Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol Brief

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Project Title:	Dual Antiplatelet Therapy in COPD Study
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1. Background and Significance

Chronic obstructive pulmonary disease (COPD) and emphysema are globally important chronic lower respiratory diseases and a leading cause of death in the United States and the world.[1] COPD is diagnosed by airflow obstruction that is not completely reversible, while emphysema is defined on pathology as permanent airspace dilation,[2] and there is significant heterogeneity in these features among patients. Currently, no pharmacologic therapy improves mortality or alters disease progression,[3-6] except in alpha-1 antitrypsin deficiency.[7]

The percent of emphysema-like lung on computed tomography (CT) has been associated with greater morbidity and mortality.[8-10] One proposed etiology of emphysema is microvascular disease, as pulmonary capillaries are structurally important to the alveolar wall, implicated in mouse models of emphysema,[11,12] and damaged in emphysematous areas of human lungs.[13,14] In prior work, we have identified several vascular-related factors that influence the rate of emphysema progression on CT.[15-17] In COPD, there is a reduction in microvascular perfusion evident on contrast-enhanced CT and MRI, which appears reversible in mild disease.[18,19]

Platelet activation is a pathway relevant to the microvasculature that has been implicated in COPD.[20-22] In 126 smokers with and without COPD in the Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study, we found greater platelet activation in those with a lower oxygen saturation, even within the normal range.[23] Aspirin irreversibly inhibits cyclooxygenase, reducing thromboxane (TX) A_2 and inhibiting platelets.[24] In 4,257 MESA Lung participants we found a slower 10-year progression of percent emphysema in aspirin users,[16] and in SPIROMICS, a study of nearly 3,000 participants with and without COPD, those using aspirin were found to have had fewer exacerbations and respiratory symptoms compared to matched participants not on aspirin.[25] Antiplatelet therapy for 7 days improves perfusion of the skin,[26-28] however it is unknown whether inhibiting platelet activation improves pulmonary microvascular perfusion.

2. Specific Aims and Objectives

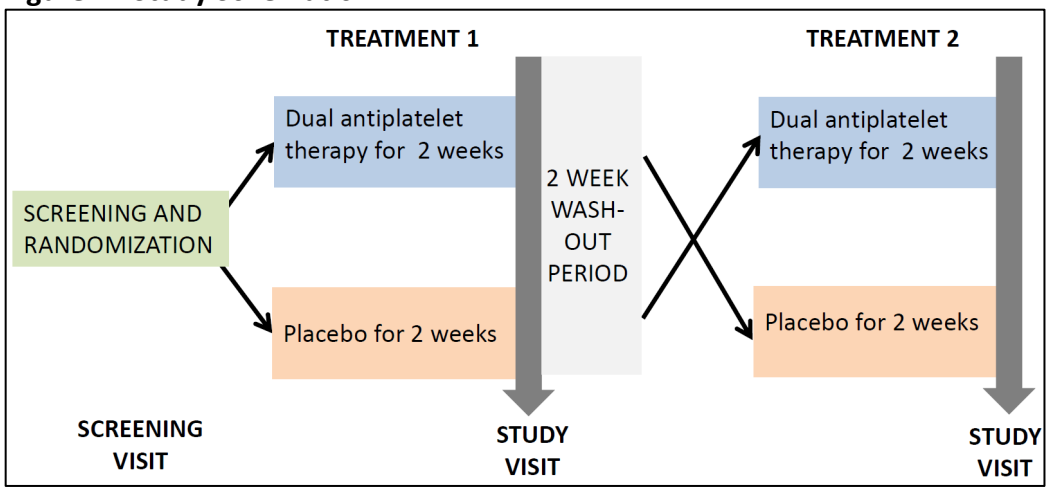
Hypothesis: Pulmonary blood flow will improve in underperfused lung regions while on dual antiplatelet therapy compared to placebo, and to a greater degree in persons with mild to moderate COPD compared to those without COPD.

Objective: To determine whether randomization to aspirin 81mg and clopidogrel 75mg daily for 2 weeks will reduce the coefficient of variation in pulmonary microvascular perfusion on dual-energy CT compared to placebo in cases with mild to moderate COPD and controls without COPD.

3. General Description of Study Design

The proposed study is a single-center Phase IIa randomized cross over study comparing dual antiplatelet therapy (aspirin 81mg and clopidogrel 75mg) to placebo. The study will accrue 30 subjects (20 COPD cases, 10 controls) and enroll up to 40.

