	40.1 ± 2.4	43.6 ± 2.7	45.7 ± 2.7
BR (%)	86.1 ± 1.7	66.5 ± 2.6	54.3 ± 3.8	35.1 ± 6.4	11.4 ± 3.3*
Dyspnea	0.0 ± 0.0	1.6 ± 0.5	2.6 ±1.0	3.4 ± 0.9	5.5 ± 0.7
			NFL (n = 8)		
$\dot{V}_E$ (L.min^{-1}	11.3 ± 2.1	21.9 ± 1.2	28.8 ± 1.0	38.3 ± 1.1	69.0 ± 6.7
Ti (s)	1.42 ± 0.18	0.80 ± 0.08	0.73 ± 0.07	0.64 ± 0.05	0.46 ± 0.02
Te (s)	2.38 ± 0.45	1.02 ± 0.09	0.88 ± 0.06	0.72 ± 0.07	0.51 ± 0.03
Ti/Ttot	0.43 ± 0.04	0.43 ± 0.01	0.45 ± 0.01	0.45 ± 0.01	0.47 ± 0.01
Pif (L.s^{-1})	0.54 ± 0.09	1.08 ± 0.05	1.30 ± 0.03	1.66 ± 0.05	2.53 ± 0.19
Pef (L.s^{-1})	0.60 ± 0.12	0.90 ± 0.04	1.16 ± 0.03	1.48 ± 0.06	2.46 ± 0.25
V_T/FVC	31.0 ± 4.2	29.5 ± 1.8	34.3 ± 1.8	38.8 ± 3.5	49.5 ± 2.0
BR (%)	84.5 ± 2.1	65.7 ± 4.7	54.6 ± 5.6	40.3 ± 6.5	-0.1 ± 3.7
Dyspnea	0.0 ± 0.0	1.0 ± 0.3	1.8 ± 0.4	2.3 ± 0.5	5.9 ± 1.0

Values are means ± SE. FL, flow limited group; NFL, non flow limited group; $\dot{V}_E$, ventilatory flow; Ti, inspiratory time; Te, expiratory time, Ti/Ttot, duty cycle; Pif, breathing peak inspiratory flow; Pef, breathing peak expiratory flow; V_T/FVC, volume tidal relative to forced vital capacity; BR, breathing reserve. Significant difference between FL and NFL: ***** P<0.05, ****** P<0.01

Figure 1

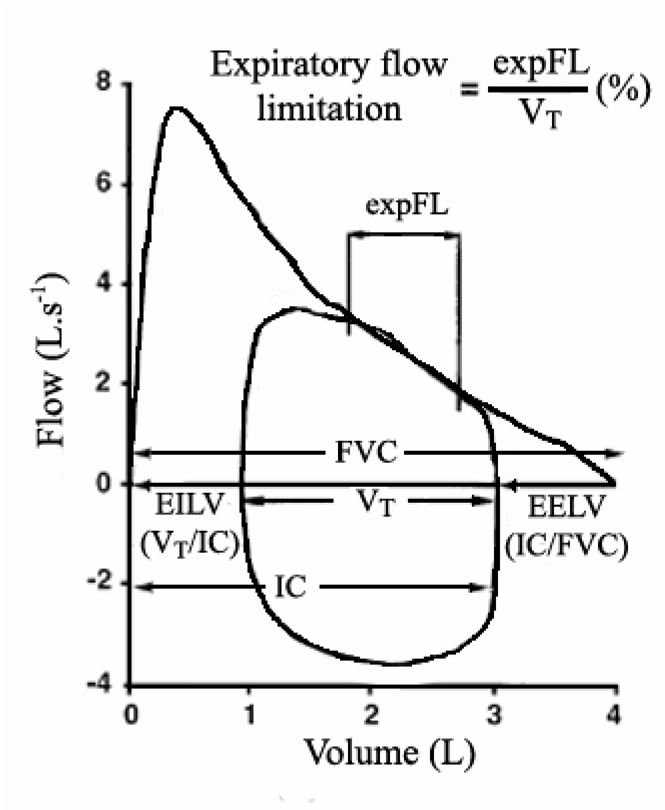
Expiratory flow limitation = expFL / V_T (%)
expFL
FVC
V_T
EILV (V_T/IC)
EELV (IC/FVC)
IC
Flow (L.s^{-1})
Volume (L)
8
6
4
2
0
-2
-4
0
1
2
3
4

