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Endothelial function in patients with COPD: an updated systematic review of studies using ~~flow~~ flow-mediated dilatation

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Abstract

Background Cardiovascular disease is a~~n import~~ significant cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD). Endothelial dysfunction is on the trajectory ~~may be involved in the pathogenesis~~ of cardiovascular disease pathogenesis, and m~~. Over the past years, ultiple several~~ studies report ~~on~~ endothelial dysfunction in COPD ~~have been published~~. ~~Therefore, in t~~This article summarized the current knowledge ~~paper we provide an update on the scientific literature~~ on peripheral endothelial function in persons ~~patients~~ with COPD.

Methods Databases were screened for studies using ultrasound-based flow-mediated dilation in ~~stable~~ persons with stable COPD ~~patients~~. Pooled effect sizes were calculated using random effects model. Meta-regression analyses ~~were performed to~~ assessed the effects of ~~the possible effect of important~~ demographic and clinical variables

Results 34 studies were identified, with a total of 1982 participants (1365 COPD patients; ~~-~~617 controls). Pooled analysis demonstrated an impaired endothelial-dependent dilation (-2.33%; 95% confidence interval (CI) -3.30 to -1.35; p<0.001; I^2=95%) and endothelial-independent dilation (-3.11%; 95%CI -5.14 to -1.08; p=0.003; I^2=61%) in persons with COPD ~~patients~~ when compared to non-COPD controls. Meta-regression identified that ~~a~~ higher age, a worse severity of airflow obstruction, and current smoking were significantly associated with impaired endothelial function in COPD. Studies evaluating the effects of various pharmacological and non-pharmacological interventions on endothelial function in persons ~~patients~~ with COPD demonstrated conflicting ~~findings~~results.

Conclusion This up-to-date~~dated~~ review provides more ~~further~~ evidence about ~~for~~ impaired peripheral endothelial function in COPD. Interventions to improve endothelial function in persons ~~patients~~ with COPD provide inconsistent results~~mixed evidence~~. Considering the high ~~burden~~ prevalence of endothelial dysfunction in COPD and its relation ~~with~~ to cardiovascular morbidity, more focus is warranted ~~needed~~ on identifying~~identification of~~ cardiovascular risk factors ~~phenotyping an~~and interventions ~~aimed at improving~~to improve endothelial function in persons ~~patients~~ with COPD.

Key words COPD, cardiovascular disease, endothelial function, ~~flow~~ flow-mediated dilatation, cardiovascular risk

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined by ~~the presence of~~ chronic airflow limitation, though it is considered a complex, heterogeneous and multicomponent disease (1). Cardiovascular comorbidities are frequently present in COPD (2). Indeed, persons ~~patients~~ with COPD have a two to five times higher risk of cardiovascular diseases ~~compared to~~than non-COPD (smokers?)? (3). Cardiovascular co-comorbidity ~~, which~~ seriously contributes to the disease severity (4, 5). The mechanisms underlying the strong association between COPD and cardiovascular diseases are ~~not well~~poorly understood. C~~, though, c~~hanges in vascular endothelial function ~~have suggested~~appear to accompany the increased cardiovascular risk in COPD (6, 7).

The endothelium plays a ~~major~~ significant role in ~~the regulation of~~regulating vascular tone, controlling tissue blood flow and inflammatory responses, and maintaining blood fluidity. ~~Normal~~ Nitric oxide (NO) is the primary mediator of endothelial function, ensuring~~endothelial function ensures~~ a balanced response between vasoconstrictive and vasodilatory stimuli~~, with nitric oxide (NO) as a primary mediator~~ (8, 9). ~~An I~~An i~~i~~mbalance in NO production is ~~as~~ an essential ~~major~~ mechanism of endothelial dysfunction (9). Also,~~ and~~ it has been recognized that endothelial dysfunction is an early, potentially reversible precursor of vascular disease (8). Important risk factors for endothelial dysfunction are smoking, aging, family history of early cardiovascular diseases, elevated triglycerides, elevated low-density lipoprotein cholesterol and reduced high-density lipoprotein cholesterol, hyperglycemia, hypertension, physical inactivity, obesity, and ~~presence of~~ systemic inflammation~~,~~ (8-10).

~~In an earlier systematic review, W~~w~~e~~ documented in an earlier systematic review ~~demonstrated~~ that persons~~patients~~ with COPD have a significantly impaired ~~peripheral~~ endothelial function as measured ~~, assessed~~ via flow-mediated dilation (FMD) or nitroglycerin-mediated dilation (NMD) (11). FMD using ultrasound is the most widely used method for ~~the assessment of~~assessing ~~peripheral~~ endothelial function, and it has prognostic value for future cardiovascular events (12). FMD~~It~~ measures the change in brachial arterial diameter at rest, and after reactive hyperemia, produced after a five-minute occlusion by ~~a~~ supra-systolic cuff inflation~~,~~. In addition, NMD quantifies the ~~endothelium~~ endothelium-independent

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vasodilation after administration of an exogenous NO donor, such as nitroglycerin spray or sublingual tablets (13, 14).

Over the past years, several studies on endothelial dysfunction in COPD have been published. Therefore, ~~in this paper~~ we ~~provide an update on~~update the scientific literature on ~~peripheral~~ endothelial function assessed by FMD or NMD using ultrasound in persons with stable ~~patients with~~ COPD. In addition, we assess ~~ed~~ differences in endothelial function between persons ~~patients~~ with COPD and non-COPD control subjects.

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2. Methods

2.1 Data sources and search strategy ~~es~~

We performed an update of our previous systematic review. For the current systematic review, an additional computerized literature search was performed in Medline/PubMed, Web of Knowledge, and Embase up to August 2022. The search strings used to identify relevant articles are included in the supplementary file.

2.2 Study selection

Studies that met the following criteria were included: 1) Participants: ~~stable~~ persons ~~patients~~ with stable COPD; 2) Outcome: extrapulmonary endothelial function; 3) Methods: noninvasive assessment of endothelial function using FMD and/or NMD. Titles and abstracts were screened for inclusion criteria, and potentially eligible articles were retrieved. References from these articles and previous reviews were also scanned for additional relevant articles. Non-English language articles, review articles, editorials, qualitative studies, methodology studies and congress abstracts were excluded. In addition, studies investigating pulmonary endothelial function were excluded.

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2.3 Screening, data extraction, and quality assessment

~~Study screening and data extraction were performed by AWV~~AWV performed study screening and data extraction. Details of study designs and relevant results were obtained in a predesigned data form. ~~For each study,~~Each study's authors, journal, year of publication, participant characteristics (sex, age, disease severity), methods to assess endothelial function, outcome parameters, and main outcomes were recorded. If necessary, the authors of the included study were contacted directly to request additional data.

The methodological quality of studies included in the meta-analyses was assessed using the Newcastle-Ottawa Scale (NOS), which is developed for quality assessment of non-randomized observational studies. The NOS contains eight items categorized into three domains (selection, comparability, and exposure). Scores range from 0 to 9, where a higher score indicates a better methodological quality (15).

2.4 Statistics

Meta-analytic techniques were conducted in RevMan version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A funnel plot was used to check for publication bias. Egger's regression test and Begg and Mazumdar rank correlation test were used to assess publication bias, in which $p<0.10$ is considered statistically significant (16).

For studies reporting median and range or interquartile range values, we calculated mean and SDs values based on relevant formulas (17). If a study included more than one control group (e.g. smoking and non-smoking non-COPD controls), groups were combined to create a single pair-wise comparison ~~in order~~ to avoid a unit-of-analysis error (18).

The I^2 was calculated for each model to determine the proportion of observed variance due to heterogeneity. Values of 25%, 50%, and 75% were ~~used as~~ boundary limits for low, moderate, or high heterogeneity, respectively (19). ~~In the case that~~If ~~significant between-study heterogeneity was identified,~~ Rrandom effects meta-analysis was used to calculate pooled effect estimates if significant between-study heterogeneity was identified. All studies reporting differences in endothelial function between persons ~~patients~~ with COPD and non-COPD control subjects were included in the models. Subgroup comparisons were performed between former smoking persons ~~patients~~ with COPD and control subjects and between patients with COPD and smoking and non-smoking controls~~, in which t~~. We split the ~~he~~ total number of persons ~~patients with COPD was divided up~~, and the means and standard deviations were left unchanged (18). In addition, meta-regression analyses were performed to assess the possible effect of important demographic and clinical variables (including sex~~gender~~, age, disease severity, BMI, smoking history, and cardiovascular comorbidities) using Comprehensive Meta-analysis [Version 3, Biostat, Englewood, USA).

