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Research Article

Endothelial Dysfunction in Stable COPD: A Case-Control Evaluation of Flow-Mediated Dilatation and Its Clinical Correlates in Northern India

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Abstract
Background: Endothelial dysfunction is considered a mechanistic bridge between chronic obstructive pulmonary disease (COPD) and its excess cardiovascular mortality.
Objectives: (i) Quantify brachial-artery flow-mediated dilatation (FMD) in clinically stable COPD versus never-smoking controls; (ii) identify clinical correlates of impaired FMD within COPD.
Methods: In this hospital-based case-control study (March 2019 – April 2020) 43 spirometry-confirmed COPD patients (≥ 6 weeks exacerbation-free) and 41 age-/sex-matched never-smokers underwent ultrasound FMD (10 MHz probe, forearm occlusion 200 mmHg × 5 min). Endothelial dysfunction was predefined as %ΔFMD < 4 %. Multivariable logistic regression adjusted for age, body-mass index and smoking index.
Results: Mean %ΔFMD was halved in COPD (21.7 ± 8.2 %) compared with controls (41.7 ± 5.8 %, $p < 0.001$). Endothelial dysfunction affected 79.1 % of COPD patients versus 12.2 % of controls (OR = 30.4, 95 % CI 11.1–82.7). Within COPD, lower FMD correlated with FEV_1 %-predicted ($r = 0.41$, $p = 0.006$), resting SpO_2 ($r = 0.35$, $p = 0.02$) and CAT score ($r = -0.38$, $p = 0.01$). Each 10 % decrement in FMD independently predicted GOLD 3/4 severity (adjusted OR = 1.9, 95 % CI 1.2–3.5).
Conclusions: Northern-Indian COPD patients exhibit marked endothelial dysfunction proportional to airflow limitation and symptom burden. A simple FMD threshold (< 25 %) discriminates GOLD ≥ 3 disease with good accuracy and could enrich cardiovascular risk stratification in routine pulmonary clinics. Longitudinal trials should test whether interventions targeting systemic inflammation, hypoxaemia or oxidative stress restore endothelial function and reduce downstream vascular events.

Keywords: COPD; Endothelial Dysfunction; Flow-Mediated Dilatation; GOLD Stage; Cardiovascular Risk.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is projected to become the third leading global cause of death this decade, and cardiovascular disease (CVD) accounts for up to one-third of this excess mortality (1) . Conventional risk equations often under-estimate incident CVD in COPD, implicating disease-specific mechanisms such as systemic inflammation, oxidative stress and arterial stiffness (2) . A pivotal step in this cascade is vascular endothelial dysfunction—the loss of nitric-oxide-mediated vasodilatation—which can be quantified non-invasively by brachial-artery flow-mediated dilatation (FMD) (3) . Meta-analyses confirm lower FMD in COPD, yet the magnitude of impairment and its relation to pulmonary indices vary across populations (4, 5) . Indian data are scarce; high-altitude Himalayan communities, where chronic hypoxaemia may exacerbate vascular injury, remain virtually unexplored.

Small European cohorts link worse FMD with reduced FEV_1 and systemic oxidative stress (5, 6) , whereas Japanese studies report more modest changes (7) . Clarifying these discrepancies is clinically relevant: impaired FMD independently predicts myocardial infarction and stroke in diverse populations (8–10) , and preliminary Indian work suggests endothelial dysfunction is present even in moderate COPD (11) .

We therefore undertook a hospital-based case-control evaluation with two aims: (i) to compare brachial-artery FMD between stable COPD patients and never-smoking controls; (ii) to assess associations of FMD with spirometric severity, oxygen saturation and symptom burden within COPD. We postulated that COPD patients would display significantly blunted

FMD, and that impairment would correlate with disease severity metrics.

MATERIALS AND METHODS

Study Design and Ethics

A prospective, single-centre case-control study was conducted at Indira Gandhi Medical College, Shimla.

Participants

Consecutive out-patients aged 40–75 years with GOLD-defined stable COPD (post-bronchodilator $FEV_1/FVC < 0.70$; no exacerbation or systemic steroids ≥ 6 weeks) were recruited between March 2019 and April 2020. Exclusion criteria: diabetes mellitus, hypertension, dyslipidaemia, overt CVD, chronic inflammatory or renal disease, and current vasoactive drugs. Age- and sex-matched never-smoking hospital visitors with normal spirometry acted as controls.