Figure 2

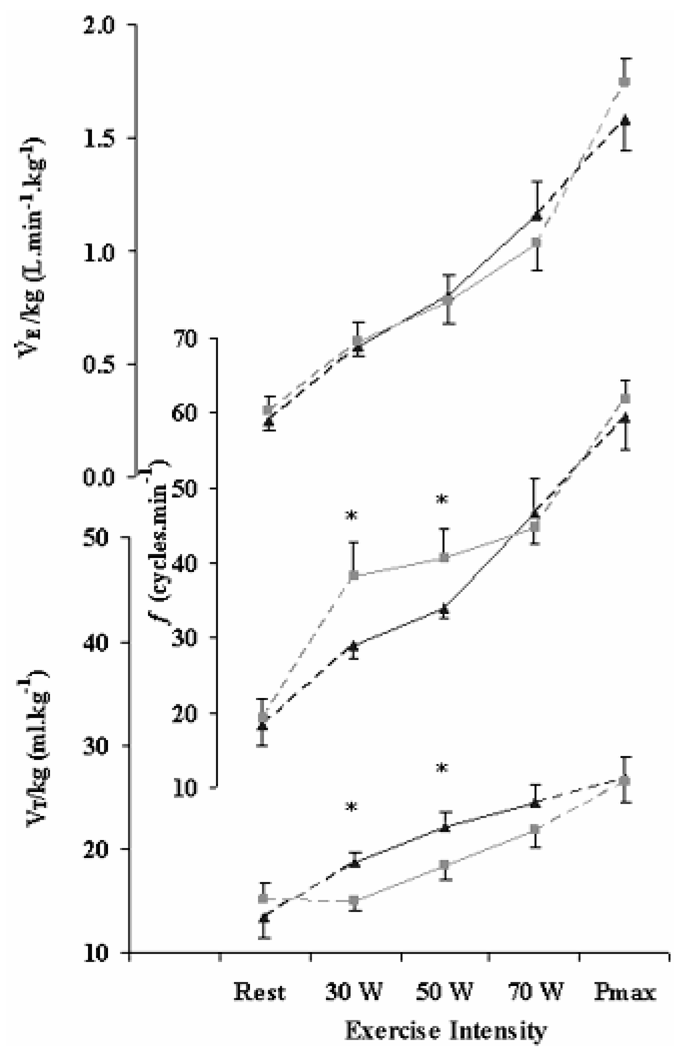
2.0
1.5
1.0
0.5
0.0
$\dot{V}_E$/kg (L.min^{-1}.kg^{-1})
70
60
50
40
30
20
10
f (cycles.min^{-1})
50
40
30
20
10
V_T/kg (ml.kg^{-1})
*
*
*
*
Rest
30 W
50 W
70 W
Pmax
Exercise Intensity