3. Results

Search results

A total of 47 new studies were retrieved from the literature search, of which 30 were excluded (Figure 1). So, 34 studies were included in this systematic review; 17 new eligible studies (20-36) and 17 studies from our previous work (37-53) (Table 1 and 2).

A total number of 1982 participants was evaluated: 1365 individuals ~~patients~~ with a spirometry-based diagnosis of COPD (71% men; mean age: 66±4 years; body mass index (BMI): 27±2 kg/m^2) and 617 non-COPD controls (55% men; mean age: 62±7 years; BMI: 27±2 kg/m^2) (Table 1).

Endothelial function assessed via flow-mediated dilation (FMD)

A pooled analysis to study the difference in endothelium-dependent FMD between persons with stable ~~patients with~~ COPD and non-COPD controls included nineteen studies (20, 21, 26, 29, 32, 33, 35, 38, 42-50). ~~Methodological~~ The methodological quality of these studies ranged from 5 to 9 points on the NOS (Table E1 of Supplementary file). Thirteen studies could not be included in the meta-analyses because the ~~studies only measured patients with COPD and~~ only measured persons with COPD and did not include a non-COPD control group (22-25, 27, 28, 30, 31, 36, 39-41, 53). F~~;~~ ~~f~~our of these studies focused on determinants of endothelial function (25, 39, 40, 53), and eight studied the effect of an intervention on endothelial function in persons ~~patients~~ with COPD (23, 24, 27, 28, 30, 31, 36, 41) ~~and t~~. Two studies investigated ~~studied longitudinal changes of endothelial function~~endothelial function changes over time (22, 53). Additionally, two studies were~~two studies were~~ removed ~~excluded~~ from the analysis since ~~percentage mean change in brachial artery diameter and standard deviation were not~~ the percentage mean change in brachial artery diameter and standard deviation were unavailable (37, 51).

Pooled analysis of nineteen studies showed that persons ~~patients~~ with COPD (n=636) had a significantly lower increase in FMD~~,~~ compared to controls (n=501) (FMD (%): -2.33; 95% confidence interval (CI) -3.30 to -1.35; p<0.001; Figure 2) (20, 21, 26, 29, 32-35, 38, 42-50). FMD ranged from -0.6 to 14.2% in persons ~~patients~~ with COPD and from 1.6 to 17.5% in controls. Heterogeneity across studies was high (I^2=95%) and was not reduced by the exclusion of individual studies.

Meta-regression identified that age (coefficient: -0.12; p<0.001), forced expiratory volume in 1 second (FEV_1) (coefficient ~~=~~ 0.06; p=0.020), smoking status (coefficient =-0.04; p=0.047) and pack-years of smoking (coefficient =-0.06; p=0.041) were significantly associated with

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FMD. Subgroup analyses demonstrated that the impaired endothelial function in persons ~~patients~~ with COPD is predominantly present when compared to non-smoking controls (FMD (%): -3.38; 95% CI -4.83 to -1.92; p<0.001), while no significant differences were shown with smoking controls (FMD (%): -2.29; 95% CI -5.73 to 1.16; p=0.19; Figure E1a and E1b of the supplementary file). Furthermore, there were no differences ~~were found~~ between former smoking persons with COPD ~~patients~~ and non-smoking control subjects (FMD (%): -0.75; 95% CI -2.61 to 1.11; p=0.43; Figure E1c of the supplementary file).

Asymmetry in the funnel plot indicates that the possibility of publication bias could not be excluded (Figure E2 of supplementary file). ~~Though, despite this apparent asymmetry, both~~Despite this apparent asymmetry, ~~the~~ Egger's regression test and Begg and Mazumdar's rank correlation test were not statistically significant (Supplementary file).

Endothelial function assessed via ~~nitrate~~ nitrate- mediated dilation (NMD)

Twelve studies determined ~~the~~ endothelium-independent vasodilation after sublingual nitroglycerin administration (24-26, 28, 44-46, 48-50, 52, 53). Six studies were not included in the pooled analyses because of the lack of a non-COPD control group (24, 25, 28, 46, 53) or missing standard deviation (49).

Pooled analysis of the six studies showed that persons ~~patients~~ with COPD (n=200) had a significantly lower NMD compared to controls (n=140) (NMD (%): -3.11; 95% CI -5.14 to -1.08; p=0.003; Figure 3) (26, 44, 45, 48, 50, 52). ~~Methodological~~ The methodological quality of these studies ranged from 7 to 9 points on the NOS (Table E1 of Supplementary file). Heterogeneity was moderate (I^2=61%) and was not reduced by the exclusion of individual studies.

Meta-regression of these studies identified that age (coefficient=-0.21; p<0.001), FEV_1 (coefficient ~~:~~=-0.10; p=0.025), and pack-years of smoking (coefficient~~:~~=-0.09; p=0.033) were significantly associated with NMD.

~~Funnel~~ The funnel plot did not suggest publication bias (Figure E3 of Supplementary file), ~~which was~~ confirmed by ~~the~~ Egger's regression test and Begg and Mazumdar's rank correlation test (Supplementary file).

Determinants of endothelial function

Studies identified significant associations between FMD and lung function parameters, including FEV_1 (26, 32, 37, 40, 44), FEV_1/vital capacity (VC) ratio (44, 49), and diffusing capacity for carbon monoxide (TLCO) (32, 35).

In addition, significant positive associations were found between FMD and physical activity (21, 40), capillary oxygen tension (26), and significant negative associations between FMD and systemic inflammation (44), fasting serum glucose levels, and insulin resistance (53). A weak, but significant, association was found between FMD and the number of circulating progenitor cells by Pizarro et al. (r =-0.27, p<0.05) (52), whilst . In contrast, this association was found to be nonsignificant in the study of Tura-Ceide et al. (r = -0.20, p=0.30) (34).

A higher FMD was found in polycythemic persons patients with COPD (patients with an increased red blood cell volume) compared to normocythemic persons patients (3.97±0.39 vs. 2.85±0.25%, respectively, P<0.02) (39), whilst . At the same time, there were no significant differences were demonstrated in FMD or NMD between persons patients with COPD caused by tobacco or by biomass smoke exposure (25).

Longitudinal changes in endothelial function

Two studies investigated longitudinal changes in endothelial function(22, 53). Urban et al. showed a significant decrease in FMD over a 12-month period12 months (from 13.5% (10.5–14.9%) at baseline to 9.8% (6.4–11.8%) at follow follow-up; p=0.002), but no significant difference was found in the percentage of NMD between baseline and follow-up (22.1% (19.9–28.0%) versus 19.9% (16.0–25.0%); p=0.133) (53). In addition, Clarenbach et al. found an relative annual decrease in FMD of 5.6% (22). Changes in endothelial function appeared to be related to changes in FEV_1 (22, 53) and insulin resistance(53).

Interventional effects

Pavti RCT

Several studies investigated the effect of an intervention on endothelial function in COPD; ten randomized controlled studies (23, 24, 27, 28, 30, 31, 33, 36, 41, 47) (of which three placebo-controlled cross-over studies (30, 33, 47), three placebo-controlled studies (24, 27, 31), and one sham-controlled study randomized controlled study (23)) and two case-control intervention study (45, 46).

Fisk et al. demonstrated that 16 weeks of treatment with an anti-inflammatory drug, losmapimod, marginally improved NMD compared to placebo (treatment effect: +3.25; 95% CI 0.41 to 6.1; p=0.03), with whilst no significant effect was found on FMD (24).

