ORIGINAL ARTICLE

Lung Deflation and Cardiovascular Structure and Function in Chronic Obstructive Pulmonary Disease

A Randomized Controlled Trial

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Abstract

Rationale: Patients with chronic obstructive pulmonary disease develop increased cardiovascular morbidity with structural alterations.

Objectives: To investigate through a double-blind, placebo-controlled, crossover study the effect of lung deflation on cardiovascular structure and function using cardiac magnetic resonance.

Methods: Forty-five hyperinflated patients with chronic obstructive pulmonary disease were randomized (1:1) to 7 (maximum 14) days inhaled corticosteroid/long-acting β_2-agonist fluticasone furoate/vilanterol 100/25 μg or placebo (7-day minimum washout). Primary outcome was change from baseline in right ventricular end-diastolic volume index versus placebo.

Measurements and Main Results: There was a 5.8 ml/m^2 (95% confidence interval, 2.74–8.91; $P < 0.001$) increase in change from baseline right ventricular end-diastolic volume index and a 429 ml ($P < 0.001$) reduction in residual volume with fluticasone furoate/vilanterol versus placebo. Left ventricular end-diastolic and left atrial end-systolic volumes increased by 3.63 ml/m^2 ($P = 0.002$) and 2.33 ml/m^2 ($P = 0.002$). In *post hoc* analysis, right ventricular stroke volume increased by 4.87 ml/m^2 ($P = 0.003$); right ventricular ejection fraction was unchanged. Left ventricular adaptation was similar; left atrial ejection fraction improved by +3.17% ($P < 0.001$). Intrinsic myocardial function was unchanged. Pulmonary artery pulsatility increased in two of three locations (main +2.9%, $P = 0.001$; left +2.67%, $P = 0.030$). Fluticasone furoate/vilanterol safety profile was similar to placebo.

Conclusions: Pharmacologic treatment of chronic obstructive pulmonary disease has consistent beneficial and plausible effects on cardiac function and pulmonary vasculature that may contribute to favorable effects of inhaled therapies. Future studies should investigate the effect of prolonged lung deflation on intrinsic myocardial function.

Clinical trial registered with www.clinicaltrials.gov (NCT 01691885).

Keywords: lung hyperinflation; chronic obstructive pulmonary disease; cardiac function; cardiac magnetic resonance; fluticasone furoate/vilanterol

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At a Glance Commentary

Scientific Knowledge on the Subject: Significant cardiovascular morbidity and mortality exists in chronic obstructive pulmonary disease. Associations between lung hyperinflation and cardiac structure and function exist, although it is unknown whether these changes are reversible with pharmacologic therapy.

What This Study Adds to the Field: This single-center, randomized, placebo-controlled, crossover cardiac magnetic resonance study demonstrates for the first time that consistent, physiologically plausible and beneficial alterations of cardiovascular structure and function are achievable with short-term pharmacologic lung deflation.

Chronic obstructive pulmonary disease (COPD) is a complex, multimorbid condition in which 50% of patients often succumb to cardiovascular diseases rather than respiratory failure. It is now apparent that this relationship is independent of smoking and other common shared risk factors. Several different mechanisms have been proposed. Lung hyperinflation, caused by the loss of elastic recoil combined with expiratory flow limitation, is associated with a twofold increase in all-cause mortality (1–3).

In cross-sectional studies, increased levels of static lung hyperinflation and emphysema are associated with reduced cardiac chamber size and function (4–7). The extent to which these structural alterations could potentially be modified through pharmacologic treatment of lung hyperinflation has never been studied in a prospective manner.

Studies investigating cardiac function in COPD have traditionally used echocardiography, thermodilution, or cardiopulmonary exercise testing, which have their own inherent limitations, having poor acoustic windowing in hyperinflated lungs, being highly invasive, and representing surrogates of cardiac function, respectively. Cardiac magnetic resonance (CMR) provides unparalleled image quality noninvasively, with excellent accuracy and reproducibility of cardiac structure and function (8). Furthermore, novel imaging techniques allow tracking of myocardial deformation, providing information on intrinsic function.

The primary objective of this study was to test the hypothesis that cardiac structural and functional alterations seen in stable hyperinflated COPD are modifiable through pharmacologic lung deflation. Some of the results from this study have been previously reported in the form of an abstract (9).

Methods

Study Design and Participants

This study was a single-center, phase IIIb, randomized, double-blind, placebo-controlled, crossover study (Figure 1A).

From November 2012 to August 2014, a total of 96 patients with COPD without hypoxia with greater than or equal to 15 pack-year history of smoking were recruited (Figure 1B). Eligible patients were older than 40 years, demonstrating post-bronchodilator FEV_1% predicted and FEV_1/FVC ratio less than 70%, and a Medical Research Council score of greater than one. Furthermore, evidence of lung hyperinflation, defined by a residual volume (RVol) greater than 120% predicted, was required, which improved by greater than or equal to 7.5% after 400 μg of inhaled salbutamol. For a full list of the exclusion criteria, please refer to the study protocol provided in the online supplement. All patients gave written informed consent. The study was approved by the local ethics review committee and conducted in accordance with the Declaration of Helsinki.