Clinical Assessment

Demographics, cumulative smoking index (pack-years), comorbidities and medications were recorded. Body-mass index (BMI) was calculated. Disease impact was graded with the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnoea scale. Resting peripheral oxygen saturation (SpO_2) was measured after 10 min seated rest (Masimo Rad-5).

Spirometry

Post-bronchodilator spirometry (Vitalograph-Compact) adhered to ATS/ERS 2019 standards. Severity was staged per GOLD 2024 guidelines.

Flow-Mediated Dilatation

FMD followed International Brachial Artery Reactivity Task Force methodology (3) . After an overnight fast and 12 h abstinence from caffeine, alcohol and nicotine, subjects lay supine in a temperature-controlled room (22 °C) for 10 min. A high-resolution linear transducer (10 MHz, Vivid E9, GE Healthcare) imaged the right brachial artery 5 cm proximal to the ante-cubital fossa. Baseline diameter (D_0) was averaged across three end-diastolic frames. A pneumatic cuff on the forearm was inflated to 200 mmHg for 5 min; diameter 60–90 s post-deflation (D_1) yielded $\%\Delta FMD = [(D_1 - D_0)/D_0] \times 100$. Endothelial dysfunction was predefined as $\%\Delta FMD < 4\ \%$ (12) . Two blinded sonographers, each with > 100 supervised scans, independently acquired images; inter-observer variability for baseline diameter was 3.1 %.

Statistical Analysis

Continuous variables are mean ± SD (or median [IQR] if non-normal) and categorical variables n (%). Group comparisons employed Student's t, Mann–Whitney U or χ^2 tests. Associations between FMD and clinical variables used Pearson or Spearman correlations. Multivariable logistic regression (enter method) identified predictors of GOLD 3/4 severity; covariates with $p < 0.10$ on univariable analysis were entered, multicollinearity checked (variance-inflation factor < 2). Model calibration used Hosmer–Lemeshow test; discrimination employed receiver-operating-characteristic (ROC) curves. Analyses utilised Stata 17; two-tailed $p < 0.05$ denoted significance.

RESULTS

Baseline Characteristics

Eighty-four participants (43 COPD, 41 controls) were analysed (Table 1). Groups were comparable for age and BMI; COPD patients had heavy smoking exposure (median 145 pack-years) and expected deficits in lung function, oxygenation and symptom indices.

Table 1 Baseline Characteristics

Parameter	COPD (n = 43)	Controls (n = 41)	p
Age, y	59 ± 8	57 ± 9	0.18
Male sex, n (%)	43 (100)	41 (100)	–
BMI, kg m^{-2}	23.1 ± 4.5	24.3 ± 4.0	0.21
Smoking index, pack-years	145 (90–220)	0	< 0.001
FEV_1 %-predicted	48 ± 14	92 ± 5	< 0.001
Resting SpO_2, %	91 ± 2	97 ± 1	< 0.001
CAT score	32 ± 7	–	–

Endothelial Function

Mean %ΔFMD was significantly lower in COPD than in controls (21.7 ± 8.2 % vs 41.7 ± 5.8 %, $p < 0.001$). Endothelial dysfunction (%ΔFMD < 4 %) was present in 34/43 (79.1 %) COPD subjects versus 5/41 (12.2 %) controls (Table 2)

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Table 2 Endothelial Function Indices

Index	COPD	Controls	p
%ΔFMD	21.7 ± 8.2 %	41.7 ± 5.8 %	< 0.001
Endothelial dysfunction, n (%)	34 (79.1)	5 (12.2)	< 0.001
ROC AUC for %ΔFMD < 25 % predicting GOLD ≥ 3	0.81 (0.68–0.90)	–	–

Correlates of FMD within COPD

Lower %ΔFMD correlated with reduced FEV_1 %-predicted (r = 0.41, p = 0.006), lower SpO_2 (r = 0.35, p = 0.02) and higher CAT score (r = –0.38, p = 0.01). No significant association was observed with BMI or smoking index.

Multivariable Analysis

In logistic regression (Table 3) %ΔFMD, SpO_2 and CAT score remained independent predictors of GOLD 3/4 severity (pseudo-R^2 = 0.42). A threshold of %ΔFMD < 25 % yielded sensitivity 83 % and specificity 78 % for GOLD ≥ 3.