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Studies exploring the effects of dietary supplements on FMD yielded varying results. Pavitt et al. demonstrated that an acute dose of dietary nitrate significantly improved FMD in individuals with a hypoxic COPD phenotype compared to placebo (median (interquartile range (IQR)) +4.1%- (−1.1% to 14.8%) vs.~~s~~ −5.0% (−10.6% to –0.6%); estimated treatment effect −11.9% (95% CI −18.9 to −7.15) (p<0.001) (30). The beneficial effect of dietary nitrate supplementation on FMD was also shown in persons ~~patients~~ with COPD undertaking an 8-week pulmonary rehabilitation program (+6.6% (0.6, 17.6) in the nitrate-rich supplement group ~~versu~~s. −4.7% (−21.5, 11.8) in the ~~group with~~ nitrate-depleted placebo group; estimated treatment effect −20.3% (95% CI −33.8 to 3.4); p=0.046) (31). Contrary, six months of high-dose fish oil supplementation did not significantly improve endothelial function in persons ~~patients~~ with COPD compared to placebo (-2.6% (95% CI -5.6 to 0.3 in the fish oil group and -1.6% (95% CI -4.5 to 0.3) in the placebo group; p=0.59) (27).

Three studies investigated the effects of antioxidant supplementation on endothelial function (33, 46, 47). Ives et al. demonstrated that an acute antioxidant cocktail, composed of 2 separate doses of Vitamin C, Vitamin E, and alpha-lipoic acid, significantly improved FMD in patients with COPD (4.7±0.6 % in the intervention group vs. 3.1±0.5% in the placebo group; p<0.05) (47). Similarly, Hartmann et al. found that an intravenous vitamin C infusion significantly improved FMD in COPD (from 6.0±0.9% to 8.1±1.3%; p<0.05) (46). Finally, Rodriguez-Miguelez et al. showed that a single dose of tetrahydrobiopterin (BH_4) significantly improved FMD in persons ~~patients~~ with COPD to values comparable~~similar~~ to control subjects (from 4.7±2.3% to 6.8±2.5%; p<0.05) (33).

Clarenbach et al. showed that persons with COPD ~~patients~~ undergoing lung volume reduction surgery had a significant improvement in FMD compared to non-surgical control persons ~~patients~~ after 3 months (2.4±1.3 to 4.8±1.7 in the intervention group versus 2.0±0.9 to 1.5±1.0 in the control group; effect: +2.9%; 95% CI +2.1 to +3.6%; P<0.001), providing evidence for a link between lung function impairment and vascular disease in persons ~~patients~~ with COPD (41). In addition, non-invasive positive pressure ventilation (NiPPV) applied during a bout of high-intensity aerobic exercise ~~can~~ acutely modulated FMD in persons ~~patients~~ with coexisting COPD and heart failure (NiPPV: 9.2 ± 3.1% vs. sham intervention: 3.6 ± 0.7%, p < 0.05) (23).

Merlo et al. demonstrated that an 8-week supervised walking-based training program significantly improved FMD (+3.04±1.97% in the exercise group vs. −0.37±0.73% in the control group; p<0.001) (36). Contrary, Gelinas et al. did not ~~found~~ find an improvement in FMD after

an aerobic exercise program (45). Finally, Kohlbrenner et al. found evidence that increasing steps per day after a combined physical activity counselling and pedometer-based feedback intervention ameliorates the impaired FMD in persons ~~patients~~ with severe and very severe COPD (β = 0.07, 95% CI = 0.04-0.10, p < 0.001) (28). This~~, and that this~~ effect was not modulated~~influenced~~ by smoking status, the severity of airflow obstruction, exacerbation frequency, and lung diffusion capacity (28). In contrast, there was no association ~~was found~~ between the change in NMD and the change in daily step counts (β = -0.00, 95% CI -0.00-0.00, p=0.261) (28).

4. Discussion

This ~~updated~~ systematic review and meta-analysis provi~~des further evidenc~~e that persons ~~patients~~ with COPD demonstrate ~~a~~ reduced ~~peripheral~~ endothelial function compared to controls without COPD. Pooled analyses showed differences in ~~both FMD and NMD in patients with COPD compared with~~FMD and NMD in persons with COPD compared to smoking and non-smoking control subjects. Studies evaluating the effects of various pharmacological and non-pharmacological interventions on endothelial function in persons ~~patients~~ with COPD demonstrated conflicting findings.

In recent years, peripheral endothelial assessment has gained interest in COPD, and multiple studies have been published since our previous systematic review and meta-analysis (11). Indeed, this update included seventeen new studies~~,~~ and strengthens the evidence that persons ~~patients~~ with COPD have impaired endothelial-dependent and endothelial-independent function compared to control subjects (11, 54). Furthermore, Theodorakopoulou et al. recently concluded that endothelial dysfunction was not only present in the conduit arteries~~,~~ but also ~~in~~ the microvasculature (55). In addition, our results identified that age, the severity of airflow obstruction, and smoking status ~~are~~ significantly associate~~d~~ with impaired ~~peripheral~~ endothelial function in COPD.

Previously, a ~~FMD less than 4.1% has shown to be strongly related with~~n FMD of less than 4.1% was strongly related to vascular damage (56). Furthermore, a cut-off value of FMD for discrimination between subjects with and without an increased risk for developing CVD was set ~~drawn~~ at 7.1% (57), and an FMD less than 8.1% was shown to be a strong independent

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predictor for cardiovascular events in persons ~~patients~~ with peripheral artery disease (58). These findings suggest that noninvasive assessment of endothelial function using FMD may serve as a surrogate marker for cardiovascular disease risk. Applying these earlier established FMD cutoff values to persons ~~patients~~ with COPD, it is apparent that ~~a high proportion of~~many ~~patients is considered to~~ have an increased cardiovascular risk (Figure 2). This result highlights the importance ~~for~~ of a more comprehensive cardiovascular assessment in persons with COPD to better phenotype individuals ~~patients~~ and address their cardiovascular risk. Based on our findings, cardiovascular risk is ~~expected to be~~ highest in older, smoking persons ~~patients~~ with more severe COPD. Furthermore, acute COPD exacerbations can ~~has been shown to~~ significantly affect FMD~~, probably~~ due to ~~owing to~~ increased arterial carbon dioxide tension, oxidative stress, hypoxia, and systemic inflammation. Therefore, ~~, suggesting that~~ an impaired FMD plays an ~~important~~ essential role in the increased cardiovascular risk during an~~-~~ acute COPD exacerbation (59).

Given the predictive value of endothelial dysfunction, preservation or recovery of endothelial function can be a~~n important~~ crucial therapeutic aim in ~~the prevention of~~preventing cardiovascular diseases (12, 60, 61). Earlier meta-analyses ~~already~~ provided evidence that drugs, such as statins, beta-blockers, angiotensin-converting enzyme inhibitors, and anti-inflammatory drugs, have beneficial effects on FMD in participants with and without overt cardiovascular diseases (62-64). Furthermore, lifestyle (e.g. physical activity/exercise, smoking cessation, weight loss) ~~–~~and nutritional (e.g. Mediterranean diet, antioxidant foods and vitamins) interventions can ~~have shown to~~ improve FMD (65). Our review included several studies evaluating pharmacological, nutritional and/or lifestyle interventions to improve FMD in persons ~~patients~~ with COPD (23, 24, 27, 28, 30, 31, 33, 36, 41, 45-47)~~, h~~. However, the findings are contradictory.

We have identified only one study investigating the effects of a pharmacological intervention on FMD in persons ~~patients~~ with COPD, in which no improvements were found after 16 weeks of anti-inflammatory drug treatment (24).

In addition, several studies investigated the effects of dietary supplements on FMD (27, 30, 31, 33, 46, 47). ~~It has previously been suggested that n~~Nutritional supplementation with antioxidant capacity may be relevant, as oxidative stress is the main pathophysiologic mechanism leading to impaired NO bioavailability and endothelial dysfunction (8, 14, 66).

Furthermore, there is increasing evidence that dietary nitrate intake contributes substantially to NO availability, ~~hereby~~ improving endothelial function (67). In addition, supplementation with omega-3 fatty acids (i.e. fish oil) significantly improved endothelial function in persons ~~patients~~ with cardiovascular diseases or cardiovascular disease risk factors by enhancing the release of NO (68). Studies in persons ~~patients~~ with COPD indeed found beneficial effects on FMD after antioxidant supplementation (33, 46, 47), ~~,~~ dietary nitrate supplementation (30, 31), and an acute dose of BH_4, which is an essential cofactor for nitric oxide synthase (33). ~~Contrary, six months of high-dose fish oil supplementation did not chang~~On the contrary, six months of high-dose fish oil supplementation did not change the endothelial function in COPD (27).