All long-acting bronchodilators, inhaled corticosteroids, and oral COPD medications were stopped before screening, after which participants entered a 7 ± 3–day run-in period where they received short-acting bronchodilators only. Randomization occurred at visit 2 after baseline CMR. Eligible patients were randomly assigned 1:1 to the two-period, complete-block crossover, receiving fluticasone furoate/vilanterol (FF/VI) 100/25 μg followed by placebo or placebo followed by FF/VI 100/25 μg once daily over two 7-day (maximum 14) treatment periods separated by a 7 ± 2–day washout period. Additional detail on the method for making these measurements is provided in the online supplement.

Subsequent visits occurred at the beginning and end of each treatment period and 1 week after trial completion (Figure 1A).

Procedures

Baseline 1.5-T CMR imaging (Achieva; Philips, Amsterdam, the Netherlands) and lung function were performed predose at the beginning of treatment period 1 and after each treatment period.

Cardiac volume and function data were acquired according to local protocol and international guidance, as described previously (10). Endocardial and epicardial contours were manually segmented and summed using semiautomated software (CVI 42; Circle Cardiovascular Imaging Inc., Calgary, Canada).

Aortic distensibility and pulmonary artery (PA) pulsatility are measures of local arterial stiffness. These were derived from cine images acquired at end-expiration in planes perpendicular to the thoracic aorta at the level of the PA (thoracic ascending aorta and thoracic descending aorta), 10 cm inferiorly at the level of the abdominal aorta, and perpendicularly to the main, right, and left PAs (11).

All analyses of the magnetic resonance imaging data were performed before database freeze and the unblinding of the study. Furthermore, at the time of analysis, I.S.S. and S.E.P. were masked to the results of the other treatment periods. I.S.S. analyzed all the CMR imaging for all participants. S.E.P. reviewed the analysis to confirm correct placement of the endocardial and epicardial contours.

Carotid-femoral pulse wave velocity and augmentation index, measures of global arterial stiffness, were measured using the Vicorder device (Skidmore Medical, Bristol, UK) before CMR and lung function maneuvers (12). Additional detail on the method for making these measurements is provided in the online supplement.

Outcomes

The primary outcome was change in right ventricular end-diastolic volume index (RVEDVI) from baseline versus placebo after 7 (maximum 14) days of

