Lung Hyperinflation and Cardiac Impairment in Chronic Obstructive Pulmonary Disease

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Accessibility
Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) commonly coexist. In patients with cardiovascular disease, COPD is associated with increased cardiovascular morbidity and mortality independent of smoking. This association is likely multifactorial, related to mechanical interdependence of the heart and lungs, systemic and regional inflammation, and cardiovascular remodeling. However, the relative significance of these factors and their mechanistic relationships are poorly understood. Recent evidence suggests that lung hyperinflation is independently associated with increased mortality in patients with COPD and that a reduction in hyperinflation with lung volume reduction surgery (LVRS) improves cardiac performance. However, there is very limited knowledge about the mechanism by which hyperinflation impairs cardiac performance in individuals with COPD and existing heart disease. The overall goal of this proposal is to clarify the role of cardiopulmonary interdependence in patients with coexisting COPD and CVD.

Prior imaging studies evaluating cardiac structures and physiology have been limited by the poor acoustic windows characteristic of COPD patients undergoing transthoracic echocardiography (TTE). Newer imaging approaches such as cardiac magnetic resonance imaging (CMR) allow a more precise evaluation of left and right heart function and intrinsic cardiac alterations without some of the technical limitations of TTE in COPD patients. Right heart catheterization (RHC) remains the gold standard for ascertaining cardiac hemodynamic indices, but is limited by its invasiveness. Complementary-directed evaluation of heart function with both CMR and RHC can leverage the advantages of each and possibly yield novel insights about critical determinants of cardiopulmonary relationships in COPD patients.

A key strategy to study the impact of mechanical forces is reducing hyperinflation in COPD subjects and evaluating changes in cardiovascular function. Current deflation approaches include bronchoscopic or surgical lung volume reduction, which both carry significant risks and are limited by confounding effects of the procedures. To overcome these shortcomings, our lab has developed a novel, validated reverse pressure pulse device that accomplishes transient deflation. This approach allows for monitoring real-time hemodynamic responses and limits confounding effects of surgery, or changes in lung parenchymal mechanics.

Our overall hypothesis is that impaired cardiac performance in patients with COPD and CVD is due in part to mechanical cardiopulmonary interdependence, which can be attenuated by deflation. I propose to utilize CMR derived measures of cardiac structure and function to clarify intrinsic cardiac and extrinsic mechanical causes of poor cardiovascular performance in an established institutional cohort patients with COPD and CVD. I then propose using a non-invasive temporary deflation strategy using a reverse pulse pressure device in a prospective cohort of subjects with COPD and lung hyperinflation to study the immediate hemodynamic responses to deflation using non-invasive impedance cardiography. This will be accomplished via the following hypothesis-driven specific aims:

**AIM 1:** To determine the relationship between lung hyperinflation (defined by total lung capacity (TLC) > 120% predicted) and static measures of cardiac structure and function in subjects with COPD and CVD.

**AIM 1a:** To determine if lung hyperinflation impairs cardiac structure and function as measured by CMR.

Hypothesis 1a: CMR-derived indices of cardiac structure and function (cardiac output, ejection fraction, pulmonary artery diameter, chamber areas and volumes, ventricular masses and remodeling indices) are more impaired in subjects with hyperinflation compared to their nonhyperinflated counterparts.

**AIM 1b.** To determine if left ventricular physiologic dysfunction is the major determinant of poor cardiac performance in subjects with lung hyperinflation, using invasive measures of intracardiac filling.

Hypothesis 1b: Increased severity of left ventricular dysfunction as measured structurally by CMR and hemodynamically by right heart catheterization (RHC) is the predominant cause of worse cardiac performance in subjects with hyperinflation compared to their nonhyperinflated counterparts.

**AIM 2:** To assess the relationship between lung deflation and changes in noninvasive measures of cardiac function in a prospective cohort of subjects with COPD and lung hyperinflation (TLC > 120% predicted).