Figure 3

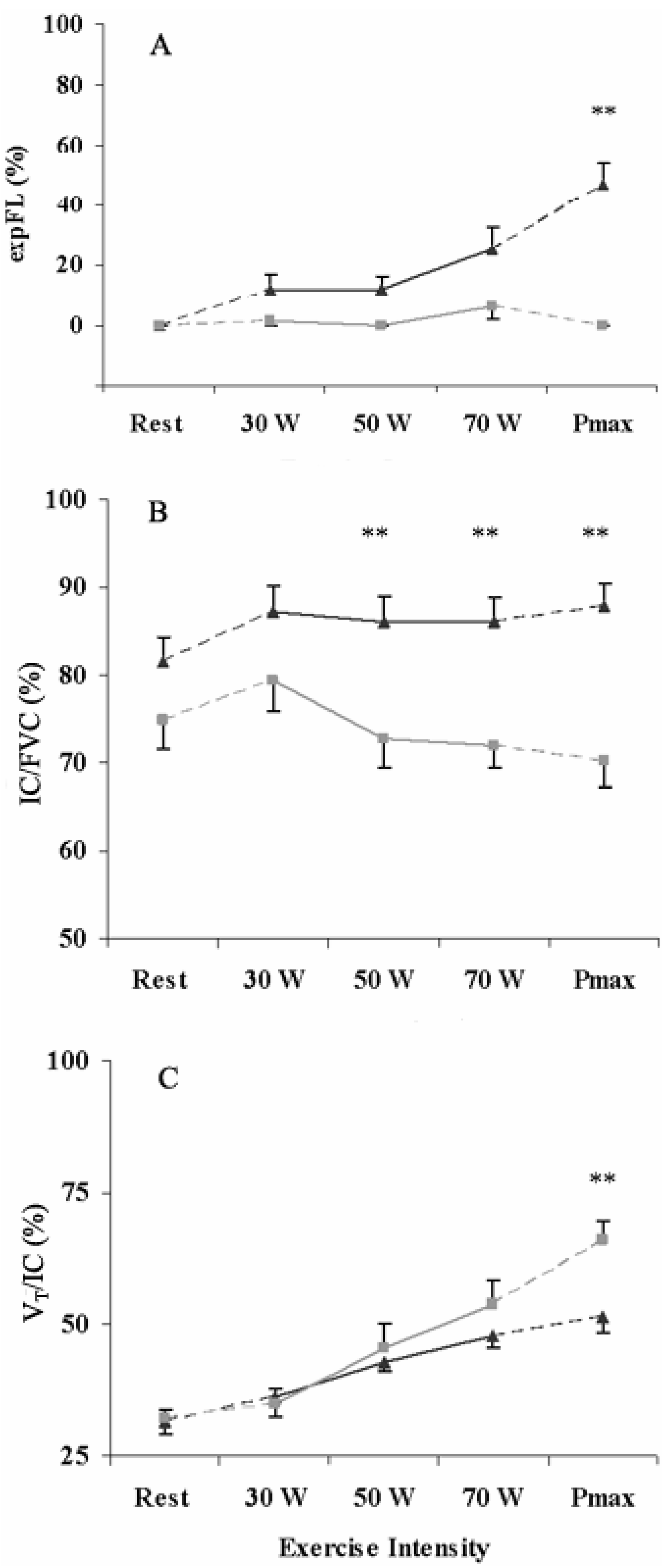
A
expFL (%)
100
80
60
40
20
0
**
Rest
30 W
50 W
70 W
Pmax
B
IC/FVC (%)
100
90
80
70
60
50
**
**
**
Rest
30 W
50 W
70 W
Pmax
C
V_T/IC (%)
100
75
50
25
**
Rest
30 W
50 W
70 W
Pmax
Exercise Intensity

Figure 4

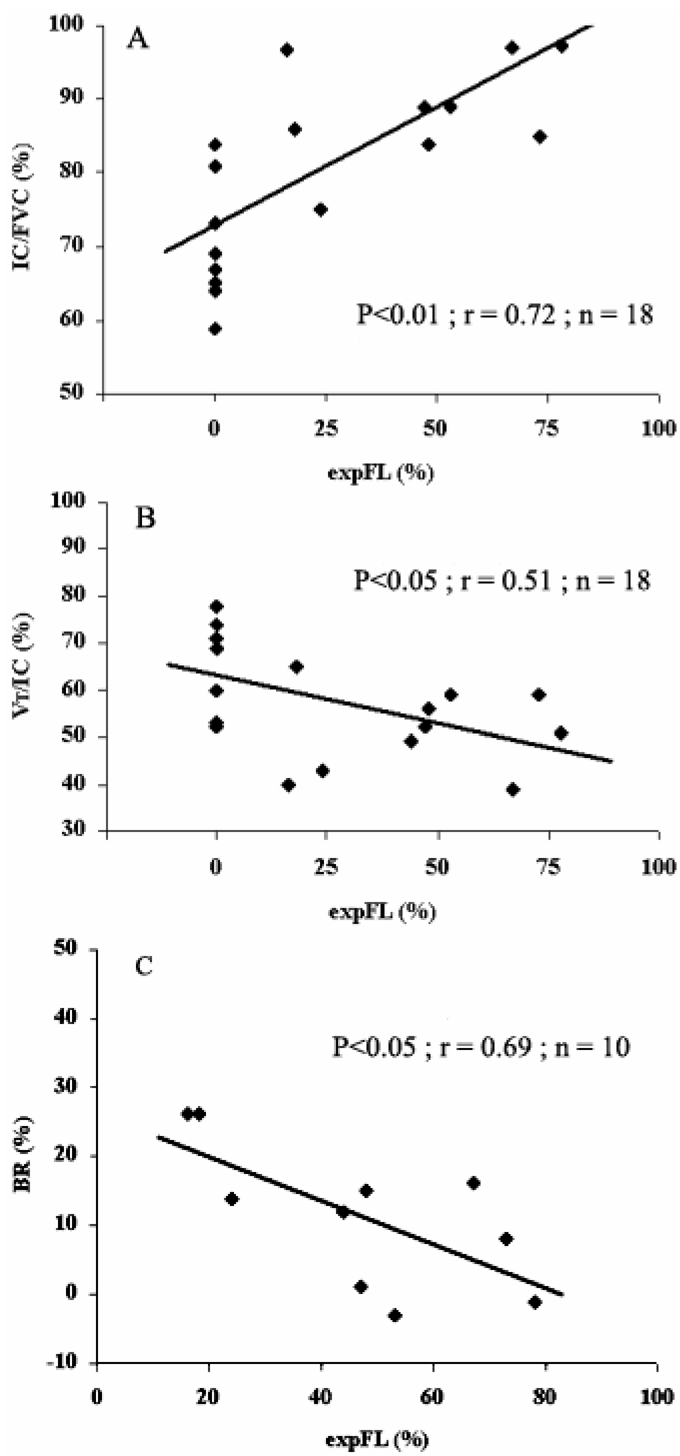
A
IC/FVC (%)
P<0.01 ; r = 0.72 ; n = 18
expFL (%)
B
VT/IC (%)
P<0.05 ; r = 0.51 ; n = 18
expFL (%)
C
BR (%)
P<0.05 ; r = 0.69 ; n = 10
expFL (%)