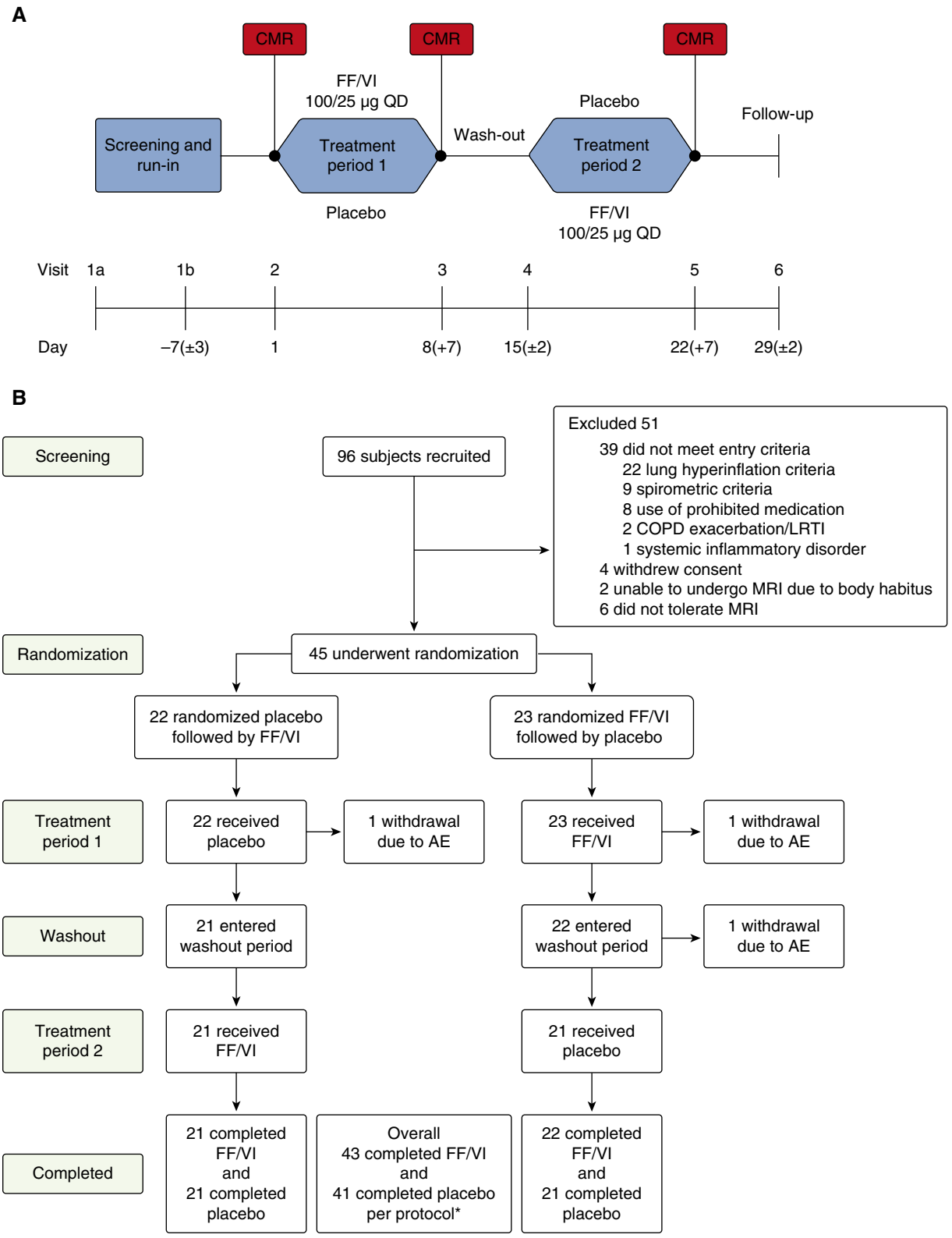

Figure 1. Study design and enrollment and outcomes. (*A*) Design of the study. Each patient, in two separate treatment periods, received 7 (maximum 14) days of treatment and matching placebo separated by a 1-week washout period. (*B*) Screening, randomization, treatment, and follow-up of patients. *One patient withdrew from the analysis owing to missing MRI data. AE = adverse event; CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; FF/VI = fluticasone furoate/vilanterol; LRTI = lower respiratory tract infection; MRI = magnetic resonance imaging; QD = once daily.

Table 1. Demographic and Baseline Clinical Characteristics of Patients in the Efficacy Population

Variable	Efficacy Population (*n* = 45)
Age at enrollment, yr	64.4 ± 9.0
Male, n (%)	28 (62)
Body mass index, kg/m^2*	25.1 ± 4.4
Race, n (%)	
White	39 (87)
African American/African heritage	6 (13)
Current smoker, n (%)	21 (47)
Smoking history, pack/yr	48.5 ± 30.9
Prestudy COPD therapy, n (%)	
ICS	3 (7)
LABA	1 (2)
ICS/LABA combination	23 (51)
LAMA	25 (56)
Exacerbation in last 3 yr, n (%)†	
Requiring antibiotics or oral corticosteroids at home	
0	8 (18)
1	7 (16)
2	9 (20)
>2	21 (47)
Requiring hospitalization	
0	34 (76)
1	8 (18)
2	2 (4)
>2	1 (2)
Lung function parameters‡	
Prebronchodilator FEV_1, L	1.26 ± 0.55
Post-bronchodilator FEV_1, L	1.47 ± 0.55
Post-bronchodilator FEV_1, % of predicted	52.5 ± 12.2
Post-bronchodilator FEV_1/FVC, %	45.3 ± 10.3
Prebronchodilator RVol, % of predicted	168.8 ± 37.0
Reversibility, % of predicted RVol§	−23.8 ± 11.2
D_{LCO}, % of predicted	56.48 ± 18.74
Symptom scores	
MRC dyspnea scale, n (%)	
1	0
2	26 (58)
3	14 (31)
4	5 (11)
5	0
Total score at baseline on COPD assessment test, units‖	18 ± 8
Cardiovascular background, n (%)	
Ischemic heart disease/angina	7 (16)
Atrial fibrillation	2 (4)
Cerebrovascular disease	1 (2)
Hypertension	16 (36)
Statin therapy	14 (33)
Diabetes	1 (2)
Family history	4 (9)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist combination; LAMA = long-acting muscarinic antagonist; MRC = Medical Research Council; RVol = residual volume. Plus–minus values are mean ± SD.

*The body mass index is the weight in kilograms divided by the square of the height in meters.

†Exacerbations during the 3 years before screening were self-reported.

‡Clinical data are from the screening visit except D_{LCO}, which is from baseline visit.

§Reversibility denotes the change in the RVol after the administration of 400 μg of salbutamol.

‖Scores on the COPD assessment test are based on a scale of 0–40, with lower scores indicating less impact; a change of 2 units is considered clinically relevant.

treatment. Other prespecified outcomes included cardiac structural, volumetric, and functional changes of the right ventricle (RV), left ventricle (LV), and left atrium compared with placebo; local and regional measures of aortic stiffness; pulmonary pulsatility; and lung function parameters.

Statistical Analysis

Analysis was performed per protocol, defined as those who received study medication without deviations impacting on RVEDVI.

Because of a lack of data relating to the cardiovascular effects of pharmacologic lung deflation, the effect size chosen was extrapolated from studies of lung-volume reduction surgery (LVRS) (13). An effect size of 5 ml/m^2 was selected because it was hypothesized that the changes after pharmacologic lung deflation would be of a smaller magnitude to those seen after LVRS.

Sample size calculations were based on Hudsmith and colleagues' (8) estimate of between-subject SD of 16 and assumed a 0.75 correlation between same-subject measurements of RVEDVI. Using the resulting within-subject SD of 8.13 and two-period crossover design, a total of 44 patients with evaluable data from both periods would provide 80% power to detect 5 ml/m^2 change in RVEDVI at a two-sided significance level of 0.05.