Hypothesis 2: Improvement in cardiac performance after acute lung deflation using a reverse pulse pressure device can be detected by examining non-invasive measurements of left ventricular stroke volume derived from thoracic impedance measurements.

Successful completion of the proposed study will both refine cardiac risk stratification in COPD subjects with CVD and identify novel adjunctive therapeutic targets in this population to improve cardiovascular outcomes.
Chronic obstructive pulmonary disease (COPD) affects up to 24 million people in the United States and is one of the leading contributors of death worldwide. A recent meta-analysis observed a 2-5 fold increased cardiovascular disease (CVD) risk from COPD.\(^3\) In fact, a significantly high proportion of COPD patients succumb to cardiovascular causes of death rather than respiratory failure.\(^12\) While COPD and cardiovascular disease (CVD) commonly coexist and share notable risk factors such as tobacco smoking, it is increasingly apparent that alternative factors other than tobacco smoke are implicated in their association.\(^1\)\(^\text{-}3\)\(^\text{-}13\)

Evidence suggests that lung hyperinflation is independently associated with heightened morbidity and mortality in patients with COPD.\(^14\)\(^\text{-}15\) However, few studies have examined the role of pulmonary hyperinflation in predicting poor cardiovascular outcomes in comorbid patients. Early studies that examined the effect of obstructive lung disease on cardiac structure and function produced conflicting results and few assessed pulmonary hyperinflation. These prior studies in largely non-hyperinflated COPD patients implicated impaired cardiac chamber size but were limited by small sample sizes and less precise imaging techniques. Subsequent transthoracic echocardiographic studies in COPD patients without cardiovascular disease suggested that hyperinflation correlated with reduced left ventricular chamber diameters and a recent cardiac magnetic resonance imaging study in a small cohort of COPD patients without cardiovascular disease suggested that hyperinflation was associated with greater left ventricular mass.\(^8\)\(^\text{-}16\)\(^\text{-}17\) However, given conflicting evidence, it remains unknown whether these observations: 1) can be replicated and explained with accurate imaging (CMR); 2) are valid in clinically hyperinflated patients; 3) explain high cardiovascular morbidity in a population with COPD and CVD; \& 4) clarifies whether cardiac geometrical alteration actually has hemodynamic consequences in this comorbid population.

Reducing hyperinflation with lung volume reduction surgery (LVRS) appears to improve cardiac performance. A post hoc analysis of 847 patients from the National Emphysema Treatment Trial (NETT), demonstrated that a decrease in hyperinflation after LVRS was associated with improved oxygen pulse (surrogate for cardiac stroke volume) 6mo after randomization compared to standard of care.\(^16\) (Figure 1) It is believed that reducing hyperinflation may improve cardiac function.\(^19\) However, the lack of clear mortality benefit with longer-term health indices reflects the high morbidity associated with LVRS.\(^5\)

While various potential mechanisms regarding cardiovascular improvement after LVRS have been postulated, most converge on an improvement in cardiopulmonary mechanical interdependence. Thus a number of studies have sought to measure intracardiac and intravascular pressures invasively to discern a causal link. Esophageal balloon manometry studies to measure extrapulmonary, intrathoracic pressures confirm that lung volume reduction surgery reduces intrathoracic pressures.\(^20\) Mineo et al showed that patients with the highest degrees of hyperinflation enjoyed the greatest cardiac improvements after LVRS by demonstrating augmentation of cardiac index at rest and with exercise.\(^21\) These authors hypothesized that postoperative hemodynamic augmentation was secondary to increased preload (or relieved intrathoracic pressures impeding blood flow outside the heart) but that further study was required.