~~It has been widely recognized that e~~Exercise training and an increased physical activity level are ~~important~~ essential to improve endothelial function and reduce cardiovascular risk in healthy subjects and persons ~~patients~~ suffering from heart failure, diabetes, and coronary artery disease (69-71). ~~Nowadays, t~~There is emerging evidence ~~on~~ of the positive role of an active lifestyle on endothelial function in persons ~~patients~~ with COPD. Indeed, in persons ~~patients~~ with COPD, physical activity has shown to be an important determinant of endothelial function (21, 40). Enhancing daily physical activity can ~~and enhancement of physical activity has the potential to~~ ameliorate the impaired endothelial function in persons ~~patients~~ with COPD (28, 36). Then again, Gelinas et al. did not ~~found~~ find an improvement in endothelial function after an aerobic exercise program (45). ~~Furthermore,~~ Pavitt et al found ~~did found~~ ~~find~~ improvements in FMD after an 8-week pulmonary rehabilitation program in persons ~~patients~~ with COPD receiving dietary nitrate supplementation~~, but~~. However, no changes were found in patients receiving pulmonary rehabilitation with a placebo (31). Though, the relatively low training intensities and thus cardiac outputs, and the relatively short duration of exercise programs may be inadequate to generate adequate shear stress to enhance endothelial function and/or restore structural changes.

Finally, earlier population-based studies already identified the independent association between smoking intensity (pack~~-~~years of smoking) and FMD (72, 73), and that an impaired FMD is reversible after smoking cessation (73). Indeed, Johnson et al. showed prolonged improvement ~~of~~ in FMD after smoking cessation ~~of~~ for one year (73). Although the number of studies was limited, pooled analyses only demonstrated significant differences in FMD between persons ~~patients~~ with COPD and non-smoking controls, while no differences in FMD

were with smoking controls. Interestingly, in former smoking persons with~~COPD patients~~, FMD appeared ~~to be~~ comparable with non-smoking controls, indicating that an impaired FMD might be reversible in persons ~~patients~~ with COPD.

Our workflow selected 34 studies, but only 19 studies could be included in the meta-analysis. Most ~~Although the majority of the~~ evaluated studies ~~that were reviewed~~ suggest that persons ~~patients~~ with COPD have reduced endothelial function in the peripheral circulation~~,~~. However, there was ~~a~~ considerable variability in FMD, and not all studies found a difference in endothelial function between persons ~~patients~~ with COPD and control subjects (29, 34, 35, 42, 43, 45, 46, 50). A low sample size of several studies (29, 46, 48) probably resulted in limited power to detect significant differences between persons ~~patients~~ with COPD and healthy controls. In addition, some studies used upper arm occlusion (30, 31, 39, 44), while others used forearm cuff occlusion (20-26, 28, 29, 32, 33, 35-37, 40-43, 45, 46, 49, 50, 52). When the cuff is placed on the upper part of the arm, reactive hyperemia typically elicits a greater percentage of change in diameter compared with the change produced by the placement of the cuff on the forearm. This observation may be due to a ~~greater~~ more significant flow stimulus ~~resulting from recruitment of more resistance vessels or to~~from the recruitment of more resistance vessels or to the direct effects of ischemia on the brachial artery (74). Furthermore, several studies did not report data on predicted values of FEV_1 (21, 30, 37, 43, 49) or smoking status and/or packyears of smoking (21, 23, 25, 30, 31, 33, 37-39, 41, 42, 50), which we found to be associated with endothelial function in persons ~~patients~~ with COPD. Other potential determinants, such as markers of systemic inflammation, blood gases, or diffusing capacity measurements TLCO (26, 32, 35, 44), are often not assessed and could ~~therefore~~ not be included in the meta-regression analyses.

This review ~~only~~ focused on ~~peripheral~~ endothelial function assessed by FMD and/or NMD. Studies using other non-invasive assessment methods for peripheral endothelial function (e.g. venous occlusion plethysmography, peripheral arterial tonometry) yielded mixed results (55). Though, when all studies are pooled together, regardless of the type of method used for assessment of peripheral endothelial function, a significant impaired endothelial function was observed in persons ~~patients~~ with COPD compared to non-COPD controls (SMD −1.19, 95% CI −1.69 to −0.68; p<0.001) (55).

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The heterogeneity of ~~the~~ studies included in the pooled analysis was moderate to high (I2=61-95%), which was not reduced after the exclusion of individual studies. ~~The significant heterogeneity can, at least partly, be explained by differences in included patients and controls~~Differences in included patients and controls can partly explain the significant heterogeneity. Indeed, there were considerable differences between the studies regarding age, sex distribution, the severity of COPD, and smoking or non-smoking controls. ~~Though, i~~It has been recognized that about a quarter of meta-analyses have I^2 values over 50%, indicating that substantial heterogeneity is common, especially in meta-analyses of observational studies (19).

Unfortunately, no meta-analysis was performed for intervention studies because of differences in study design and presentation of outcome measure. Therefore, we could not identify which ~~type of~~ intervention ~~was more effective in improving~~improved FMD in persons ~~patients~~ with COPD.

The possibility of publication bias could not be excluded due to the asymmetry in the funnel plot comparing studies using ultrasound-based FMD of the brachial artery. Additional sources may be responsible for funnel plot asymmetry, including poor methodological quality of small studies, true heterogeneity, and chance (75).

5. Conclusion

This review provides ~~further~~ evidence of impaired peripheral endothelial function in persons ~~patients~~ with COPD. ~~In recent years, several pharmacological and lifestyle interventions have~~Several pharmacological and lifestyle interventions have recently been tried ~~attempted~~ to improve endothelial function~~, h~~. However, findings are conflicting, and no ~~date~~ data are available about long-term effects. Considering the high burden of endothelial dysfunction in COPD and its relation with cardiovascular morbidity, more focus is needed on cardiovascular phenotyping and interventions aimed at improving endothelial function in persons ~~patient~~ with COPD.

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List of figures

Table 1 Subject characteristics

Authors	Population	N	Males (%)	Age (years)	COPD diagnosis	COPD severity	BMI (kg/m^2)	Smoking status	Hypertension	DMII	Coronary artery disease
Observational studies											
Barak et al. (20)	COPD patients	17	65	69±8	COPD according to GOLD guidelines	FEV_1: 32±11 %pred GOLD I: 0% GOLD II: 6% GOLD III: 35% GOLD IV: 59% GOLD A: 0%: GOLD B: 6% GOLD C: 0% GOLD D: 94%	26±5	24% smokers; 54±63 pack-years	65	18	6
	Non-smoking controls without airflow obstruction	10	70	65±7		FEV_1: 107±23 %pred	29±4	0% smokers: 29±23 pack-years	40	10	0
Barr et al. (37)	Former smokers	107	54	71±5	post-bronchodilator FEV_1/FVC ratio <0.7	No: 60% GOLDI: 11% GOLDII: 20% GOLDIII/IV: 9%	28±4	48±26 pack-years	46	12	3
Bernardi et al. (21)	COPD patients	30	100	70±6	NR	FEV_1: 60±16 %pred	27±6	17% smokers	73	6	0
	CAD patients	30	100	69±6		NR	27±3	13% smokers	93	23	100
	COPD+CAD patients	16	100	69±4	NR	NR	30±5	19% smokers	87	18	100

	Healthy controls	30	100	69±5		NR	26±4	10% smokers	40	0	0
Blum et al. (38)	COPD patients	23	100	64±8	GOLD criteria of COPD (FEV_1%/FVC <0.7)	FEV_1: 45±15 %pred	26±5	100% smokers	65	30	26
	Healthy controls	22	54	45±12		NR	25±4	0% smokers	0	0	0
Boyer et al.(39)	Polycythemic COPD patients	15	100	59±3	evidence of chronic airflow limitation on standard pulmonary function tests	FEV_1: 45±5 %pred	32±2	58±5 pack-years	23	8	NR
	Normocythemic COPD patients	13	92	63±2	evidence of chronic airflow limitation on standard pulmonary function tests	FEV_1: 36±4 %pred	26±2	52±7 pack-years	20	7	NR
Clarenbach et al.(40)	COPD patients	106	66	61±8	objectively confirmed COPD according to GOLD guidelines	FEV_1: 45±22 %pred GOLD I/II: n=38 GOLD III: n=26 GOLD IV: n=42	27±7	20% smokers; 40±24 pack-years	42	10	19
Clarenbach et al. (22)	COPD patients	76	67	64 (58-68)	COPD according to GOLD guidelines	FEV_1: 36 (28-66) %pred GOLD I/II: 41% GOLD III: 30% GOLD IV: 29%	26 (23-28)	20% smokers: 39 (23-50) pack-years	46	16	12
Costanzo et al.(42)	COPD patients	41	56	74±6	FEV_1/FVC ratio below the lower limit of normal	FEV_1: 62±17 %pred	27±5	35±37 pack-years	NR	5	NR
	Controls without COPD	35	46	74±7		FEV_1: 96±15 %pred	28±4	15±20 pack-years	NR	11	NR
de Matthaeis et al.(43)	COPD patients during and after exacerbation	96	77	72±5	COPD according to GOLD guidelines	NR	NR	50% smokers; >20 pack-years	0	0	0