Change from baseline in RVEDVI was analyzed using a mixed-model analysis, with period, treatment group, and baseline RVEDVI fitted as fixed effects, and subject as a random effect. All other prespecified outcomes and *post hoc* analyses of stroke volumes (SV) and RV ejection fraction (EF) were similarly assessed. The relationship between change in RVol and RVEDVI, and the treatment effect once patients with a history of cardiovascular disease were excluded, was explored *post hoc*. All programming was performed with SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

Of the 96 patients who were screened, 45 underwent randomization. The per-protocol population comprised 43 (96%) patients who completed FF/VI treatment and 42 (93%) patients who completed treatment with placebo (Figure 1B). Demographic and clinical characteristics are provided in Tables 1 and 2, and in Tables E1 and E2 in the online supplement. The order in which patients received treatment and placebo had no impact on the primary efficacy outcome. After treatment with FF/VI for

Table 2. Baseline Cardiovascular Efficacy Endpoints, Measured Predose at the Beginning of Treatment Period 1, for Patients that Completed the Placebo Period and for Those that Completed the FF/VI Period of this Crossover Study

Variable	N	Placebo	N	FF/VI
Cardiac structure (CMR)				
Right ventricle				
EDVI, ml/m^2	43	79.4 ± 17.4	44	78.6 ± 18.0
ESVI, ml/m^2	43	29.3 ± 8.7	44	29.2 ± 8.6
SVI, ml/m^2	43	50.0 ± 12.3	44	49.4 ± 12.8
EF, %	43	63.0 ± 6.8	44	62.8 ± 6.7
Left ventricle				
EDVI, ml/m^2	43	65.6 ± 13.3	44	65.3 ± 13.5
ESVI, ml/m^2	43	26.9 ± 7.8	44	26.8 ± 7.8
SVI, ml/m^2	43	38.7 ± 7.8	44	38.5 ± 8.0
EF, %	43	59.4 ± 6.4	44	59.4 ± 6.4
MI, g/m^2	43	53.5 ± 11.7	44	53.4 ± 11.7
Left atrium*				
EDVI, ml/m^2	43	24.0 ± 18.2	44	24.2 ± 18.0
ESVI, ml/m^2	43	40.3 ± 17.9	44	39.9 ± 18.0
SVI, ml/m^2	43	16.3 ± 5.4	44	15.7 ± 6.4
EF, %	43	43.4 ± 11.2	44	40.9 ± 17.6
Regional arterial stiffness (Vicorder)				
PWV, m/s	43	8.8 ± 1.6	44	8.8 ± 1.6
Augmentation index, %	43	22.1 ± 10.4	44	21.5 ± 10.6
Local aortic stiffness†				
CMR distensibility, %/mm Hg				
Thoracic ascending aorta	42	0.166 ± 0.11	43	0.165 ± 0.11
Thoracic descending aorta	42	0.205 ± 0.11	43	0.206 ± 0.11
Abdominal aorta	42	0.333 ± 0.19	43	0.331 ± 0.19
Pulmonary artery stiffness†				
CMR pulsatility, %				
Main pulmonary artery	42	24.9 ± 8.4	43	24.7 ± 8.5
Right pulmonary artery	42	34.2 ± 8.4	43	33.8 ± 8.1
Left pulmonary artery	41	29.6 ± 9.5	42	28.9 ± 9.1

Definition of abbreviations: CMR = cardiac magnetic resonance; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; FF/VI = fluticasone furoate/vilanterol; MI = mass index; PWV = carotid-femoral pulse wave velocity; SVI = stroke volume index.
Data expressed as mean ± SD. Indexed values are calculated as raw values divided by body surface area.
*Left atrium EDVI is the volume of the left atrium at the end of ventricular diastole. Left atrium ESVI is the volume of the left atrium at the end of ventricular systole just before mitral valve opening.
†Reduced patient numbers for a particular endpoint because data were excluded on the basis of poor image quality.

7 (maximum 14) days, there was a mean increase in change from baseline in the primary efficacy outcome RVEDVI of 5.8 ml/m^2 (95% confidence interval [CI], 2.74–8.91; $P < 0.001$) compared with placebo (Figure 2, Table 3), an increase of 7.4% relative to the placebo-adjusted mean. There were corresponding improvements in all measures of lung hyperinflation and airflow limitation from baseline, with a 429 ml RVol reduction and increases of 261 ml, 4.6%, 220 ml, and 350 ml in inspiratory capacity, inspiratory capacity/total lung capacity, FEV_1, and FVC, respectively (Table 4).

After increases in RVEDVI, there was an adaptive RV SV increase (+4.87 ml/m^2; 95% CI, 1.81–7.93; $P = 0.003$), resulting in a maintained RV end-systolic volume index (ESVI; +0.95 ml/m^2; 95% CI, −0.66 to 2.57; $P = 0.240$) and RVEF (+1.28%; 95% CI, −0.72 to 3.28; $P = 0.203$). Consistent with the primary outcome, LV and atrial volumes were increased from baseline versus placebo (left ventricular end-diastolic volume index +3.63 ml/m^2 [95% CI, 1.39–5.88; $P = 0.002$]; left atrial ESVI +2.33 ml/m^2 [95% CI, 0.88–3.77; $P = 0.002$]). The increased SV without alterations in pulse resulted in an improvement in cardiac index by +0.203 L/min/m^2 (95% CI, 0.069–0.337; $P = 0.004$). The left atrium also demonstrated small but significant improvements in EF (+3.17%; 95% CI, 1.65–4.68; $P = 0.0001$). The unchanged LV mass over the treatment duration described was expected and confirms the high reproducibility of CMR (Table 3, Figure 3).

