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ABSTRACT

Background Regular exercise positively affects cardiovascular physiology, translating into the adequate capacity of microvascular blood vessels to dilate in response to acute bouts of exercise. However, this remains unstudied in patients with chronic obstructive pulmonary disease (COPD), who often suffer from cardiovascular comorbidity. Therefore, we studied acute changes in retinal blood vessel diameters in response to high-intensity exercise in patients with COPD. The effect of an exercise-based 8-week pulmonary rehabilitation (PR) program was evaluated. We consider changes in these retinal metrics as an indicator of microvascular reactivity.

Methods Demographics and clinical characteristics of 41 patients were collected at the start and end of the PR program. Patients performed a high-intensity exercise test on a cycle ergometer at the start and end of the PR program, during which we collected retinal images. Fundus images were taken immediately before and 0, 5, 10, 15, and 30 minutes after the ergometer test. Widths of retinal blood vessels, represented as Central Retinal Arteriolar and Venular Equivalents (CRAE and CRVE), were calculated.

Results Thirty patients with COPD completed the study protocol (57% males; mean age: 64±7 years; mean FEV_1: 45±17 %pred). We did not observe a change in retinal vessel widths following the ergometer test at the start of the PR program. This null result remained at the end of the 8-week PR program. Our observations did not alter when considering responders and non-responders to PR.

Conclusion Retinal blood vessel diameters of patients with COPD did not change following an exercise test on an ergometer. The exercise-based PR program of eight weeks did not counteract the blunted retinal microvascular response.

INTRODUCTION

Persistent respiratory symptoms and airflow limitation characterize chronic obstructive pulmonary disease (COPD). These effects occur because of airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases [1]. However, COPD is more than respiratory disease.[1] Cardiovascular disease is common in patients with COPD.[2] Impaired vascular reactivity may represent a pathophysiological link between COPD and cardiovascular disease.[3, 4]

Analysis of the microvasculature using fundus imaging is a non-invasive technique to assess cardiovascular risk and disease state.[5, 6] Cohort studies showed that narrower retinal arteriolar diameters strongly associate with hypertension and wider retinal venular diameters are associated with obesity, dyslipidaemia, hyperglycaemia, and inflammatory markers.[5, 7]

Earlier studies in healthy adults and cardiac patients also showed dilatation of retinal blood vessels in response to acute dynamic exercise, suggesting a preserved endothelial function.[8-10] Regular exercise can improve the functional status of retinal blood vessels and contribute to retinal microvascular

reactivity.[9, 11, 12] Decreased arteriolar and venular retinal microvascular responses, measured via changes in retinal blood vessel widths, have been reported in cardiac patients compared to age-matched healthy controls. Exercise training appeared to induce beneficial effects because the microvascular responses of cardiac patients improved and became comparable to those of healthy controls after six weeks of exercise training.[9]

This study investigated acute changes in retinal blood vessel diameters in response to high-intensity exercise in patients with COPD as an indicator of microvascular reactivity. In addition, we studied the effect of an exercise-based 8-week pulmonary rehabilitation (PR) program on retinal microvascular reactivity. We hypothesized that the response of retinal blood vessel diameters following exercise is impaired in patients with COPD because of endothelial dysfunction.[4] We expected this response to improve at the end of the PR.

METHODS

Study design

This research was embedded in the principal study, in which we investigated microvascular changes and microvascular reactivity in stable patients with COPD using non-invasive retinal imaging.[13] The Medical Research Ethics Committees United (Nieuwegein, the Netherlands) approved the current research study (R16.020). The study was registered on www.trialregister.nl (NTR5896) before enrolment of the first volunteering participant. All patients gave written informed consent before inclusion.

Patients were recruited at Ciro (Horn, the Netherlands) before starting a comprehensive PR program between July 2016 and July 2017. Patients were eligible to participate in this study when they had a COPD diagnosis and had no acute exacerbation in the previous four weeks. Patients with abnormalities in the lens or retina, leading to a difficult retina visualization, were excluded. Patients with known retinal diseases and patients who could not provide informed consent because of cognitive problems or inability to speak and understand Dutch or English were excluded.

All patients with COPD participated in a comprehensive eight-week inpatient PR program at Ciro,[14] as defined by the latest international American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation.[15] Patients underwent a baseline and outcome assessment as described before.[16] PR comprised group-based exercise training, including strength training and high-intensity interval training on a stationary cycle ergometer (12x1 min exercise at 80% of maximal exercise capacity (Wmax) alternating with 1 min rest), and treadmill (12x1 min exercise at 100% of average speed on six-minute walk test (6MWT) alternating with 1 min rest). The PR program also included non-exercising components, such as occupational therapy, nutritional counselling, psychosocial

counselling, breathing strategies, exacerbation management, optimizing medication use, and educational sessions.