	Elderly subjects	76	33	70±7		NR	NR	NR	NR	NR	NR
Eickhoff et al.(44)	COPD patients	60	55	62±8	evidence of airflow obstruction on spirometry	FEV_1: 41±18 %pred	25±4	43% smokers; 66±39 pack-years	NR	NR	0
	Smoking controls without COPD	20	40	59±9		FEV_1: 99±12 %pred	26±3	100% smokers; 39±23 pack-years	NR	NR	0
Golpe et al. (25)	COPD patients; caused by smoking	20	75	70±7	COPD according to GOLD guidelines	FEV_1: 54±16 %pred	30±5	63±38 pack-years	65	0	NR
	COPD patients; caused by biomass exposure	20	75	70±9	COPD according to GOLD guidelines	FEV_1: 58±14 %pred	32±5	Never smokers	70	5	NR
Keymel et al. (26)	Coronary artery disease patients with COPD	17	100	66±8	FEV_1/FVC ratio <0.7	FEV_1: 59±17 %pred	29±3	0% smokers; 50±20 pack-years	NR	NR	100
	Coronary artery disease patients without COPD	16	100	64±10		FEV_1: 95±17 %pred	28±4	0% smokers; 30±17 pack-years	NR	NR	100
Kuzubova et al.(51)	COPD patients	63	100	60±1	FEV_1/FVC spirometry	FEV_1: 45±2 %pred	NR	100% current or ex-smokers; 33±2 pack-years	75	NR	NR
	Controls without COPD	95	100	57±2		NR	NR	57% current or ex-smokers	NR	NR	NR
Luehrs et al. (29)	COPD patients	10	50	66±8	COPD according to GOLD guidelines	FEV_1: 64±16 %pred	29±7	40% smokers; 46±21 pack-years	NR	0	NR
	Controls without COPD	9	44	59±13		FEV_1: 110±15 %pred	29±5	22% smokers; 6±13 pack-years	NR	0	NR
Marchetti et al.(48)	COPD patients	8	50	61±8	COPD defined using recent guidelines	FEV_1: 33±22 %pred	29±7	13% smokers; 51±22 pack-years	50	13	0

	Healthy non-smoking controls	9	67	53±6		NR	NR	0% smokers; 0 pack-years	11	0	0
Moro et al.(49)	COPD patients	44	61	77	COPD according to American Thoracic Society standards	FEV_1: 1.43 L	29±7	30% smokers; 25±30 pack-years	73	23	16
	Controls without COPD	48	27	73		FEV_1: 1.91 L	27±6	15% smokers; 15±26 pack-years	81	15	23
Özben et al.(50)	COPD patients	30	73	64±11	COPD according to the guidelines of the American Thoracic Society / European Respiratory Society	FEV_1: 51±15 %pred	29±4	100% ex-smokers	87	43	33
	Controls without COPD	20	75	62±7		NR	29±4	100% ex-smokers	90	45	40
Piccari et al. (32)	COPD with pulmonary vascular dysfunction	15	87	64±6	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 30±10 %pred GOLD I: 0% GOLD II: 7% GOLD III: 33% GOLD IV: 60%	NR	13% smokers; 69±29 pack-years	67	33	NR
	COPD without pulmonary vascular dysfunction	46	83	62±7	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 48±20 %pred GOLD I: 7% GOLD II: 35% GOLD III: 28% GOLD IV: 30%	NR	30% smokers; 62±29 pack-years	46	4	NR
	Smoking controls without COPD	20	45	54±8		FEV_1: 103±10 %pred	NR	100% smokers; 30±24 pack-years	15	0	NR
	Non-smoking controls without COPD	27	44	56±8		FEV_1: 107±12 %pred	NR	0% smokers; 4±8 pack-years	19	4	NR

Pizarro et al.(52)	COPD patients	62	94	62±8	COPD according to GOLD guidelines	FEV_1: 83±18 %pred	26±3	47% smokers; 60±32 pack-years	NR	NR	NR
	Non-smoking healthy controls	18	39	58±6		FEV_1: 106±7 %pred	25±3	non-smokers; 0 pack-years	NR	NR	NR
	Smoking healthy controls	17	71	59±8		FEV_1: 100±12 %pred	25±3	100% smokers; 41±21 pack-years	NR	NR	NR
Tura-Ceide et al. (34)	COPD	25	96	59±6	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 51±22 %pred	25±3	58% smokers; 60±34 pack-years	NR	NR	NR
	Controls without COPD	14	64	57±7		FEV_1: 92±11 %pred	25±2	43% smokers; 39±22 pack-years	NR	NR	NR
Urban et al. (53)	COPD patients	18	67	67 (65-70)	evidence of airflow obstruction on spirometry (FEV_1/FVC ratio <70 %)	FEV_1: 39 (28–55)	27 (24-28)	0% smokers	0	0	0
Zelt et al. (35)	COPD patients	16	31	66±8	COPD GOLD 1A according to GOLD 2017 criteria	FEV_1: 86±14 %pred	29±4	25% smokers; 42±15 pack-years	19	NR	25
	Healthy controls	16	44	64±8		FEV_1: 105±13 %pred	29±4	6% current smokers; 9±14 pack-years	25	NR	19
Interventional studies											
Clarenbach et al. (41)	COPD patients scheduled for lung volume reduction surgery	13	69	65±6	COPD according to GOLD guidelines	FEV_1: 26±6 %pred	24±3	53±13 pack-years	46	23	38

	COPD patients who underwent lung volume reduction surgery	14	57	61±10	COPD according to GOLD guidelines	FEV_1: 28±7 %pred	26±2	37±12 pack-years	29	21	14
da Luz Goulart et al. (23)	Patients with coexisting COPD and heart failure	14	100	70±7	FEV_1/FVC ratio <0.7	FEV_1: 66±28 %pred GOLD I: 50% GOLD II: 35% GOLD III: 14%	25±4	NR	NR	NR	NR
Fisk et al. (24)	COPD patients - intervention	36	69	67±8	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 50±19 %pred	26±4	12% smokers; 48±24 pack-years	31	NR	14
	COPD patients - placebo	37	70	68±7	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 52±22 %pred	26±4	9% smokers; 43±25 pack-years	19	NR	8
Gelinas et al. (45)	COPD patients	24	54	70 (64-75)	FEV_1/FVC<0.7 and <lower limit of normal	FEV_1: 68±19 %pred	28±3	0% smokers; 35±19 pack-years	0	0	0
	Healthy controls	20	50	62 (62-66)		FEV_1: 113±16 %pred	26±3	0% smokers; 6±10 pack-years	0	0	0
Hartmann et al.(46)	COPD patients	10	40	67±3	airflow obstruction (FEV_1/FVC< 0.70) evident on spirometry	FEV_1: 60±5 %pred	25±2	0% smokers 45±5 pack-years	50	0	0
	Healthy controls	10	40	66±2		FEV_1: 107±4 %pred	25±1	0% smokers 5±4 pack-years	10	0	0
Ives et al.(47)	COPD patients	30	50	66±2	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 55±4 %pred	26±1	0% smokers	57	0	7