There were no differences in any of the six strain or strain-rate parameters involved in assessing the intrinsic myocardial function of the RV compared with placebo (*see* Table E3). In the LV, there was an improvement compared with baseline in the reverse-peak value of midventricular circumferential strain by −1.5% (95% CI, −2.92 to −0.02; $P = 0.047$) compared with placebo. The other eight parameters that assessed the LV global, systolic, or diastolic intrinsic myocardial function were unchanged.

There were no alterations to systemic arterial stiffness on a local or regional level, with no changes in pulse wave velocity, augmentation index, or distensibility at three aortic locations versus placebo. However, the change from baseline pulsatility was numerically increased in the pulmonary circulation compared with placebo in all three regions analyzed, reaching statistical significance in the main PA and left PA (PA +2.9% [95% CI, 1.20–4.59; $P = 0.001$]; left PA +2.67% [95% CI, 0.28–5.06; $P = 0.030$]) (Table 3, Figure 3).

There were no significant treatment interactions affecting change from baseline RVEDVI by any of the prespecified categorical or continuous subgroups. *Post hoc*, no relationship was found between change from baseline in RVol and RVEDVI. Excluding patients with a history of cardiovascular disease, totaling seven from placebo and eight from the FF/VI periods, did not affect the primary outcome measure (+5.62 ml/m^2; 95% CI, 2.27–8.98; $P = 0.002$).

The incidence of on-treatment adverse events in placebo and FF/VI 100/25 periods were five (12%) and six (14%), respectively (*see* Table E4). There was one reported drug-related adverse event in each treatment group. All withdrawals were caused by COPD exacerbations (FF/VI 100/25, 2 patients [5%]; placebo, 1 patient [2%]). No serious adverse events were reported.

Discussion

To our knowledge, this is the first randomized placebo-controlled study to demonstrate that changes in cardiac structure and function can be achieved after

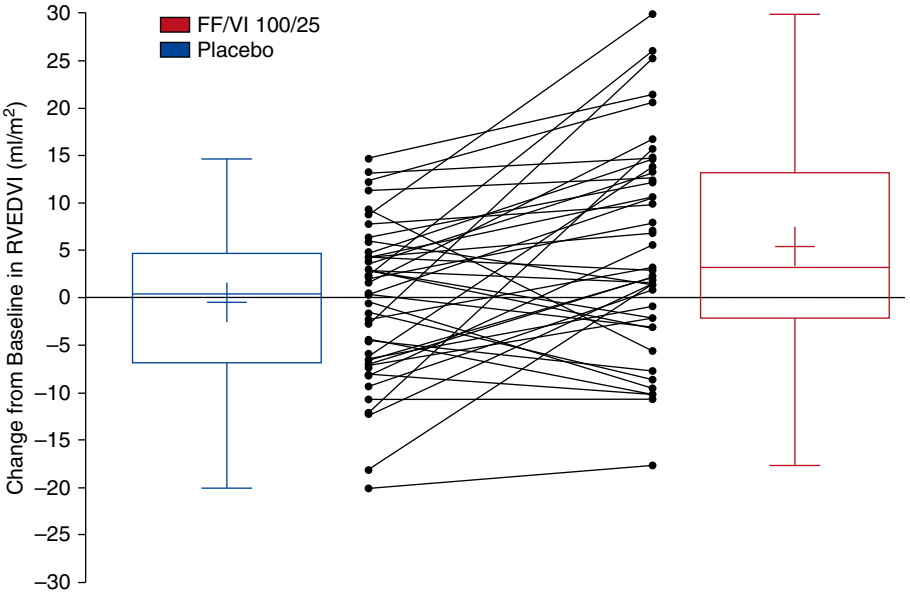

Figure 2. Primary cardiovascular efficacy outcomes. Box plot of change from baseline in right ventricular end-diastolic volume index (RVEDVI) for fluticasone furoate/vilanterol (FF/VI) 100/25 μg once daily versus placebo after 7–14 days of treatment. Baseline is the assessment taken at predose on Day 1.

the pharmacologic treatment of lung hyperinflation. In stable hyperinflated COPD, lung deflation with FF/VI results in structural alterations to both sides of the heart, improved biventricular SV, left atrial function, and pulsatility within the pulmonary circulation.

Lung deflation in this short-term study had no effect on systemic vascular function, intrinsic systolic or diastolic myocardial function, or EF of either ventricle. We have shown in hyperinflated COPD that reduced cardiac chamber size exists because of reduced preload effect, and that lung deflation in the short term results in decompression of the heart and associated pulmonary vasculature. This leads to relative normalization of EDV and subsequent improvement in SV.

Reduced RV size in hyperinflated COPD has been a consistent finding in recent CMR studies. RVEDV indexed to body surface area, the primary endpoint in this study, has been shown to be reduced in volume by 18 ml/m^2 compared with age, sex, and body size matched control subjects in patients with severe emphysema (7). In a prospective, multicenter, cohort study of more than 6,000 participants, involving two subgroups from the Multi-Ethnic Study of Atherosclerosis (MESA), a 10% increase in computerized tomography (CT)-defined emphysema was associated with a reduction in RVEDV by 2.43 ml (95% CI, 0.7–4.16) and 3.25 (95% CI, 2.29–4.20) for current and ex-smokers, respectively (6). Given that CT-emphysema values of 40% can be seen, based on the body surface area of our study, up to a 7.22 ml/m^2 reduction in RVEDVI may be attributed to emphysema. RVEDVI was selected as the primary endpoint for this study because the thin-walled RV was considered most sensitive to changes in preload conditions. We have demonstrated a 5.8 ml/m^2 change from baseline compared with placebo suggesting partial reversal of the changes attributed to lung hyperinflation.