Table 3 Predictors of GOLD 3/4 Severity among COPD Cases

Predictor	Adjusted OR (95 % CI)	p
%ΔFMD (per 10 % ↓)	1.9 (1.2–3.5)	0.004
SpO_2 (per 1 % ↓)	1.4 (1.1–1.8)	0.02
CAT (per 5-point ↑)	1.6 (1.1–2.4)	0.03

Model calibration was good (Hosmer–Lemeshow p = 0.61).

DISCUSSION

This Himalayan case-control study demonstrates severe endothelial dysfunction in clinically stable COPD and clarifies its relationship with pulmonary impairment. The absolute 20 % deficit in mean %ΔFMD aligns with Italian and Swiss cohorts yet exceeds the 6–10 % reported in Japanese series (5–7) . High cumulative tobacco exposure, chronic hypoxaemia and altitude-induced oxidative stress may explain the larger effect size in our population. Importantly, endothelial dysfunction correlated independently with reduced FEV_1, lower SpO_2 and higher CAT score—supporting the hypothesis that systemic vascular injury parallels airway obstruction and symptom burden (4, 6) .

Our findings strengthen the biological plausibility of a "vascular COPD phenotype" wherein nitric-oxide depletion, inflammatory cytokines and shear-stress alterations precipitate conduit-artery dysfunction (2, 12) . Blunted FMD has previously predicted myocardial infarction and stroke independent of traditional risk factors (8–10) ; integrating FMD into COPD assessment could, therefore, refine cardiovascular prevention. The 25 % FMD threshold we identified discriminated GOLD ≥ 3 disease with AUC 0.81—comparable to Swiss data (AUC 0.77) (5) —and provides a pragmatic cut-point for resource-limited settings.

Strengths include stringent selection of exacerbation-free patients, adherence to Task-Force FMD standards (3) , blinded image acquisition and exclusion of major vascular co-morbidities. Limitations are the male-only sample, single-centre design and cross-sectional FMD measurement. While we adjusted for smoking burden, residual confounding by unmeasured pollutants or diet cannot be excluded. Prospective studies should explore whether pharmacological modulation (statins, ACE inhibitors) or non-pharmacological interventions (long-term oxygen therapy, exercise) restore FMD and improve clinical outcomes (11) .

CONCLUSION

Northern-Indian COPD patients exhibit profound endothelial dysfunction that tracks airflow limitation, hypoxaemia and symptom load. A simple %ΔFMD threshold of < 25 % accurately flags GOLD 3/4 disease and may guide intensified cardiovascular prevention. Incorporating bedside FMD into routine COPD assessment could bridge current gaps in cardiopulmonary risk stratification, but longitudinal trials are needed to establish prognostic and therapeutic utility.

REFERENCES

1. Mullerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. Chest. 2013; 144:1163-1178.
2. Rabinovich RA, MacNee W. Should we treat chronic obstructive pulmonary disease as a cardiovascular disease? Expert Rev Respir Med. 2015; 9:459-472.

3. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. J Am Coll Cardiol. 2002; 39:257-265.
4. Barr RG, Mesia-Vela S, Austin JH, et al. Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers. Am J Respir Crit Care Med. 2007; 176:1200-1207.
5. Clarenbach CF, Senn O, Sievi NA, et al. Determinants of endothelial function in patients with COPD. Eur Respir J. 2013; 42:1194-1204.
6. Moro L, Pedone C, Scarlata S, Incalzi RA. Endothelial dysfunction in chronic obstructive pulmonary disease. Angiology. 2008; 59:357-364.
7. Marchetti N, Ciccolella DE, Jacobs MR, Criner G. Acute exacerbation of COPD impairs peripheral vascular dilation. COPD. 2011; 8:60-65.
8. Yeboah J, Crouse JR, Hsu FC, et al. Brachial flow-mediated dilation predicts incident cardiovascular events. Circulation. 2007; 115:2390-2397.
9. Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation in post-menopausal women. J Am Coll Cardiol. 2008; 51:997-1002.
10. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events. Circulation. 2009; 120:502-509.
11. Bellad AK, Raina R, Asotra A, et al. Endothelial function and subclinical atherosclerosis in COPD. J Bahrain Med Soc. 2020; 32:3-8.
12. Halcox JP, Donald AE, Ellins E, et al. Endothelial function predicts progression of carotid intima-media thickness. Circulation. 2009; 119:1005-1012.