Overall, studies evaluating the effects of lung volume reduction on cardiovascular hemodynamics are mixed and critical gaps persist. Jorgensen et al performed simultaneous RHC and transesophageal echocardiography on 15 patients (5 controls, 10 with severe emphysema undergoing LVRS) argued that lower left ventricular (LV) preload was the primary determinant of decreased cardiac function in the setting of hyperinflation.\(^22\) In contrast, Criner et al showed that LV preload decreased after LVRS.\(^23\) And lastly, Montes de Oca et al described an inverse relationship between inspiratory intrathoracic pressures and maximal O\(_2\) pulse in 25 patients with advanced COPD, suggesting that reduced LV afterload may also be an important mechanism in improving stroke volume after LVRS.\(^24\) Thus, the reason for improved cardiac performance after lung deflation remains unclear, in part due to the reliance of the field on invasive methods to determine cardiac function in small sample populations. Some also argue that simply the decompressing effects of open
thoracotomy alone in those with severe hyperinflation might actually modulate cardiac performance independently of lung deflation. Additionally, given the high prevalence of comorbid COPD and CVD, prior studies evaluating hyperinflation largely have studied those without CVD limiting generalizability. Cardiac impairment affects a substantial portion of the COPD population and is out of proportion to the expected contribution from comorbid risk factors.³ Our study is designed to address the critical gaps in the literature to gain a better understanding of the relationship between hyperinflation and cardiac performance in COPD. We will use a unique local well-phenotyped cohort with a high burden of cardiovascular disease referred for cardiac MRI to study this relationship. By studying hyperinflation in those with concomitant COPD and CVD our study will be tailored to be representative of the COPD patient population at risk for cardiovascular complications. Furthermore, by using a custom-designed pulse pressure generator at the mouth (to overcome expiratory flow limitation) as a “deflation tool”, we will study the effects of lung deflation on the heart without the confounders and limitations of surgical methods to reduce lung volume (LVRS or transplantation).

The successful completion of the proposed aims should have three important implications: (1) improve our ability to characterize high-risk patients; (2) allow us identify novel targets for therapy; and (3) inform potential preventive measures for this population.

RESEARCH STRATEGY: INNOVATION

Some of the innovative aspects of this proposal are:

1. **We have a cohort of 8,000 subjects who have undergone cardiac MRI and are poised to leverage this large dataset to gain mechanistic insights while prior approaches using transthoracic echocardiography (TTE) are limited by poor acoustic windows common to COPD subjects.** We are uniquely positioned to understanding temporal-spatial consequences of lung hyperinflation on cardiac geometry that has not been possible with prior studies. (Figure 2)

2. **By leveraging a cohort with a high burden of cardiovascular disease, we are able study the effects of hyperinflation in patients with both COPD and cardiovascular disease in a case-control fashion.** Prior epidemiological studies are limited by very large populations with rare cardiac disease and minimal amounts of lung inflation that is of unclear clinical significance.²⁵,²⁶ However, given the high comorbidity of COPD and CVD, these types of studies are clearly important. We are uniquely positioned with an enriched and highly phenotyped cohort to study this clinically important patient population.

3. **To develop a more complete understanding of the impact of lung hyperinflation on cardiovascular performance, we will utilize a novel, custom-built low-risk, non-invasive short-term “lung deflation” tool.** Mixed results evaluating hemodynamics in patients undergoing lung volume reduction surgery are likely related to small numbers from recruitment challenges and confounding from the various hemodynamic effects of open thoracotomy and anesthesia independent of lung volume reduction itself. Using a device that overcomes expiratory flow limitation for a brief period will allow repeated measurements before and after lung deflation without confounding procedural alterations in lung or cardiac physiology.

RESEARCH STRATEGY: APPROACH

Aim #1: To determine the relationship between lung hyperinflation and static measures of cardiac structure and function in subjects with COPD and CVD.

Aim 1.a: To determine if lung hyperinflation impairs cardiac structure and function as measured by CMR.

Preliminary studies for Aim 1.a.
Using a database of nearly 8,000 cardiac MRIs performed over the last 10 years through Partners Healthcare, I performed a preliminary investigation of 40 consecutive subjects with COPD and existing ischemic heart disease. I collected anthropometrics and comorbidities on all subjects who underwent pulmonary function testing and chest computed tomography (CT) within one month of CMR.