Reduced cardiac chamber size in COPD has been attributed to the stiffening of the mediastinum or, alternatively, decreased ventricular preload through vascular remodeling in emphysema or increased intrathoracic pressure caused by gas trapping and airflow obstruction (1, 3–5). Given the irreversible nature of emphysema, alterations to airway resistance and increased functional strength are likely to be responsible for the lung deflation and subsequent cardiac decompression presented here (14).

The long-term clinical consequences of the changes in cardiac size and function presented here are not fully determined. Subclinical changes in RV morphology have recently been shown to affect patient-centered outcomes and may be an early marker of cardiopulmonary dysfunction. On a population level, one SD decrement (11 ml/m^2) in RVEDVI has been associated with a 12% increase in the risk of dyspnea after adjustment for spirometric measurements and CT-defined emphysema (15). Furthermore, increases in cardiac output are associated with improvements in walking intensity across all severities of COPD, whereas reduced atrial EF, independent of atrial size, predicts the development of atrial fibrillation in patients with dyspnea (16–18). The ability to modify cardiac morphology and function does therefore seem to independently impact on relevant clinical and patient-centered outcomes, and highlights the importance of identifying and optimally treating this "lung-deflator" clinical phenotype (19).

The ability to alter ventricular size and SV through lung deflation has also been seen after LVRS. Mineo and colleagues (13), using thermodilution, demonstrated an increase of 9 and 3 ml/m^2 in RVEDVI and RV SV index, respectively. *Post hoc* data from the National Emphysema Treatment Trial demonstrated improvements in O_2-pulse, an exercise-testing surrogate for SV, after LVRS in surgical "lung-deflators." The modalities used to measure cardiac volumes are not directly comparable. Despite this, the direction of RVEDVI changes shown here are in line with those after LVRS but, given the volume reductions typically achieved after surgery, are of a smaller magnitude (13, 20, 21).

The proposed mechanisms causing alterations to the heart after short-term changes in lung volume are corroborated by changes in the opposite direction observed in patients receiving ventilator support in critical care. Incremental increases in positive end-expiratory pressure and RVol decreased the RVEDVI by 4 to 5 ml/m^2 in those patients with a nondilated RV without affecting transmural pressure, whereas a second study demonstrated that reduced cardiac output was caused by a decreased preload rather than contractility (22, 23).

In addition to its effects on the chambers of the heart, the intriguing finding that lung deflation results in improved PA pulsatility warrants further

Table 3. Results of Cardiovascular Efficacy Outcomes of FF/VI 100/25 versus Placebo

Variable	Placebo N	Placebo Least-Squares Mean Change from Baseline (SE)	FF/VI N	FF/VI Least-Squares Mean Change from Baseline (SE)	Difference of FF/VI 100/25 from Placebo	95% CI	*P* Value
Cardiac volumes, mass, and function							
Primary efficacy outcome							
Right ventricle							
EDVI, ml/m^2	41	−0.47 (1.39)	43	5.35 (1.36)	5.83	2.74 to 8.91	0.001*
Other efficacy outcomes							
Right ventricle							
ESVI, ml/m^2	41	0.28 (0.77)	43	1.23 (0.76)	0.95	−0.66 to 2.57	0.240
SVI, ml/m^2	41	−0.76 (1.24)	43	4.11 (1.21)	4.87	1.81 to 7.93	0.003*
EF, %	41	−0.44 (0.85)	43	0.85 (0.84)	1.28	−0.72 to 3.28	0.203
Left ventricle							
EDVI, ml/m^2	41	0.03 (1.01)	43	3.66 (0.99)	3.63	1.39 to 5.88	0.002*
ESVI, ml/m^2	41	0.60 (0.63)	43	1.29 (0.62)	0.70	−0.88 to 2.27	0.375
SVI, ml/m^2	41	−0.62 (0.85)	43	2.37 (0.84)	2.99	1.11 to 4.87	0.003*
EF, %	41	−1.36 (0.82)	43	0.20 (0.80)	1.55	−0.35 to 3.46	0.107
MI, g/m^2	41	−1.27 (0.68)	43	−1.35 (0.67)	−0.07	−1.65 to 1.51	0.927
Left atrium†							
EDVI, ml/m^2	41	0.51 (0.49)	43	0.68 (0.48)	0.17	−0.68 to 1.02	0.690
ESVI, ml/m^2	41	0.8 (0.87)	43	3.12 (0.86)	2.33	0.88 to 3.77	0.002*
SVI, ml/m^2	41	0.27 (0.54)	43	2.45 (0.53)	2.18	1.20 to 3.16	<0.001*
EF, %	41	−0.65 (0.86)	43	2.51 (0.85)	3.17	1.65 to 4.68	<0.001*
Regional arterial stiffness (Vicorder)							
PWV, m/s	42	−0.03 (0.13)	43	−0.14 (0.13)	−0.11	−0.39 to 0.16	0.405
AI, %	42	1.66 (1.17)	43	3.18 (1.16)	1.53	−1.06 to 4.11	0.241
Local aortic stiffness							
CMR distensibility, %/mm Hg‡							
Thoracic ascending aorta	39	−0.014 (0.009)	41	−0.005 (0.009)	0.009	−0.009 to 0.027	0.326
Thoracic descending aorta	39	−0.012 (0.011)	41	0.010 (0.011)	0.023	−0.001 to 0.046	0.056
Abdominal aorta	39	−0.015 (0.020)	41	0.013 (0.019)	0.028	−0.015 to 0.071	0.189
Pulmonary artery stiffness							
CMR pulsatility, %‡							
Main pulmonary artery	39	−0.33 (0.98)	40	2.56 (0.97)	2.90	1.20 to 4.59	0.001*
Left pulmonary artery	38	−0.30 (0.91)	40	2.37 (0.89)	2.67	0.28 to 5.06	0.030*
Right pulmonary artery	39	0.93 (1.13)	41	2.22 (1.10)	1.29	−1.26 to 3.84	0.313