Figure 5

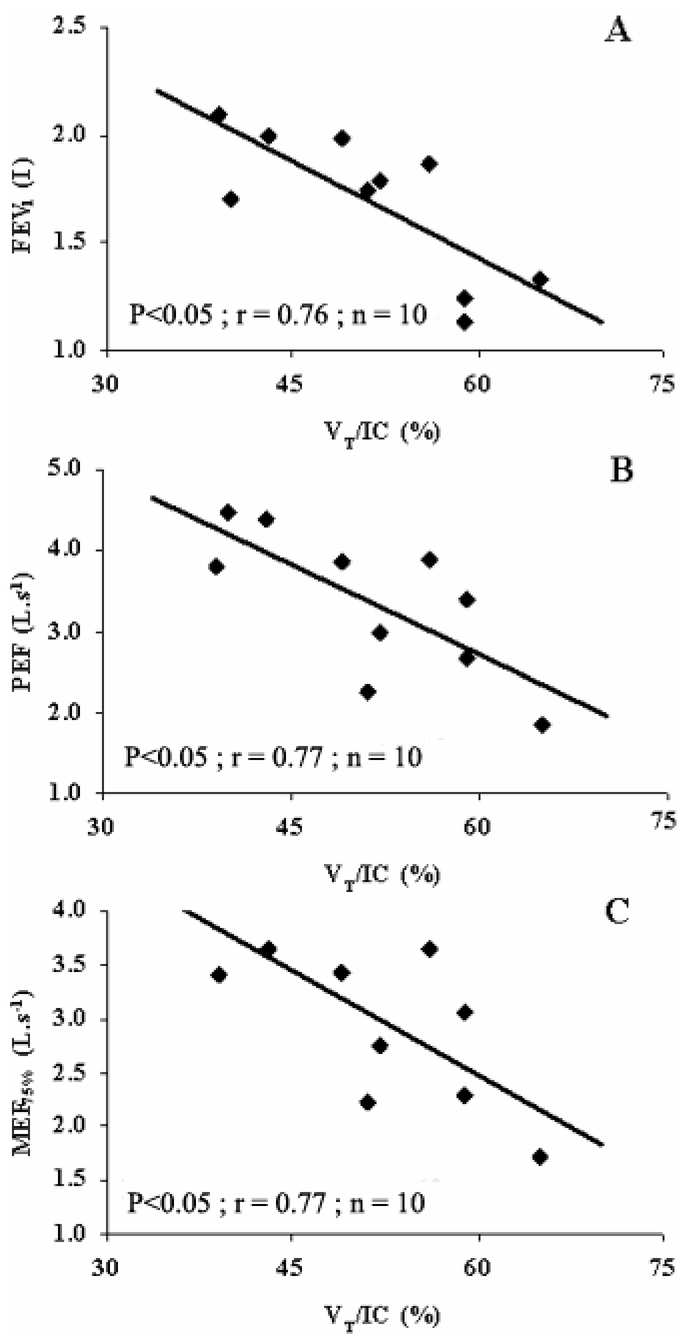
A
2.5
2.0
1.5
1.0
FEV1 (l)
P<0.05 ; r = 0.76 ; n = 10
30
45
60
75
VT/IC (%)
B
5.0
4.0
3.0
2.0
1.0
PEF (L.s-1)
P<0.05 ; r = 0.77 ; n = 10
30
45
60
75
VT/IC (%)
C
4.0
3.5
3.0
2.5
2.0
1.5
1.0
MEF50% (L.s-1)
P<0.05 ; r = 0.77 ; n = 10
30
45
60
75
VT/IC (%)