Overall, 32% were women, median age 63 years (52-74), median pack-years of smoking 30 pack-years (10-100) and median FEV1 % predicted 54% (36-72). Amongst all subjects, increasing TLC % predicted was associated with decreasing cardiac output (-0.016 L/min/TLC%, p=0.05), left ventricular mass (-0.88 g/TLC%, p=0.016), and left ventricular end diastolic volume (beta=-1.38 ml/TLC%, p=0.03) and right ventricular end diastolic volume (-0.82 ml/TLC%, p=0.014) (Figure 3). Despite similar degrees of systolic function by ejection fraction, increasing degrees of lung inflation in patients with COPD and cardiovascular disease is associated with diminishing cardiac chamber size and cardiac output.

This observed preliminary correlation supported a case-control approach to minimize effects of referral bias. Of the 40 subjects, fourteen met clinical criteria for hyperinflation and were matched by age, gender and co-morbidities to fourteen subjects with COPD but without hyperinflation for a case-control analysis. Amongst subjects with hyperinflation, the aforementioned hemodynamic parameters were lower in comparison to their non-hyperinflated counterparts. Specifically, subjects with hyperinflation had lower mean cardiac indices (-0.31 L/min/m², p= 0.09) and left ventricular mass indices (-10.3 g/m², p=0.08). Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were not significantly different between the groups. This preliminary analysis further supports an association with diminished effective cardiac function and altered cardiac geometry from hyperinflation in patients with both COPD and CVD.

Experimental methods for Aim 1.a.

A database of nearly 8,000 CMRs completed through Partner’s Healthcare since 2002 was established to study the utility of CMR in different cardiac disease states. At the time of imaging, subjects’ medications, comorbidities and cardiac diagnosis were recorded. Retrospectively, data regarding chest CT, smoking history, pulmonary function testing, laboratory tests, echocardiograms and cardiac catheterizations completed within one month of the CMR were included in the database. 947 of these subjects underwent pulmonary function testing within 4 weeks of CMR. Using the established GOLD criteria for COPD (forced expiratory volume over one second / forced vital capacity < 0.7) without clear evidence of obstruction reversibility, 298 of these subjects have documented COPD. The analyses for Aim 1 will involve two subsets of subjects from this cohort, all of whom have documented cardiovascular disease in addition to concurrent pulmonary function testing and CMR data: (1) 75 subjects with COPD by spirometric measurement but without hyperinflation; and (2) 75 subjects with COPD and hyperinflation by spirometry. Hyperinflation will be defined by total lung capacity > 120% predicted.

Noninvasive cardiologists and cardiac radiologists have previously completed measures of cardiac output, ejection fraction, atrial and ventricular chamber areas and volumes, and transvalvular gradients from the CMR images. Currently, under this IRB-approved study, we are measuring pulmonary artery diameter, ventricular masses, myocardial characteristics (ie. myocardial fibrosis) and remodeling indices in the proposed subjects.

The primary analysis endpoints will be: (1) cardiac output; (2) left ventricular end-diastolic volume; and (3) left ventricular mass. Secondary outcome variables will be left ventricular end-systolic volume, left ventricular ejection fraction, right ventricular end-diastolic and end-systolic volumes, right ventricular ejection fraction, right ventricular mass, pulmonary artery diameter, supravalvular aortic diameter, left atrial volume, right atrial volume, degrees of mitral and tricuspid regurgitation, and extent of myocardial fibrosis.

Aim 1b: To determine if left ventricular physiologic dysfunction is the major determinant of poor cardiac performance in subjects with lung hyperinflation, using invasive measures of intracardiac filling.

Preliminary studies for Aim 1.b.
Right heart catheterization (RHC) to invasively measure cardiovascular hemodynamics was developed in the 1970s and remains the gold standard for characterizing an individual’s hemodynamic profile. A balloon-tipped catheter sequentially measures pressures in the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position (as a surrogate for left atrial pressure). Using thermodilution or measures of oxygen consumption with differences in arterial-venous oxygen content, cardiac output is determined.