	Controls without COPD	30	50	66±2		FEV_1: 107±4 %pred	25±1	0% smokers	23	3	3
Kim et al. (27)	COPD patients randomized to fish oil	20	50	68±7	post-bronchodilator FEV_1/FVC ratio <0.7	FEV_1: 45±13 %pred GOLD II: 30% GOLD III/IV: 70%	27±9	Former smokers with ≥ 10 pack-years	40	10	0
	COPD patients randomized to placebo	20	60	66±8		FEV_1: 43±16 %pred GOLD II: 30% GOLD III/IV: 70%	30±4	Former smokers with ≥ 10 pack-years	50	15	0
Kohlbrenner et al. (28)	COPD patients	57	67	66±9	COPD according to GOLD guidelines	FEV_1: 35±9 %pred	25 (22-28)	14% smokers; 44 (40-60) pack-years	NR	NR	NR
Merlo et al. (36)	COPD patients randomized to exercise group	10	70	70±9	FEV_1 ≥30% and ≤80%pred	56±13	29±6	30% smokers; 50±x28 pack-years	NR	NR	0
	COPD patients randomized to control group	10	70	70±7	FEV_1 ≥30% and ≤80%pred	62±13	28±4	10% smokers; 41±19 pack-years	NR	NR	0
Pavitt et al. (31)	COPD patients randomized to nitrate-rich beetroot juice	57	58	70 (64-78)	COPD according to GOLD guidelines	FEV_1: 73 (37-65) %pred GOLD II: 54% GOLD III: 35% GOLD IV: 11%	27 (24-32)	45 (26-60) pack-years	NR	NR	NR
	COPD patients randomized to nitrate-deplete beetroot juice	65	59	68 (62-74)	COPD according to GOLD guidelines	FEV_1: 48 (33-63) %pred GOLD II: 42%	26 (23-31)	45 (29-60) pack-years	NR	NR	NR

						GOLD III: 37% GOLD IV: 21%					
Pavitt et al. (30)	COPD patients	20	60	68±9	COPD according to GOLD guidelines	FEV_1: 0.7 (0.6-1.0) L GOLD III: 35% GOLD IV: 65%	25±5	52±22 pack-years	NR	NR	NR
Rodriguez-Miguelez et al. (33)	COPD	17	55	56±7	post-bronchodilator FEV1/FVC ratio <0.7	FEV_1: 58±15 %pred	32±8	41% smokers	53	0	0
	Controls without COPD	15	33	58±7		FEV_1: 103±14 %pred	27±6	13% smokers	13	0	0

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; NR: not reported

Table 21 Main study results

Authors	Year	Non-invasive assessment method	Outcomes
Observational studies			
Barak et al. (20)	2017	FMD	- At rest, FMD was 36% lower in the COPD patients than in controls (5.03 ± 1.51 vs. 7.88 ± 1.81%; P < 0.01). - The retrograde intervention induced significant decreases in brachial artery FMD and FMD% (relative terms) in in both patients and control (p<0.01). - Supplemental O2 appeared to improved endothelium-dependent vasodilation for a given stimulus. - Acutely disturbed blood flow with increased retrograde shear stress further deteriorates the already impaired endothelial function in patients with moderate-severe COPD.
Barr et al.(37)	2007	FMD	- 1 standard deviation decrease in FMD was associated with a 132-ml (95% CI: 16–248 ml; p=0.03) decrement in FEV_1 and a 2.6% (95% CI: 0.5–4.7%; P<0.02) increase in CT percentage of emphysema in fully adjusted models. - Impaired endothelial function was associated with lower FEV_1 and higher CT percentage of emphysema in former smokers early in COPD.
Bernardi et al. (21)	2018	FMD	- FMD in COPD (+5.0±1.6%) is reduced and is in an intermediate position between healthy subjects (+7.6±2.2%) and coronary artery disease (CAD) (+3.6±1.4%) or COPD+CAD (+3.5±0.7%). - The only determinant independently associated with FMD in all subjects is the physical activity level (r^2=0.55; p=0.025), irrespective of the traditional risk factors (i.e., smoke, dyslipidemia, hypertension). - FMD in COPD is an intermediate position between healthy subjects and CAD or COPD+CAD; this impairment can contribute to explain the higher prevalence of cardiovascular disease in COPD. PA appears to have a positive role on endothelial function.

Blum et al. (38)	2014	FMD	- Baseline diameter of the brachial artery was larger in COPD patients compared with controls (0.41±0.06 cm vs. 0.35±0.06 cm; p=0.003). - The absolute change in diameter post hyperemia was significantly less in patients (0.004±0.02 cm vs. 0.05±0.02 cm; p<0.001). - COPD patients responded to the hyperemic trigger by constriction instead of dilatation (FMD% :−0.6±6.3% in patients vs. 15.6±7.6% in controls; p<0.001). - Patients with COPD had severe endothelial dysfunction manifested as impairment in the ability to dilate the brachial artery.
Boyer et al.(39)	2011	FMD	- Polycythemic patients had larger brachial artery diameter than normocythemic patients (5.2±0.2 cm vs. 4.5±0.2 cm; p<0.02). - FMD was increased in the polycythemic patients compared to normocythemic patients (0.25±0.02 vs. 0.15±0.02 mm; p=0.01 or 3.97±0.39 vs. 2.85±0.25%; p<0.02). - Acetylcholine-induced vasodilation was markedly impaired in the polycythemic patients (p=0.03). - Polycythemia induced by chronic or intermittent hypoxia may have no adverse effects on vascular function.
Clarenbach et al.(40)	2013	FMD	- FMD was associated with FEV_1 % predicted (β=0.04; p<0.01). - FMD in patients with GOLD stage I/II was 4.3±2.0% pred and was progressively impaired in patients with stage III (2.8±1.5% pred) and stage IV (2.0±1.3% pred). - FEV_1 and physical activity were independently associated with FMD. - Results in inactive patients (below the median number of steps per day) showed a stronger association between FEV_1 and FMD compared to the active patients (above the median number of steps per day)(β=0.06; p<0.01 vs. β=0.03; p=0.11). - Severity of airflow obstruction is a significant determinant of endothelial function in patients with COPD. A high level of physical activity seems to have a favorable effect on this association.

Clarenbach et al. (22)	2017	FMD	- Annual decrease in endothelial function of -0.14% (95% CI -0.25/-0.04), equal to a relative decrease of -5.6%. - COPD patients with a higher FMD at baseline had a greater decline over time vs. patients with a lower FMD at baseline (Coef. -0.22, 95% CI -0.29/-0.16, p<0.001). - In multivariable analysis a greater annual decline in FEV_1 tends to be independently associated with a decrease in FMD (p=0.085). - COPD patients showed a significant annual decrease in endothelial function, indicating progressive vascular dysfunction and an enhanced cardiovascular risk. A greater annual decline in lung function showed a trend towards greater decrease in FMD over time; no other independent predictors for FMD decline could be identified.
Costanzo et al.(42)	2016	FMD	- No difference in FMD between COPD and controls (14.2±8% vs. 12.3±6.8%; p=0.10). - No difference in arterial stiffness between COPD and controls (30.0±6.4% vs. 28.2±9.8%; p=0.30) - No difference in mean concentrations of inflammation markers (IL-6 and CRP; p>0.05). - Among COPD patients there was an inverse correlation between arterial stiffness and FEV_1 (r =-0.349; p=0.02), which is explained neither by endothelial function nor by systemic inflammation.
de Matthaeis et al.(43)	2014	FMD	- No significant difference in mean FMD between COPD at baseline and controls (10.0%±2.8% vs. 9.6%±2.7%; p=0.344). - Significant differences in mean values of FMD before and after standard treatment for acute exacerbation of COPD (10.0%±2.8% vs. 8.28%±2.01%; p<0.001) and blood flow rate (1.5±0.3 m/s vs. 1.5±0.3 m/s; p=0.001). - Significant correlations were found for FMD values and pCO_2 values at baseline (r=0.294; p=0.004) and for relative changes in FMD and pCO_2 levels before and after standard treatment for acute exacerbation of COPD (r=0.23; p=0.023). - Patients with higher baseline FMD (>10%) showed greater modification with regard to pCO_2 changes (2.6±1.39 vs. 1.59±1.4, P=0.012). - Hypercapnia during acute exacerbations of COPD can influence endothelium-dependent vasodilation, and a larger decrease in FMD could point to greater reactivity to pCO_2.