Retinal imaging

During the first and last week of PR, two high-resolution images of the fundus of the right eye were taken immediately before, 5, 10, 15, and 30 minutes after the high-intensity interval test on a stationary cycle ergometer (12x1 min exercise at 80% of maximal exercise capacity (Wmax) alternating with 1 min rest). We collected the images using a Canon CR-2 45° 6.3 megapixels static non-mydriatic fundus camera (Hospithera, Belgium). A trained grader masked to patient characteristics analyzed the retinal images using semi-automated MONA REVA vessel analysis software (version 2.1.1) developed at VITO (Belgium; http:\\mona.health).[17] The diameters of the retinal arterioles and venules that passed entirely through the circumferential zone 0.5 to 1 disc diameter from the optic disc margin were calculated automatically using the software. The trained grader verified and corrected vessel diameters and vessel labels (arteriole or venule) with the vessel editing toolbox. We used the diameters of the 6 largest arterioles and 6 largest venules in the revised Parr-Hubbard formula for calculating the Central Retinal Artery Equivalent (CRAE) and Central Retinal Venular Equivalent (CRVE).[18, 19] We could not synchronize image collection with blood pressure on the cardiac cycle. Instead, we averaged the results from the two consecutively taken images to minimize random variation in retinal vessel diameter that may have come with blood pressure variations or different cardiac cycle stages. [20] We expressed changes in retinal blood vessel diameter in response to exercise as absolute changes.

Statistics

Data are presented as mean and standard deviation (SD) unless noted otherwise. Sample size was calculated using G*Power 3.1.9.4. With an estimated dropout rate of 15%, a sample size of 33 allows detecting a moderate effect size (0.55) with 80% power and a two-sided significance level of 5%. Mixed models analysis for repeated measurements was used to investigate changes in retinal blood vessel diameter in response to exercise, with each patient serving as his/her control over time, and corrected for age, sex, body mass index (BMI), smoking status, diabetes, hypertension, dyslipidaemia, cardiovascular comorbidities, pulmonary and cardiovascular medication and fellow vessel diameter (i.e. for CRVE models of CRAE, and vice versa). We compared retinal blood vessel response pre and post PR with a mixed model including an interaction term (time point retina image*pre/post PR). A sensitivity analysis evaluated potential differences induced by high-intensity exercise. For this analysis, we used ten patients with the highest (best responders) and ten patients with the lowest (worst responders) sum of Z-scores for change in six-minute walk test (6MWT) and cycle endurance time on

the constant work rate test (CWRT) following PR. All analyses were performed using SPSS 25.0 (SPSS Inc; Chicago, Illinois).

RESULTS

Two hundred and eight patients with COPD referred for a PR program at Ciro were screened between July 2016 and July 2017. One hundred and fifty-eight patients were ineligible for various reasons, including clinical instability, abnormalities of the lens, or inability to perform high-intensity exercise training. In addition, nine eligible subjects declined participation because of disinterest. Of the 41 patients who underwent fundus photography at the start of PR, 11 patients had no measurement after PR because of an exacerbation (n=3), inability to perform high-intensity training during PR (n=3), a dropout from PR (n=4), or recent eye problems (n=1). Finally, 30 patients completed the study. We observed no significant differences in baseline characteristics between participants who completed the study and those who left the study.

Characteristics

Table 1 lists the characteristics of the participants. Slightly more than half of the patients were males, and the mean age was 64±7 years. Patients had mild to very severe COPD based on the GOLD classification. In addition, 60% of the patients were hypertensive, and blood tests confirmed that 40% had (pre)diabetes, 77% had dyslipidaemia, and 15% had elevated levels of high-sensitivity C-reactive protein (hs-CRP), an indicator of the general level of inflammation. Patients showed impaired aerobic capacity, as assessed by CPET (58% pred) and 6MWT (65% pred). A mean (SD) CRAE of 153.8 (11.4) µm and mean (SD) CRVE of 233.5 (18.4) µm characterized the retinal microvasculature.

Exercise capacity significantly improved following PR (mean change (SD) 6MWT: +24 (48) m and CWRT: +415 (373) s; $p<0.01$). We found no significant changes in retinal blood vessel diameters at the end of PR.