Definition of abbreviations: AI = augmentation index; CI = confidence interval; CMR = cardiac magnetic resonance; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; FF/VI = fluticasone furoate/vilanterol; MI = mass index; PWV = carotid-femoral pulse wave velocity; RVEDVI = right ventricular end-diastolic volume index; SVI = stroke volume index.

Analysis performed using an analysis of covariance model with covariates of treatment, baseline, period, and subject as a random effect. Indexed values are calculated as raw values divided by body surface area. For the primary endpoint of change in RVEDVI from baseline, the least-squares mean (SE) RVEDVI for placebo and FF/VI 100/25 are 79.10 (1.39) and 84.92 (1.36), respectively.

*$P < 0.05$.

†Left atrium EDVI is the volume of the left atrium at the end of ventricular diastole. Left atrium ESVI is the volume of the left atrium at the end of ventricular systole just before mitral valve opening.

‡Reduced patient numbers compared with primary efficacy endpoint because some data excluded on basis of poor image quality.

consideration. There is a scarcity of published data on PA stiffness in COPD. The MESA-COPD study has shown that, in patients with COPD free from cardiovascular disease, pulsatility was reduced compared with smoking control subjects in adjusted models (24). A second echocardiographic study used Doppler flows and maximal systolic frequency shift to estimate PA stiffness, and found it to be reduced in COPD compared with age and sex-matched, nonsmoking control subjects.

Although these changes may have been a result of raised PA pressures (30 ± 7.9 mm Hg), Hilde and colleagues have demonstrated a disparity between PA pressures and RV remodeling in COPD (25, 26). They identified a cohort of patients with reduced PA compliance, rather than raised pulmonary pressures, with echocardiographic appearances typically associated with pulmonary hypertension. This suggests a role for altered PA intrinsic elastic properties in RV adaptation. An altered inflammatory profile from cigarette smoke leading to endothelial dysfunction has been implicated (27, 28). It is unlikely that the PA inflammatory profile during this short-term study will have been altered sufficiently by the inhaled corticosteroids component of FF/VI to modify the intrinsic elastic properties (29, 30). Increased pulsatility may be caused by increased SV and subsequent PA distention. Alternatively, lung deflation may have altered the elastic properties through decompression of the PA. Such alterations have been known to occur earlier than changes in RV performance, and early work

Table 4. Results of Pulmonary Efficacy Outcomes of FF/VI 100/25 versus Placebo

Variable	Placebo N	Placebo Least-Squares Mean Change from Baseline (SE)	FF/VI N	FF/VI Least-Squares Mean Change from Baseline (SE)	Difference of FF/VI 100/25 from Placebo	95% CI	*P* Value
Spirometry							
FEV_1, L	43	0.00 (0.052)	44	0.22 (0.052)	0.22	0.12 to 0.31	<0.001*
FVC, L	43	0.11 (0.071)	44	0.46 (0.071)	0.35	0.21 to 0.49	<0.001*
FEV_1/FVC, %	43	−0.9 (1.10)	44	1.1 (1.09)	2.0	−0.3 to 4.3	0.092
Body plethysmograph							
RVol, L	42	0.028 (0.074)	43	−0.401 (0.073)	−0.429	−0.59 to −0.27	<0.001*
IC, L	42	−0.012 (0.044)	43	0.249 (0.044)	0.261	0.17 to 0.35	<0.001*
IC/TLC, %	42	−0.5 (0.54)	43	4.1 (0.54)	4.6	3.1 to 6.0	<0.001*

Definition of abbreviations: CI = confidence interval; FF/VI = fluticasone furoate/vilanterol; IC = inspiratory capacity; RVol = residual volume; TLC = total lung capacity.
Analysis performed using an analysis of covariance model with covariates of treatment, baseline, period, and subject as a random effect.
*$P < 0.05$.