Figure 1. Study Schematic



4. Subject Selection

a. Inclusion criteria for 20 COPD cases:
   i. Age between (and including) 50 to 80 years old
   ii. COPD (post-bronchodilator $FEV_1/FVC < 0.7$, $FVC \geq LLN$), GOLD Stage I/II ($FEV_1 \geq 40\%$)*
   iii. Former smoker at least 8 pack years

b. Inclusion criteria for 10 controls:
   i. Age between (and including) 50 to 80 years old
   ii. Normal lung function (post-bronchodilator $FEV_1/FVC \geq 0.7$, FEV_1 and $FVC \geq LLN$)*
   iii. Former smoker at least 8 pack years

*using the GLI race-neutral prediction equations for spirometry (Bowerman et al, AJRCCM 2023)

c. Exclusion criteria:
   i. Platelet count < 150,000/dL;
   ii. Self-report of a bleeding disorder;
   iii. Current use of aspirin, clopidogrel, or another antiplatelet medication;
   iv. Regular use of non-steroidal anti-inflammatory drugs (more than once/week);
   v. Allergy to aspirin, clopidogrel, iodine contrast or albuterol;
   vi. History of intracranial hemorrhage, severe GI bleed or other life-threatening bleed;
   vii. Use of blood thinner (e.g. warfarin, lovenox or novel oral anti-coagulants);
   viii. Daytime use of supplemental oxygen at home, use only on exertion or only at night is ok;
   ix. Regular use of oral steroids, theophylline, roflumilast or loop-diuretics (thiazides or K-sparing diuretics are ok) more than once/week);
   x. History of organ transplant;
   xi. History of autoimmune disease on current systemic anti-inflammatory therapy (e.g. rheumatoid arthritis, lupus);
   xii. Use of a biologic medication (to control inflammation, with regular injections) with last dose within 4 half-lives of the biologic drug;
   xiii. Other current lung disease (interstitial lung disease, idiopathic pulmonary fibrosis, asthma), however asthma/COPD overlap is ok;
   xiv. Intravenous drug use within the last year;
   xv. History of a lung surgery to remove part of the lung;
   xvi. Chest CT scan (most recent) that shows a significant lung mass, infiltrate (ground glass or other consolidation), or scarring/fibrosis of the lungs;
   xvii. Bullae or advanced destructive emphysema in more than 1/3 of the lung on the most recent Chest CT;
   xviii. Systemic therapy for cancer or local treatment to the thorax, such as a lumpectomy for breast cancer or radiation therapy to the thorax within the last 12 months (however surgical removal of a skin cancer or treatment of a localized cancer, e.g. prostate cancer, would be ok; use of ongoing hormonal therapy for cancer treatment is ok);
   xix. Known diagnosis of pulmonary hypertension;
   xx. Known systolic heart failure (right or left ventricular ejection fraction < 40%);
   xxi. BMI > 35.4;
   xxii. Acute or chronic renal insufficiency (estimated glomerular filtration rate [GFR] <60 mL/min/1.73 m^2 or self-report). GFR will be calculated using the CKD-EPI 2021 equation;
   xxiii. Current or planned pregnancy in the next year;
   xxiv. Regular marijuana smoking (more than monthly use or less frequent but unwilling to stop for the duration of the study);
   xxv. Exacerbation of respiratory symptoms within 6 weeks of the Visit 1 date, such as that requiring hospitalization, oral prednisone or antibiotics to control symptoms, or more than 6 weeks and not yet returned to baseline; and

xxvi. Chest, abdominal or eye surgery, or a heart attack or stroke, within 3 months of the date of screening (due to spirometry exclusion criteria).

a. Intervention

i. Aspirin 81 mg and clopidogrel 75 mg daily x 2 weeks. Aspirin 81mg is a commonly used over-the-counter medication that is generally regarded as safe. At the dose of 81mg aspirin is an antiplatelet medication. Clopidogrel is a prescription antiplatelet medication. The most common adverse effect of aspirin is minor gastrointestinal upset, and a common adverse effect of both aspirin and clopidogrel is minor bleeding. The two medications are used together to provide a more significant antiplatelet effect commonly in patients with coronary artery disease.

ii. Placebos daily x 2 weeks. Placebo pills will look exactly like aspirin and clopidogrel, but will not contain any medication.

iii. Participants will be asked to bring back the pill vials at the end of each treatment period so that pill counting can be performed to assess adherence.

iv. The planned treatment periods are 14 days each, but participants will be given 20 pills in case the date of the visit needs to be changed (due to weather or other unforeseen circumstances).