			- Vascular reactivity in acute COPD exacerbations in the elderly depends on integrity of the vascular endothelium.
Eickhoff et al. (44)	2008	FMD and NMD	- Baseline brachial artery diameter was significantly higher in patients with COPD compared to nonsmoking controls (3.64±0.63 mm vs. 3.28±0.61 mm; p>0.05). - Both FMD and NMD of the brachial artery were significantly lower in patients with stable COPD compared to smoking and nonsmoking control subjects (11±3% and 22±6% vs. 16±2% and 26±7% and 19±3% and 29±7%, respectively; p<0.05). - Levels of inflammatory mediators were higher in patients than they were in control subjects (p<0.05). - Stepwise multiple regression analysis showed that age, sex, baseline brachial artery diameter, CRP level, leukocyte count, blood glucose level, and FEV_1%pred were independent predictors of FMD in patients with COPD. There was no relation between FMD and pack-years of smoking. - Baseline brachial artery diameter was the only independent predictor of NMD in patients with COPD. - Both endothelium-dependent and endothelium-independent vasodilation is significantly impaired in patients with stable COPD. - Impaired flow-mediated dilation was strongly related to systemic inflammation and airway obstruction, which may help explain the increased cardiovascular morbidity in patients with COPD.
Golpe et al. (25)	2018	FMD and NMD	- There were no significant differences between patients with COPD caused by tobacco and patients with biomass-related COPD in FMD (4.82 % (95% CI: 2.66-9.19) vs. 5.98 % (95% CI: 2.74-9.16); p=0.89) and NMD (15.86 % (95% CI: 10.59-22.94) vs. 13.19 % (95% CI: 10.41-27.37); p=0.58). - The study does not support the hypothesis of a different cardiovascular effect of biomass or tobacco smoke in patients with COPD.
Keymel et al. (26)	2018	FMD and NMD	- Coronary artery disease (CAD) patients with coexisting COPD had significant impaired FMD compared to patients with CAD (3.4±0.5 vs. 4.2±0.6%; p<0.001), whilst NMD was comparable (7.8±2.5 vs. 8.9±2.5%, p=0.461). - FMD correlated with FEV_1 %pred (r=0.620, p≤0.001) and capillary oxygen pressure (pO_2, r=0.608; p≤0.001). - Subgroup analysis in COPD patients with pO_2 > 65 mm Hg and pO_2 ≤ 65 mm Hg revealed even lower FMD in patients with lower pO_2 (3.0±0.5 vs. 3.7±0.4%; p<0.01).

			- Multivariate analysis showed that pO_2 was a predictor of FMD (β=0.024; p=0.043) independent of the FEV_1 and pack years. - Data in healthy showed that exposure to hypoxic air led to an acute decrease in FMD (7.08±0.29% to 4.89 ±0.24%; p≤0.001)., whereby exposure to 100% oxygen did not change vascular function. - Patients with CAD and coexisting COPD had an impaired endothelial dysfunction as compared with sole CAD. Data suggest that in CAD patients with COPD, decreased systemic oxygen levels contribute to vascular dysfunction and that acutely decreasing oxygen levels may induce endothelial dysfunction.
Kuzubova et al.(51)	2013	FMD	- Endothelial dysfunction (FMD<10%) was present in 48% of COPD patients. - Detectable endothelial dysfunction in COPD patients was shown to correlate with high-producer D allele of ACE gene (odds ratio: 6.632, CI: 1.67-26.31; chi^2=8.39; p=0.004). - A high-producer D allele of ACE-1 gene seems to be associated with endothelial dysfunction in COPD patients, thus confirming a pathogenic significance of this gene polymorphism which is known to predispose for various types of other common vascular disorders.
Luehrs et al. (29)	2018	FMD	- FMD was comparable between patients with mild to severe COPD and non-COPD controls (5.0±2.1 % vs. 6.8±5.1%; p=0.32). - Lung air-trapping was not associated FMD in patients with COPD (r=0.14; 0=0.71) -or the entire cohort (r=0.06; p=0.80). - FMD was not different between patients with COPD and non-COPD controls. There was no evidence of an association between lung air-trapping and endothelial function.
Marchetti et al.(48)	2011	FMD and NMD	- In acute exacerbation of COPD FMD was markedly reduced compared to controls (2.8±1.7% vs. 10.8±4,7%; p<0.001). - NMD was markedly impaired during AECOPD compared to controls (8.0±4.3% vs. 21.4±6,0%; p<0.001). - Significant improvements were found in FMD (2.6±1.5% vs. 5.1±2.4%; p=0.04) and NMD (5.0±2.6% vs. 13.3±4.5; p=0.02) after resolution of acute exacerbation of COPD.

			- Endothelial and vascular smooth muscle function is markedly impaired during AECOPD requiring hospitalization and improves following resolution.
Moro et al. (49)	2008	FMD and NMD	- COPD patients had worse mean FMD and NMD compared to controls (5.4% vs. 8.9%; p<0.001 and 12.0% vs. 13.9%; p=0.007, respectively). - FMD was inversely related to FEV_1/VC ratio (r =−0.327; p=0.030). - The negative association between COPD and FMD and between COPD and NMD was confirmed after correction for potential confounders in a multiple linear regression model (β=−0.019; p=0.002 and β= 0.396; p<0.001, respectively). - Endothelial-dependent and, to a lesser extent, endothelial-independent dilations are significantly impaired in COPD, and the impairment is proportional to the severity of bronchial obstruction.
Özben et al.(50)	2010	FMD and NMD	- Parameters of FMD during acute exacerbation were significantly lower than those obtained after recovery (absolute change: 0.23±0.12 mm vs. 0.38±0.17 mm; p<0.001; percentage change: 6.44±3.99% vs. 10.42±4.86%; p<0.001) and compared to those of the control group (absolute change: 0.36±0.13 mm; p=0.001; percentage change: 9.77±3.83%; p=0.003), whilst no differences were observed for NMD. - FMD increased significantly after recovery, yielding similar values to those of the controls. Improvements in FMD were significant in both sexes. - Acute COPD exacerbation is associated with worsening endothelial function, increasing the risk for cardiovascular morbidity.
Piccari et al. (32)	2020	FMD	- FMD was lower in COPD patients with (2.70% (0.78–4.70) or without PVD (5.40% (3.13–7.30), compared to non-smoking controls (10.10% (6.15–14.30) (p<0.05); and in patients with COPD+PVD compared to smoking controls (2.70% (0.78–4.70) vs. 6.60% (4.58–9.50); p<0.05).

			- FMD correlated significantly with FEV_1 (r=0.402; p<0.001), diffusing capacity for carbon monoxide (r=0.354; p<0.001) and systolic pulmonary artery pressure (r=0.412; p<0.007) in all subjects. - In patients with COPD, the presence of PVD is associated with systemic arterial dysfunction, characterized by worse endothelial function in systemic arteries. This association is irrespective of the presence of cardiovascular risk factors, which are more prevalent in COPD patients with PVD.
Pizarro et al.(52)	2014	FMD and NMD	- FMD was worse in both COPD patients and control smokers compared to control nonsmokers (0.9 (-1.3 to 2.3)% and 0.0 (-0.8 to 1.6)% vs. 2.4 (1.1 to 4.1)%, respectively). - Interleukin-6, fibrinogen, high sensitivity C-reactive protein, vascular endothelial growth factor and tumor necrosis factor were increased in COPD. - In COPD patients, the number of circulating progenitor cells was inversely related to the flow-mediated dilation of systemic arteries. - Systemic vascular impairment in COPD is associated with smoking status but not with the reduced number of circulating hematopoietic progenitors. The latter appears to be a consequence of the disease itself not related to smoking status.
Tura-Ceide et al. (34)	2019	FMD	- COPD patients had significantly reduced progenitor cells compared to non-COPD subjects. - COPD patients and non-COPD subjects showed similar FMD values (1.8±1.0% vs 1.6±1.7%, respectively). - FMD was unrelated to the number of circulating progenitor cells (r = −0.2, p =0.30) or to the presence of progenitor cells in the intima of pulmonary arteries (r = −0.1, p=0.40). - In COPD, the decrease of circulating progenitor cells is associated with their recruitment in pulmonary arteries, which in turn is associated with endothelial dysfunction and vessel remodeling, suggesting a mechanistic link between these phenomena.

