



Supervised exercise training improves endothelial function in COPD patients: a method to reduce cardiovascular risk?

To the Editor:

Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of cardiovascular diseases, particularly coronary artery disease (CAD) [1]. Endothelial dysfunction is a marker of cardiovascular risk [2]; a validated and standardised method to assess endothelial function is flow-mediated dilation (FMD) [3].

Previous studies have shown impaired endothelial function in COPD patients compared to that in healthy subjects [4, 5], with intermediate function between CAD patients and healthy subjects [6].

Endothelial function is positively associated with physical activity and is improved by exercise training in sedentary elderly subjects and cardiac patients [7]. Regarding COPD, this relationship has been reported in retrospective studies, but has not been confirmed in prospective studies [8, 9].

The objective of the present study was to determine whether an 8-week supervised walking-based training programme can improve endothelial function in COPD.

20 COPD (14 males and six females) with forced expiratory volume in 1 s (FEV_1) $\geq 30\%$ and $\leq 80\%$ predicted [10] who were in a stable clinical condition for ≥ 6 weeks were consecutively recruited from the Respiratory Disease Outpatient Clinic, Ferrara University Hospital (Italy). Exclusion criteria were: 1) major cardiovascular diseases (*i.e.* CAD, uncontrolled hypertension, arrhythmias or heart failure); 2) orthopaedic and neuromuscular exercise limitations; and 3) current structured exercise performance.

The Ethics Committee of Ferrara University approved the study (number 140794). Each subject gave informed consent.

At baseline (t_0), all patients underwent spirometry and a 6-min walk test (6MWT) [11]. The Charlson Comorbidity Index was calculated and a blood analysis (≤ 3 months) was collected.

On a separate day, blood pressure was measured in triplicate after 20 min of rest and the FMD test was subsequently performed on the opposite arm.

Daily physical activity was monitored for 7 days with the activity and metabolic Holter SenseWear Armband (BodyMedia, Pittsburgh, PA, USA).

An 8-week supervised walking-based training programme was described, and the subjects were randomised into two groups: exercise and control. Neither group changed medication; the control group maintained their lifestyle habits, checked with a questionnaire [12].

The exercise group performed a maximal incremental cardiopulmonary exercise test on a cycle ergometer ($10\text{--}15\text{ W}\cdot\text{min}^{-1}$) to determine the exercise capacity.

After 8 weeks (t_1), the subjects repeated all the tests.



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Exercise training, supervised by an exercise expert, was performed on a treadmill two times per week for 8 weeks. In addition, two 30-min home sessions were recommended. The patients trained at moderate intensity (60–70% of the maximum heart rate) with a Borg score of 5–6 out of 10. The workload was increased throughout the 8 weeks according to the perception of dyspnoea. The training session duration increased from 20 to 40 min.

All measures were performed by the same expert technician according to the recommendations of THIJSSSEN *et al.* [3]. A 12-MHz linear array ultrasound probe was positioned above the antecubital fossa of the brachial artery. Reactive hyperaemia was induced by inflating the cuff (positioned around the forearm) to 200 mmHg or 50 mmHg above the systolic pressure for 5 min. After deflation, images were continuously recorded for 2 min. Data were analysed using FMD-i software (Flowmedi, Brussels, Belgium). FMD was expressed as the change in the percentage of the baseline diameter.

All analyses were blinded.

Statistical analysis was performed with MedCalc version 15.6.1 (Ostend, Belgium). ANOVA was used to verify the differences between the two groups and between t_0 and t_1 . To improve the accuracy of the FMD data, the analysis was corrected for the baseline artery diameter. Cohen's coefficient D was used to verify the effect size. The accepted level of significance was $p \leq 0.05$.

All subjects completed the study. In table 1, the anthropometric, clinical and functional data are reported.

TABLE 1 Anthropometric, clinical and functional data of the subjects, randomised into two groups: exercise and control

	Exercise	Control	p-value
Subjects n	10	10	
Age years	70±9	70±7	0.85
BMI kg·m⁻²	29±6	28±4	0.42
Charlson Comorbidity Index score	4±1	4±1	0.83
Laboratory parameters			
Total cholesterol mg·dL ⁻¹	217±55	209±34	0.74
HDL mg·dL ⁻¹	71±32	53±11	0.17
Glucose mg·dL ⁻¹	99±13	104±6	0.42
Smokers			
Ex-smokers	6 (60%)	9 (90%)	
Current smokers	3 (30%)	1 (10%)	
Exposure pack-years	50±28	41±19	0.40
Respiratory function			
FEV ₁ % pred	56±13	62±13	0.33
Physical activity			
Average METs per day	1.14±0.16	1.26±0.16	0.11
Steps per day	4712±3035	6534±2702	0.17
Exercise capacity			
6MWT m	351±66	398±49	0.09
Blood pressure mmHg			
Systolic/diastolic blood pressure at t_0	140±20 [¶] /80±7 ⁺	133±9/ 79±5	0.30/0.70
Systolic/diastolic blood pressure at t_1	130±14 [¶] /74±6 ⁺	131± 9/ 78±5	0.85/0.09
Endothelial function test			
t_0			
Baseline artery diameter mm	3.9±0.7	4.4±0.6	0.13
FMD [#] %	3.7±1.1	4.5±0.9	0.08
Time to peak s	57±3	60±6	0.29
t_1			
Baseline artery diameter mm	3.7±0.8	4.4±0.5	0.05
FMD [#] %	6.7±2.2	4.1±0.9	0.003
Time to peak s	55±4	61±6	0.03
ΔFMD t_1-t_0	+3.04±1.97	-0.37±0.73	0.00007