Since our 8,000 patients with CMR have been referred for clinical indications, the majority (~75%) have had recent right heart catheterization as part of their diagnostic work-up. Thus we are distinctly positioned to study structure, function, and hemodynamics with the gold standard tests across each sample. The rate of RHC performance on COPD individuals is not significantly different than those without COPD (p>0.1).

Velocity-encoded phase-difference CMR can provide accurate estimates of cardiac output and is concordant with invasive approaches to cardiac output determination. As noted above, preliminary matched analyses of 14 hyperinflated cases and 14 controls suggest diminished cardiac output (p=0.09) by CMR in those with hyperinflation. RHC will ascertain whether alterations in intracardiac pressures contribute to this parameter. Jorgensen et al evaluated the changes in measures of left ventricular preload (pulmonary capillary wedge pressure (PCWP)) with LVRS in patients with severe emphysema and showed that LVRS increased PCWP (12.0+/−1.3 to 14.7+/−2.1). We would expect similar differences in preload between COPD patients with CVD who have hyperinflation and those who do not have hyperinflation.

Experimental methods for Aim 1.b

Samples for this analysis will be derived from our cohort of 8,000 subjects as previously described in Aim 1.a above. COPD and hyperinflation will be defined as above in Aim 1.a. A set of individuals with COPD and CVD who have had RHC within one week of CMR acquisition will be defined. Subsequently, 50 individuals with COPD, CVD, and hyperinflation will be randomly sampled from this set and non-hyperinflated counterparts will be selected in a 1:1 matching fashion as described earlier. RHC values have already been acquired from the electronic health record via an approved IRB protocol. All RHCs have been performed and interpreted by a licensed invasive cardiologist in a cardiac catheterization laboratory.

The primary analysis endpoints will be: (1) pulmonary capillary wedge pressure, (2) right atrial pressure, and (3) cardiac output. The secondary outcomes analyzed will include additional measures of intracardiac filling (pulmonary arterial diastolic pressure, right ventricular diastolic pressure) and measures of pulmonary hypertension which is highly prevalent in individuals with chronic lung disease (pulmonary arterial systolic pressure, right ventricular systolic pressure).

Statistical considerations and power analyses for Aim 1.

The overall goal of this analysis is to understand how lung volumes alter cardiac chamber size, function, hemodynamics, and remodeling. Using a case-control approach to limit ascertainment bias, I will compare the CMRs of 75 subjects with COPD and CVD with hyperinflation and 75 subjects with COPD and CVD without hyperinflation with a 1:1 matching approach by age +/- 5 years, gender, ethnicity, body-mass index, and smoking status. Since many but not all subjects have undergone right heart catheterization, I will compare 50 cases and 50 controls selected by the same criteria and approach as above.

We are matching on these characteristics to limit the effects of confounding because they are each important determinants of both COPD and CVD. Outcome variables will be indexed for body surface area. If the distribution of paired differences for any outcome departs from a normal distribution or extreme values are observed, we will consider a proper Box-Cox power transformation before t-test or Wilcoxon’s Signed Rank test. In order to control for the simultaneous comparisons of three primary outcomes for each sub-aim, we will apply a Bonferroni’s correction to limit the overall type-1 error rate to 0.05. As the selection of the non-carriers will be conducted by matched sampling, we will examine compatibility as well as potential overmatching by using post-matching propensity score analysis, and we will conduct an adjusted analysis if necessary.

At a sample size of 75 cases and matched controls for an analysis of CMR, from my preliminary analyses presented above, I estimate that we will have 90% power to detect a difference in cardiac index of 0.4 L/min/m2 for a Bonferroni-corrected alpha=0.05. At a sample size of 50 cases and matched controls for an analysis of RHC, assuming a standard deviation of 2mmHg for PCWP, we have 90% power for detecting a 1.2mmHg PCWP difference for a Bonferroni-corrected alpha=0.05.