Urban et al.(53)	2014	FMD and NMD	- FMD significantly decreased from 13.5 % (11–15 %) at baseline to 9.8 % (6–12 %) at the follow-up visit after 12 months (p=0.002), whereas both fasting blood glucose concentrations and homeostatic model assessment for insulin resistance (HOMA-IR) increased from 94 mg/dl (86–103 mg/dl) to 102 mg/dl (94–111 mg/dl; p=0.027) and from 1.2 (0.8–2.1) to 1.7 (1.2–3.0; p=0.023), respectively. Decrease in NMD was not significant (from 22.1 % (20–28 %) at baseline to 19.9 % (16–25 %) at the follow-up (p=0.133). - There was a significant relationship between changes in endothelial function and changes in fasting serum glucose (r=− 0.483; p=0.009), HOMA-IR (r=− 0.441; p=.019), and FEV_1 (r=0.336, p=0.05). - Altered glucose metabolism may be associated with progression of endothelial dysfunction in patients with COPD.
Zelt et al. (35)	2018	FMD	- Patients with mild COPD had a marginally lower FMD compared to controls (4.11±3.16% vs. 5.08±2.79%; p=0.19). - TLCO and emphysema were significantly related to FMD (r values 0.51 and -0.60, respectively; p < .05). - Systemic vascular dysfunction is present in the earlier stages of COPD, particularly in patients with greater emphysema burden and low TLCO.
Interventional studies			
Clarenbach et al.(41)	2015	FMD	- FMD increased in the intervention group compared with the control group (+2.4±1.1% vs. -0.5±0.6%; p<0.001). - Endothelial function improved 3 months after lung volume reduction surgery in patients with severe COPD and emphysema. Lung volume reduction may therefore have beneficial effects on cardiovascular outcomes.
da Luz Goulart et al. (23)	2020	FMD	- Non-invasive positive pressure ventilation (NiPPV) during high-intensity exercise in patients with coexisting COPD and heart failure (HF) resulted in a significant increase in FMD (%) (NiPPV: 9.2 ± 3.1 vs Sham: 3.6 ± 0.7, p<0.05), FMD (mm) (NiPPV: 0.41 ± 0.18 vs Sham: 0.20 ± 0.11, p<0.05), - NiPPV applied during high-intensity exercise can acutely modulate endothelial function and improve exercise tolerance in COPD-HF patients.

Fisk et al. (24)	2018	FMD and NMD	- The treatment effect of losmapimod, a selective p38α/β MAPK inhibitor, compared to placebo did not result in significant improvement in FMD (+0.40% (95% CI: -1.66, 2.47), p=0.70), but did improve NMD (+3.25% (95% CI: 0.41, 6.10), p=0.03). - Although endothelial-independent vasodilatation responses improved after 16 weeks of treatment with losmapimod, there was no change in endothelial-dependent vasodilatation. These findings suggest that losmapimod is unlikely to be an effective long-term treatment for the adverse cardiovascular extra-pulmonary manifestations of COPD.
Gelinas et al. (45)	2017	FMD and NMD	- Exercise training had no significant effect on FMD independent dilation or any shear stress measures in patients with COPD or healthy controls. - FMD corrected for baseline diameter was unchanged in COPD (4.7±1.9% vs. 4.8±2.0%, p=0.78) and controls (4.3±2.3% vs. 4.6±2.2%, p=0.66). - There were no significant differences at baseline, post-training, or between change scores for any FMD or NMD variables when comparing COPD to controls. - An aerobic training program does not improve vascular structure and function in patients with COPD.
Hartmann et al. (46)	2016	FMD and NMD	- FMD% and absolute change in brachial diameter were not different between COPD and controls after sham-saline infusion (6.0%±0.9% vs. 5.9%±1.0%; p>0.05). - Vitamin C infusion significantly increased FMD% to a similar extent in both groups (8.1%±1.3% vs. 7.4%±0.8%; P>0.05). However, baseline diameter was lower after vitamin C in both groups (3.52±0.18 mm vs. 3.69±0.16 mm in COPD and 3.62±0.20 mm vs. 3.78±0.23 mm in controls; p<0.05). - NMD initiated similar responses between groups (25.6%±1.6% in COPD vs. 23.5%±2.3% in controls; p> 0.05). - Similar changes were found between groups when comparing the absolute change in brachial artery diameter with nitroglycerine administration (+0.85± 0.08 mm in COPD and +0.85±0.04 mm in controls; p>0.05). - FMD in the brachial artery was not different in COPD patients and controls. Vitamin C had an overall improvement on this parameter.

Ives et al.(47)	2014	FMD	- COPD patients displayed lower basal FMD compared to controls (3.1±0.5% vs. 6.7±0.6%; p<0.05), which was significantly improved with antioxidant cocktail in COPD (3.1±0.5% vs. 4.7±0.6%; p<0.05; placebo vs cocktail), but not controls (6.7±0.6% vs. 6.9±0.7%; p>0.05; placebo vs cocktail). - The antioxidant cocktail also improved pulse wave velocity (PWV, measure of vascular stiffness) in patients with COPD (14±1 m/s vs. 11±1 m/s; p<0.05; placebo vs. cocktail) while not affecting controls (11±2 m/s vs. 10±1 m/s; p>0.05; placebo vs cocktail. - Patients with COPD displayed impaired vascular function, as assessed by FMD and PWV, compared with controls, which can be acutely mitigated by an oral antioxidant.
Kim et al. (27)	2021	FMD	- Change in FMD after 6 months did not differ between patients receiving daily high-dose fish oil capsules or placebo arms (-1.1%, 95% CI -5.0-2.9, p=0.59). - 6 months omega-3 polyunsaturated fatty acid supplementation did not change systemic endothelial function in COPD.
Kohlbrenner et al. (28)	2021	FMD and NMD	- Baseline FMD was 2.8±1.4%, which changed by -0.56±1.64% in the intervals with stable or declining physical activity (PA) (-390 (-1411, -101) steps/day), and increased by 0.99±1.67% in the phases with enhanced PA (1102 (503, 1718) steps/day). - Baseline NMD was 15.5±7.8%, which changed by -2.1 (-4.5/2.7)% in the phases with stable or declining PA, and by -1.2 (-8.7/1.4)% in the phases with enhanced PA. - Multiple regression modelling, including adjustment for baseline step count, showed strong evidence for an association between changes in FMD and changes in PA (β=0.07; 95% CI: 0.04-0.10; p<0.001). - No evidence of any influence on the interaction between PA and endothelial function for smoking status (p=0.766), severity of airflow obstruction (p=0.838), exacerbation frequency (p=0.227), lung diffusion capacity of carbon monoxide(p=0.735). - Increasing steps per day ameliorates the heavily impaired endothelial function in patients with severe and very severe COPD and there is no evidence that this effect is influenced by smoking status, severity of airflow obstruction, exacerbation frequency, and lung diffusion capacity.

Merlo et al. (36)	2020	FMD	- An 8-week supervised walking-based training program significantly improved FMD (+3.04±1.97% in the exercise group vs. −0.37±0.73% in the control group; p<0.001). The effect size was 1.7, which indicates a very large effect of exercise training on endothelial function. - An 8-week supervised exercise training program significantly improved endothelial function in COPD and could therefore have an effect on cardiovascular health.
Pavitt et al. (31)	2020	FMD	- In patient with COPD undertaking a twice weekly 8-week pulmonary rehabilitation (PR) program, supplementation with nitrate-rich beetroot juice 3 hours before undertaking each PR session significantly improved FMD versus placebo beetroot juice (median (IQR) change: +6.6% (0.6-17.6) vs. (-4.7% (-21.5, 11.8), p=0.046). - Dietary nitrate supplementation significantly improved endothelial function in patients with COPD undertaking PR.
Pavitt et al. (30)	2021	FMD	- In patients with COPD who were established users of long-term oxygen therapy, nitrate-rich beetroot juice supplementation significantly improved endothelial function: nitrate-rich beetroot juice group: +4.1% (−1.1% to 14.8%) vs. placebo beetroot juice group: −5.0% (−10.6% to –0.6%) (p=0.0003). - Acute dietary nitrate supplementation has the potential to improve endothelial function in patients with COPD who require supplemental oxygen.
Rodriguez-Miguelez et al. (33)	2018	FMD	- FMD was significantly lower in COPD patients compared to healthy subjects (4.7±2.3% vs. 7.1±2.6%; p=0.024). - A single dose of tetrahydrobiopterin (BH_4) significantly increased FMD in patients with COPD (4.7±2.3% to 6.8±2.5%; p<0.05), improving FMD to values of control subjects (p=0.761). - An acute dose of BH_4 was able to improve endothelial function in patients with COPD to values similar to control subjects.