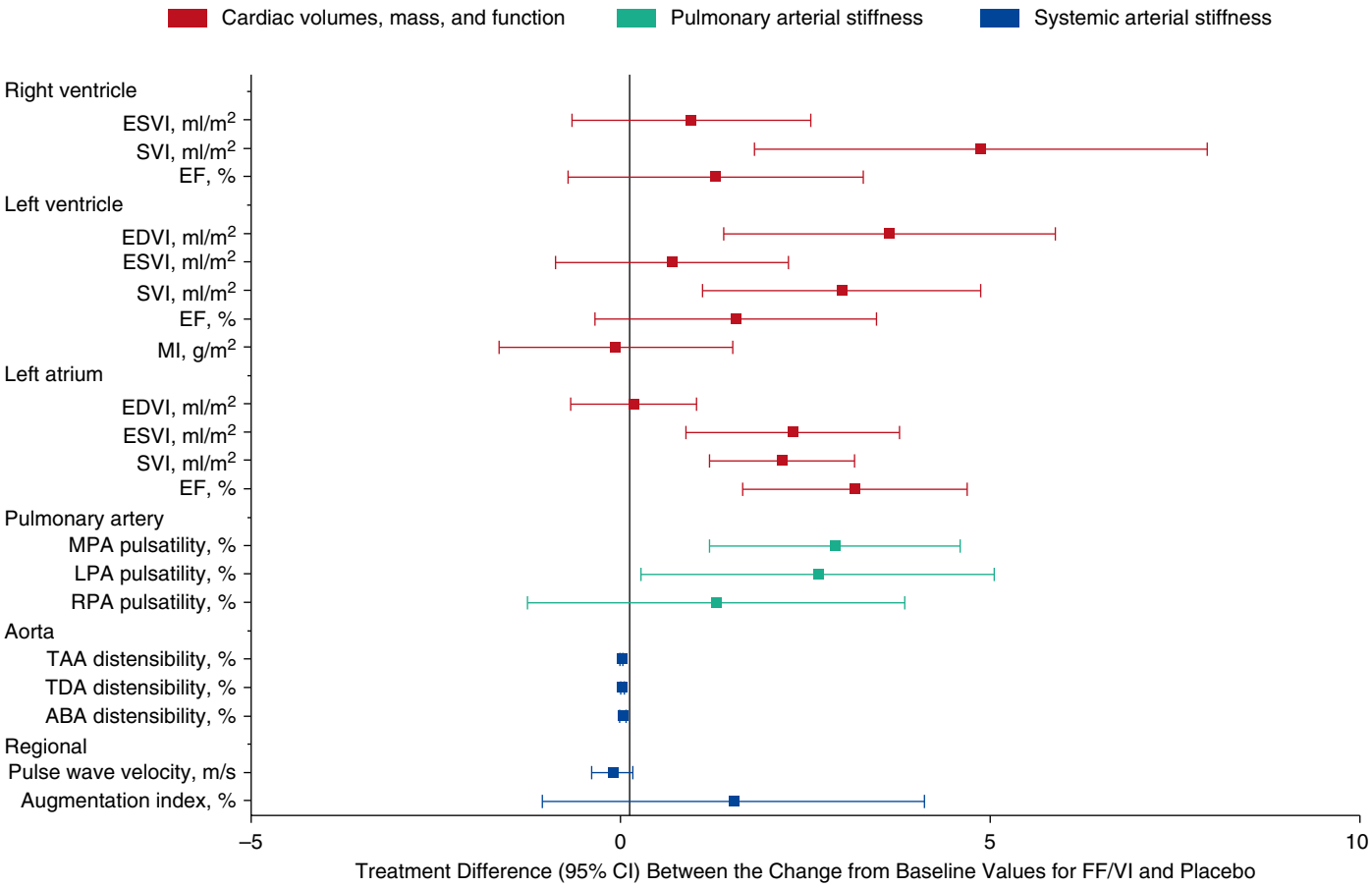

Figure 3. Forest plot of change from baseline in the other cardiovascular efficacy outcomes for fluticasone furoate/vilanterol (FF/VI) 100/25 μg once daily versus placebo after 7–14 days of treatment. Baseline is the assessment taken at predose on Day 1. Analysis was performed using an analysis of covariance model with covariates of treatment, baseline, period, and subject as a random effect. Data presented represent (change from baseline during FF/VI period – change from baseline in placebo period) with 95% CIs. ABA = abdominal aorta; CI = confidence interval; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LPA = left pulmonary artery; MI = mass index; MPA = main pulmonary artery; RPA = right pulmonary artery; SVI = stroke volume index; TAA = thoracic ascending aorta; TDA = thoracic descending aorta.

by Milnor and colleagues demonstrated that 30% of RV power is spent generating the oscillatory component of flow (31, 32). Therefore, improvements in stiffness could have potentially clinically important long-term benefits in reducing afterload, increasing ventricular efficiency, and potentially attenuating the RV adaptation seen in COPD.

There are several limitations of this study. First, it is a single-center study within a predominantly white cohort of patients with COPD, and as such may not apply to other populations. Second, we have included all patients with evidence of lung hyperinflation based on RVol, which is still considered to be the best way to evaluate therapies aimed at reducing air-trapping (33). As a consequence, participants have not been clinicoradiographically separated, according to emphysematous versus chronic bronchitic phenotypes, and we are unable to establish a differential treatment effect. Third, we have used novel cardiac imaging techniques to help understand the impact of lung deflation on cardiac deformation and vascular function but, for practical and ethical reasons, have not used invasive pressure monitoring. Finally, because of the brevity of this study there were no significant safety findings.

In summary, our study confirms that through pharmacologic treatment of COPD consistent and physiologically plausible beneficial effects on cardiac structure, function, and pulmonary vasculature can be achieved in the short term. Whether intrinsic myocardial function can be modulated through prolonged periods of lung deflation is as yet unverified and should be the focus of future clinical trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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