Retinal blood vessel response to exercise

We investigated the reactivity of the retinal microvasculature in patients with COPD and the potential effect of a PR program. We evaluated reactivity with repeated retinal blood vessel diameter measurements following an exercise challenge on a stationary cycle ergometer at the start and the end of the program. Although the bout of exercise seemed to trigger a retinal arteriolar constriction that lasted until 15 minutes after exercise, changes from baseline CRAE were not significant (Figure 1a, Table 2). In addition, dilation of retinal venules in response to the ergometer test was not significant before the PR program started (Figure 1b, Table 2). At the end of the 8-week of PR, the retinal arteriolar diameters were wider immediately after the ergometer test, but there were no significant changes

compared to the baseline CRAE (Figure 1a, Table 2). Similarly, wider retinal venular diameters after the ergometer test were not significant relative to the baseline CRVE (Figure 1b, Table 2). A sensitivity analysis with best responders and worst responders to the PR program did not find significant differences in retinal blood vessel reactivity ($p>0.05$ for all time points).

DISCUSSION

This study evaluated the acute effects of exercise on the microvasculature in patients with COPD. Our findings showed no significant changes in retinal blood vessel diameters in response to a bout of exercise on an ergometer. An 8-week PR program did not improve the retinal blood vessel reactivity.

Similar to earlier studies, we used retinal blood vessel diameter changes in response to exercise to measure microvascular reactivity.[8, 9] Microvascular reactivity is documented as a microvascular marker of endothelial function.[22, 23] Previous studies in healthy individuals already showed that exercise influences retinal microvascular function. Indeed, previous studies report acute bouts of exercise to induce retinal blood vessel dilation, lasting for at least 30 minutes after exercise.[8, 9, 24] In the current study with COPD patients, retinal blood vessel diameters did not significantly change after an ergometer test. This absence of a response could be because of the inadequate endothelium-mediated vasodilatory response, often present in COPD patients.[4] In addition, the intensity of the exercise test may not be high enough to elicit a response. Indeed, in healthy adults, the changes in CRAE and CRVE were bigger after a maximal exercise test compared to a submaximal exercise test.[8]

Regular exercise and physical activity can improve retinal microvascular reactivity.[9, 11, 12] The PR program in the current study improved patients' physical fitness, evidenced by a significant improvement in the performance on the 6-minute walk test and the constant work rate test. However, we did not observe a better retinal blood vessel reactivity at the end of the PR program. It is worth mentioning that we did not design this PR program to improve microvascular structure and function. It is possible that the duration of the exercise-based PR program may have been too short or that the exercise modalities may not provide optimal stimuli for more pronounced effects on vascular health in patients with COPD.[25] To date, only limited evidence is available on the effects of regular exercise on vascular function in patients with COPD. These studies focused on endothelial function in COPD and showed conflicting findings.[26-28] Differences in baseline patient characteristics (age, disease severity) and possibly varying exercise intensities or durations may explain these differences.

This study is the first to measure microvascular responses using retinal blood vessel analysis during a COPD PR program. Our study setup was convenient to execute, with high patient compliance. We studied a cohort of comprehensively profiled patients in a structured and state-of-the-art PR program. However, the study comes with the following limitations. We measured retinal blood vessel response using time series of static retinal images taken immediately before and after the ergometer test.

Dynamic vessel analysis (DVA) after flicker response could be investigated in follow-up studies. DVA assesses microvascular reactivity and autoregulation, which might detect subclinical endothelial dysfunction in the microvasculature and facilitate the early diagnosis of cardiovascular diseases.[22, 23] We did not measure systemic blood pressure and intraocular pressure. Suppose mean ocular perfusion pressure did not change beyond the autoregulatory capacity, then impaired retinal blood vessel response will not necessarily only reflect an impaired endothelial function. We did not include a healthy control group. Our primary aim was to investigate the effect of exercise on the retinal blood vessel response in COPD patients and not to compare the response with healthy controls. The literature already reports dilation of the retinal blood vessels of healthy adults in response to exercise.[8, 9, 11] The comparison between different studies requires caution because of the use of different retinal vessel measurement software systems. Absolute retinal vessel measurements obtained with software packages show poor agreement and this complicated interpretation between studies.[29] Our sample size was relatively small. Therefore, the study might be underpowered to demonstrate changes in retinal vessel diameter in response to exercise and compare between best and worst responders to PR. However, our power calculation indicated the feasibility of detecting significant changes in a study of this size. The proportion of patients in GOLD stage I was relatively small, and therefore we should be cautious about generalizing findings to the whole COPD population.

To conclude, the retinal blood vessel response to exercise is impaired in patients with COPD and does not improve after an exercise-based PR program. We need additional studies to corroborate our findings, including studies using dynamic retinal vessel analysis, and evaluate the clinical relevance of an impaired microvascular reactivity in patients with COPD.