Potential pitfalls / alternate approaches for Aim 1.
The population from which samples are derived is cohort of individuals referred for CMR for clinical indications. Although we propose a simple random sampling of hyperinflated individuals and 1:1 matching for non-hyperinflated individuals, the pool of individuals are not a random sampling of the general population and may lead to ascertainment bias. To minimize confounding from this, I propose a case-control study design. A population-based approach of CMR acquisition is underway within the local NHLBI Framingham Heart Study but the number of individuals with concomitant COPD and CVD who have undergone CMR is currently very low.

Other non-invasive approaches in addition to CMR may yield important insights to cardiopulmonary interactions. For example, the vast majority of individuals with COPD have had clinical chest CTs. Although not routinely collected, cardiac chamber sizes can be extracted and important insights can be gained particularly with a large sample size. But the lack of ECG-gating yields higher interindividual variances. Unlike CMR, resolution is insufficient to make determinations about ventricular mass and intrinsic myocardial changes. Other emerging tools for cardiac imaging may be used in the future to gather supplementary data. Cardiac CT coronary angiography (CCTA) to evaluate patients for the presence of atherosclerotic cardiovascular disease has emerged as a novel tool. ECG-gating permits cardiac chamber quantification at specified portions of the cardiac cycle (ie. systole, diastole). CCTA has the unique advantage of ascertaining the presence of coronary atherosclerosis. A provocative study this year suggested common genetic determinants between lung function and risk for coronary artery disease.26

Individuals with COPD and CVD referred for RHC may have more severe disease compared to those who have not within the cohort. Again, a matched case-control association approach will minimize such confounding from referral bias. Surrogates for preload (eg. left ventricular end-diastolic volume) from CMR may be used as a measure of intracardiac blood volume but does not completely represent physiologic preload that is the primary determinant of stroke volume. A prospective trial in the future would best address this limitation.

Aim 2. To assess the relationship between lung deflation and changes in noninvasive measures of cardiac function in a prospective cohort of subjects with COPD and lung hyperinflation

Preliminary studies for Aim 2.

Our group has developed a novel non-invasive model to study deflation in humans.29 The technique of “Reverse Pressure Pulses” (RPP) consists of applying high frequency (10-15 Hz) positive pressure pulses at the mouth during exhalation. It is believed that, the pressure pulses temporarily reopen the compliant, collapsed airways, allowing exhalation of trapped air. RPP derives its mechanistic insight from “pursed-lip” breathing, a common adaptation of COPD patients to ease dyspnea.30 However, instead of the steady elevated expiratory pressure generated by pursed lips, RPP exposes the opening of the airway to a pulsating pressure. Previously, an RPP device has been shown to relieve hyperinflation in the majority of the emphysematous patients that were studied.11,29

In a clinical trial of hyperinflated patients conducted by our group, it was demonstrated that RPP systematically improved blood gases, reduced cyanosis, reduced both respiratory and cardiac frequencies during exercise and patients’ self reported ease of breathing improved.29 (Table 2) The device’s respiratory effects appear to transiently mimic the effects of LVRS without the risks of open thoracotomy or introducing confounding from the thoracotomy.

And to study the dynamic hemodynamic effects of deflation in our model, we will use non-invasive impedance cardiography (ICG) (ICON, Osypka Medical, La Jolla, CA). ICG utilizes small electrical pulses as a plethysmogapher to discern blood volume changes from changes in resistance to pulse propagation.31,32 Technological advances over the past decade allow accurate hemodynamic estimates.33 Cardiac output from ICG correlates very well with RHC thermodilution estimates in several studies.33 Importantly, ICG provides accurate hemodynamic estimates in hyperinflated COPD patients.34 Although absolute values of cardiac output

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Table 2: Clinical evaluation of RPP as a therapeutic technique. *During exercise the use of RPP caused a significant (p<0.05) increase in arterial oxygen levels ($pO_2$) and oxygen saturation, and a reduction in cardiac and respiratory frequencies.
can contain errors compared to RHC thermodilution, the ICG measurements are usually very accurate for changes in cardiac output over short time scales such as proposed here.

Experimental methods for Aim 2.