Figure 6

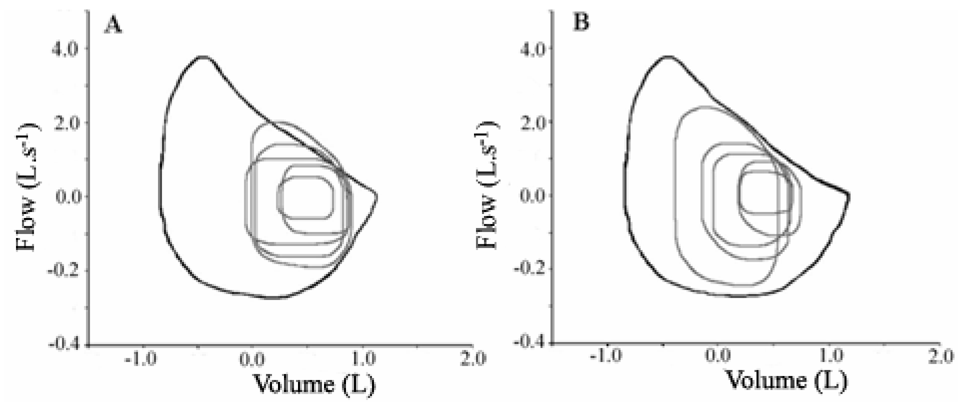

Figure 1: Exercise tidal breath plotted within the maximal expiratory flow volume loop measured at rest (MFVL). FVC, forced vital capacity; V_T, tidal volume; IC, inspiratory capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume. The expiratory flow limitation (expFL) is expressed in percentage of V_T and corresponds to the part of the tidal breath that meets or exceeds the boundary of MFVL.

Figure 2: Breathing pattern during graded exercise in FL subjects (▲) and NFL subjects (■). $\dot{V}_E$/kg, minute ventilation relative to body mass; V_T/kg, tidal volume relative to body mass; *f*, breathing frequency. Significant difference between both groups: ***** ($P<0.05$).

Figure 3: Flow-volume loops parameters during exercise in FL subjects (▲) and NFL subjects (■): (A) Expiratory flow limitation (expFL) expressed in % of tidal volume, (B) inspiratory capacity relative to forced vital capacity (IC/FVC), (C) tidal volume relative to inspiratory capacity (V_T/IC). Significant difference between groups: ***** ($P<0.05$), ****** ($P<0.01$).

Figure 4: Relationship between expiratory flow limitation (expFL) at peak exercise (expressed in % of tidal volume) and (A) inspiratory capacity relative to forced vital capacity (IC/FVC), (B) tidal volume relative to inspiratory capacity (V_T/IC), (C) breathing reserve. All the subjects were taken in account in (A) and (B). Only FL was concerned in (C), the relationship with all the subjects was not statistically significant.

Figure 5: Relationships in FL between volume relative to inspiratory capacity (V_T/IC) and (A) forced expiratory volume in one second (FEV_1), (B) peak expiratory flow (PEF), (C) maximal expiratory flow at 75 % of forced vital capacity ($MEF_{75\%}$).

Figure 6: Representative tidal flow-volume loops of mean response to graded exercise at rest, 30 W, 50 W, 70 W and peak exercise plotted within the pre-exercise maximal flow-volume curve, in FL subjects (A) and NFL subjects (B).