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Table 1 Patients characteristics (n=30). Values are given as mean (standard deviation) or as a percentage. Changes in exercise capacity and retinal microvasculature, assessed by retinal blood vessel diameters, were compared between the start (Pre-PR) and end

(Post-PR) of the 8-week pulmonary rehabilitation program. Significant differences are indicated as *: p<0.05

Clinical characteristics			
Sex, male, %		56.7	
Age, years		64.1 (6.9)	
Body mass index, kg/m^2		26.9 (5.0)	
Fat-free mass index, kg/m^2		16.6 (2.1)	
Smoking (%)	current	43.3	
	ex	53.3	
	never	3.4	
Smoking pack-years		39.1 (24.6)	
FEV_1, L		1.20 (0.47)	
FEV_1, %predicted		44.6 (17.4)	
FEV_1/FVC		36.2 (14.1)	
GOLD I/II/III/IV (%)		3.3/33.3/43.3/20.0	
Blood pressure			
Blood pressure, mmHg	systolic	130.6 (22.9)	
	diastolic	78.2 (8.9)	
Hypertension, %		60.0	
Laboratory values			
Blood glucose, mmol/L		6.1 (1.4)	
(Pre)diabetes mellitus, %		40.0	
Dyslipidaemia, %		76.7	
hs-CRP, %	low	11.5	
	borderline	30.8	
	moderately high	42.3	
	markedly high	15.4	
Exercise capacity		***Pre PR***	***Post PR***
Peak VO_2, mL/min		1050 (329)	-
Peak VO_2, %predicted		57.9 (21.3)	-
6-minute walk distance, m		414 (103)	439 (110)*
6-minute walk distance, %predicted		64.9 (15.4)	68.6 (16.5)*
Constant work rate test, s		290 (159)	699 (458)*
Retinal blood vessel diameter		***Pre PR***	***Post PR***
CRAE, µm		153.8 (11.4)	154.4 (9.7)
CRVE, µm		233.5 (18.4)	235.2 (19.1)

FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; hs-CRP=high-sensitive C-reactive protein; hs-CRP low= <1 mg/L; borderline= 1-3 mg/L; moderately high= 3.01-10 mg/L; markedly high= >10 mg/L[21]; VO_2=oxygen uptake; CRAE=central retinal arteriolar equivalent; CRVE=central retinal venular equivalent

Table 2 Absolute changes in retinal blood vessel diameters (µm) compared to baseline following an ergometer test at the start (before PR) and end (after PR) of the 8-week pulmonary rehabilitation program (n=30). Arteriolar diameters are summarized as Central Retinal Arteriolar Equivalent (CRAE), and venular diameters are summarized as Central Retinal Venular Equivalent (CRVE). Data are presented as mean (95% CI).

Timepoint after the ergometer test	**CRAE**			**CRVE**		
	Before PR	After PR	p-value	Before PR	After PR	p-value
Post	-0.40 (-3.73 – 2.93)	1.46 (-0.19 – 3.11)	0.315	1.22 (-1.03 – 3.46)	6.71 (1.41 – 12.01)	0.058
Post + 5 min	-0.83 (-3.55 – 1.89)	1.38 (-0.55 – 3.31)	0.237	1.11 (-1.52 – 3.74)	4.14 (-1.99 – 10.27)	0.373
Post + 10 min	-0.94 (-3.73 – 1.86)	1.31 (-0.61 – 3.23)	0.264	0.91 (-1.53 – 3.35)	5.16 (-0.11 – 10.20)	0.132
Post + 15 min	-1.56 (-4.11 – 0.98)	0.75 (-0.99 – 2.48)	0.150	0.93 (-1.57 – 3.43)	4.01 (-0.20 – 8.21)	0.182
Post + 30 min	-0.12 (-2.31 – 2.07)	0.27 (-1.98 – 2.52)	0.810	0.59 (-1.63 – 2.82)	2.03 (-3.42 – 7.49)	0.612

Figure 1 Retinal microvascular reactivity measured as estimated differences of change in mean Central Retinal Arteriolar Equivalent (CRAE, µm) and Central Retinal Venular Equivalent (CRVE, µm) (95% CI) following an ergometer test. The test was performed at the beginning (■) and the end (□) of an 8-week pulmonary rehabilitation program. The model was corrected for age, sex, body mass index, smoking status, diabetes, hypertension, dyslipidaemia, cardiovascular comorbidities, pulmonary and cardiovascular medication and fellow vessel diameter. The model included 30 participants.