Data are presented as mean±SD unless otherwise stated. BMI: body mass index; HDL: high-density lipoprotein; FEV₁: forced expiratory volume in 1 s; MET: metabolic equivalent of task; 6MWT: 6-min walking test; t_0 : baseline; t_1 : 8 weeks; FMD: flow-mediated dilation. #: corrected for baseline diameter; [¶]: $p=0.003$ (at t_0 versus t_1); ⁺: $p=0.009$ (at t_0 versus t_1).

There were no significant differences between the groups at t_0 in age, body mass index, pulmonary function, comorbidities, 6MWT, blood pressure or daily activity.

The exercise group completed the intervention programme with an adherence of 98%. No adverse events occurred during the training.

The average walking speed at t_0 was $2.4 \pm 0.7 \text{ km} \cdot \text{h}^{-1}$ and at t_1 , was $3.0 \pm 0.8 \text{ km} \cdot \text{h}^{-1}$; the average duration of each training session at t_0 was $29 \pm 8 \text{ min}$ and at t_1 was $47 \pm 4 \text{ min}$.

At t_1 , the exercise group showed an increased exercise capacity (maximum at t_0 $71 \pm 29 \text{ W}$, t_1 $82 \pm 25 \text{ W}$; $p=0.02$), and reductions in blood pressure and perceived dyspnoea (Borg score at t_0 8 ± 1 , t_1 6 ± 2 ; $p=0.03$).

At t_0 , no significant differences were found between the two groups in baseline arterial diameter, FMD or the time to peak ($p>0.05$). After 8 weeks, only the exercise group showed an improvement in FMD ($p=0.0009$, *versus* $p=0.15$ in the control group). The effect size was 1.7 (Cohen's D), which indicates a "very large" effect of exercise training on endothelial function.

The main result of this study is that an 8-week supervised exercise training programme significantly improved endothelial function in COPD. Regarding this topic, contradictory results have been reported in the literature [6, 8, 9, 13]; however, two recent systematic reviews demonstrated that a high percentage of COPD patients have impaired endothelial function, as assessed by FMD [4, 5].

Regarding exercise training, it is known that physical activity can improve endothelial function in healthy subjects and in patients suffering from chronic diseases, especially cardiac and metabolic diseases [7]. According to TINKEN *et al.* [14], exercise-induced increases in shear stress are responsible and essential for the beneficial impact of exercise training on vascular function and structure in healthy humans.

Regarding COPD, the information is limited and conflicting. When the present study was designed, there were no prospective studies investigating the effect of exercise training programmes on endothelial function in COPD, and the evidence was based on retrospective analysis [8, 15] showing that endothelial function was positively related to physical activity level and exercise capacity. While this study was ongoing, one prospective study was published by GELINAS *et al.* [9]. They analysed the effect of 8 weeks of training in 24 moderate COPD patients compared to the effects in well-matched, healthy subjects. They showed no significant improvement in FMD in either group, speculating that this result could be the consequence of inadequate exercise intensity. However, the patients' respiratory function and FMD were less impaired than those of the participants in the present study, making comparisons difficult.

Another interesting result of our study is that a walking-based 8-week exercise training programme can increase FMD but not arterial diameter. This finding is in accordance with a meta-analysis published by EARLY *et al.* [7]. Based on 66 studies published from 1999 to 2013, exercise training interventions significantly improve brachial artery FMD but not the baseline diameter, both in healthy subjects and in patients with cardiovascular and metabolic diseases. In the latter, the effect on FMD was larger with higher-intensity and longer-duration exercise. We cannot exclude the possibility that longer exercise programmes could also affect the brachial artery baseline diameter.

The main limitation of this preliminary report is the small sample size; the results must be confirmed in a larger sample.

In conclusion, exercise-based pulmonary rehabilitation, in addition to the known positive effects on FEV_1 decline and the risk of hospitalisation in COPD patients, could have an effect on cardiovascular health. To confirm this hypothesis, prospective, controlled studies are needed.

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