Table 1: Components of each visit

Visit #:	1	2	3
Exam component	Randomization visit	After treatment 1	After treatment 2
Informed consent	X		
Physical exam	X		
Urine - pregnancy test and cotinine	X	X	X
Height and weight	X	X	X
Blood pressure, heart rate, pulse oximetry	X	X	X
Questionnaires	X	X	X
Phlebotomy			
Cr and CBC w/ diff to BWH lab	X	X	X
Samples for transport to BCH for platelet measures		X	X
Sample prep for freezer storage for plasma biomarkers	X	X	X
Urine specimen storage for platelet activation	X	X	X
Fraction exhaled nitric oxide	X	X	X
Spirometry, pre- and post-bronchodilator	X	X	X
CT scans		X	X

b. Endpoints

i. Primary endpoint: Coefficient of variation (CV) in pulmonary blood volume across lung regions on dual-energy CT (DECT). We hypothesize that antiplatelet therapy will result in a more homogenous distribution of blood flow (i.e. lower CV) by improving perfusion to underperfused lung regions.

ii. Secondary endpoints:
   1. DECT measures of pulmonary blood volume, CV in pulmonary blood flow, and pulmonary blood flow
   2. Distal macrovascular pruning on non-contrast inspiratory CT
   3. Percent emphysema$_{-950}$ on non-contrast inspiratory CT
   4. Functional small airways disease, calculated from non-contrast expiratory and inspiratory CT
   5. Regional V/Q measures using non-contrast TLC and contrast CT images at FRC
   6. Fraction of exhaled nitric oxide (FeNO)
   7. Lung function (FEV_1, FVC, FEV_1/FVC)
   8. DLCO (this was removed in Protocol Version 1.13)
   9. Resting oxygen saturation
   10. Plasma biomarkers related to:
      a. endothelial activation (sICAM-1, sVCAM-1, sP-selectin, sE-selectin, vWF);
      b. angiogenesis (VEGF, TIMP-1 and PAI-1);
      c. inflammation (WBC, CRP, IL-6, TNF-a, myeloperoxidase);
   11. Measures of platelet activation
      a. circulating monocyte-platelet aggregates, unstimulated
      b. activated GPIIb/IIIa receptor, unstimulated, and stimulated by low and high dose arachidonic acid and adenosine diphosphate

5. Statistical Analysis

a. Data analysis: The primary analysis will use the Wilcoxon rank sum test for paired samples to compare the whole-lung mean of regional CV of microvascular perfusion on treatment vs. placebo. Similar analyses will be performed for secondary endpoints.
   i. Exploratory analyses will evaluate for period and carryover effects, and examine whether there is effect modification. We hypothesize that those with greater baseline platelet activation (by urine 11d-TXB2), greater responsiveness to aspirin and clopidogrel (by decrease in monocyte-platelet aggregates on treatment) and those with baseline pulmonary arterial pruning on non-contrast CT (BV5a/TBVa ≤ 0.60) will have stronger results.
   ii. We will examine the change in percent emphysema$_{-950}$ on treatment and placebo to evaluate whether platelet-related change in perfusion alters

measurement of percent emphysema; we do not expect emphysema to change in 4 weeks.

iii. Approaches to missing data include: 1) minimization through short study duration and efforts to retain all participants and 2) sensitivity analyses using a variety of imputed values (worst case scenario, baseline observation carried forward, last observation carried forward).

Power: Power for pulmonary microvascular perfusion was estimated for a paired t-test (more conservative than the Wilcoxon Rank sum test) to compare each individual's mean CV in non-dependent lung on the intervention vs. placebo. Based on published data[18] and assuming a correlation of 0.6 between paired scans and alpha=0.05, with 20 cases we would have the power to detect a 3.5% or greater difference in non-dependent lung CV (power=0.78). For comparison, non-dependent lung CV was reduced by 7% with sildenafil. Power will be less for smoking controls, in whom we do not expect a significant change.

12. References

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