We have already developed an IRB-approved protocol for this study. We will enroll 10 patients >45 years old with severe COPD (defined as forced expired volume in 1 sec (FEV$_1$) < 50% of predicted and forced expiratory ratio (FER) < 0.7) who were prior smokers. All subjects will have spirometric evidence of hyperinflation (TLC > 120% predicted). Exclusion criteria include history of pneumothorax, pulmonary hypertension, other known lung diseases, exposures to pneumotoxic agents (eg. asbestos, silica) and recent acute COPD exacerbation.

Each subject will undergo two study sessions: (1) one session will evaluate changes in cardiac physiology using the reverse pressure pulse (RPP) device to transiently deflate lung volumes at rest and (2) another will evaluate changes in dynamic cardiac function when using the RPP device under conditions of simulated exercise. In each session the subjects will undergo spirometry and then hemodynamic measurements with ICG. We will also measure the degree of hyperinflation with inspiratory capacity maneuvers recorded using a pneumotachometer, which is integrated into the RPP device.

During the first session, subjects will breath through the RPP device at baseline for 15 minutes. During the second session, we will administer a small amount of carbon dioxide (<5%) until the subject’s ventilation doubles, to simulate exercise since most subjects with severe COPD will be unable to attain sufficient degrees of exertion for multifactorial reasons. They will then breath through the RPP device for 15 minutes. The device creates 25 Hz pressure waves at the mouth during expiration that are 12-15 cmH20 above atmospheric pressure. During each session, heart rate, blood pressure, oxygen saturation, respiratory rate and inspiratory capacity are measured before and after use of the RPP device. Also, ICG measures of stroke volume and cardiac output will be recorded at time 0, 5, 10 and 15 minutes.

The primary analysis endpoints will be: (1) differences in stroke volume and (2) cardiac output with RPP use at simulated exercise. We hypothesize that both parameters should increase with deflation and correlate to ICG.

Statistical considerations and power analyses for Aim 2.

Given the repeated measures within the same subject, we will use a paired Student’s t test for each of the outcome variables with pre- and post-RPP status being the predictor variable. A paired approach both increases power by reducing the degrees of freedom and reducing the variance by essentially assuming similar noise. If extreme differences and/or non-normality is observed, we will consider appropriate transformation or use a non-parametric test such as a Wilcoxon signed rank test. Given the presence of two primary endpoints, we will correct for multiple hypothesis testing with a Bonferroni-corrected alpha=0.05. Outcome variables will be indexed for body surface area.

Based on experiences from LVRS studies, we expect deflation in hyperinflated individuals to yield an improvement of cardiac index of 0.73 L/min/m2 (common standard error 0.16) and stroke volume index of 7.8 mL/m2 (common standard error 2.4)\textsuperscript{20,22} Thus, with 10 pairwise analyses, we attain >90% power with a Bonferroni-corrected alpha=0.05 for these effect sizes.

Potential pitfalls / alternate approaches for Aim 2.

Newer technology has permitted ICG to be an accurate estimate of cardiac output and stroke volume but RHC is the established gold standard for assessing cardiovascular hemodynamics. One approach would be to conduct the proposed Aim with RHC but to aid safety and feasibility of the study over the award period, a validated non-invasive approach appears more well-suited.

This approach evaluates the acute hemodynamic effects of deflation and is agnostic to the longer-term effects of hyperinflation. For example, more long-term hyperinflation may be associated with specific intrinsic myocardial changes yet one would not expect such deleterious consequences to reverse over the course of several minutes of deflation. Methods to detect such changes would require longer-term studies with more durable deflation approaches. Preliminary results from the proposed study may support such future studies.

We assume that our RPP device will improve ICG measures, but it is possible that we will not attain an appreciable degree of improvement with the device. If this occurs, we could try alternative methods to improve hyperinflation such as bronchoscopic lung volume reduction using endobronchial valves, or alternatively, we could study COPD patients with hyperinflation before and after transplantation, but these studies would be invasive and subject to other potential confounders similar to LVRS.
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