PREFUL MRI Depicts Dual Bronchodilator Changes in COPD: A Retrospective Analysis of a Randomized Controlled Trial

Andreas Voskrebenzev, PhD* • Till F. Kaireit, MD* • Filip Klimeš, MS • Gesa H. Pöhler, MD • Lea Behrendt, MS • Heike Biller, MD • Korbinian Berschneider, PhD • Frank Wacker, MD • Tobias Welte, MD • Jens M. Hohlfeld, MD • Jens Vogel-Clausen, MD

From the Institute for Diagnostic and Interventional Radiology (A.V., T.F.K., F.K., G.H.P., L.B., F.W., J.V.C.) and Department of Respiratory Medicine (T.W., J.M.H.), Hannover Medical School, Carl-Neuberg-Str 1, 30625 Hannover, Germany; German Center for Lung Research (BREATH), Hannover, Germany (A.V., T.F.K., F.K., G.H.P., L.B., H.B., F.W., T.W., J.M.H., J.V.C.); Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany (H.B., J.M.H.); and Novartis Pharma, Clinical Research Respiratory, Nuremberg, Germany (K.B.). Received June 15, 2021; revision requested August 6; revision received January 21, 2022; accepted February 22.

Address correspondence to J.V.C. (e-mail: Vogel-Clausen.Jens@mh-hannover.de).

Work supported by Novartis Pharma, Germany. Indacaterol-glycopyrronium (110/50 μg) and matching placebo were provided by Novartis Pharma, Germany. Medical writing support was also funded by Novartis Pharma, Germany. Development and validation of the PREFUL algorithm was supported by PRACTIS–Clinician Scientist Program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3696/3-1).

* A.V. and T.F.K. contributed equally to this work.

Conflicts of interest are listed at the end of this article.

Radiology: Cardiothoracic Imaging 2022; 4(2):e210147 • https://doi.org/10.1148/ryct.210147 • Content codes: CA | CH | MR

Purpose: To assess whether dynamic ventilation and perfusion (Q) biomarkers derived by phase-resolved functional lung (PREFUL) MRI can measure treatment response to 14-day therapy with indacaterol-glycopyrronium (IND-GLY) and correlate to clinical outcomes including lung function, symptoms, and cardiac function in patients with chronic obstructive pulmonary disease (COPD), as determined by spirometry, body plethysmography, cardiac MRI, and dyspnea score measurements.

Materials and Methods: The cardiac left ventricular function in COPD (CLAIM) study enrolled patients aged 40 years or older with COPD, stable cardiovascular function, and hyperinflation (residual volume > 135% predicted). Dynamic MRI data of these patients were retrospectively analyzed using the PREFUL technique to assess the effect of 14-day IND-GLY treatment versus placebo on regional measurements of ventilation dynamics. After manual segmentation of the lung parenchyma, flow-volume loops of each voxel were correlated to an individualized reference flow-volume loop, creating a two-dimensional flow-volume loop correlation map (FVL-CM) as a measure of ventilation dynamics. Ventilation-perfusion match (VQM) was evaluated in combination with perfusion and regional ventilation (VQMVent) and with perfusion and the FVL-CM measurement (VQMCM). For image and statistical analysis, the lung parenchyma was segmented as a region of interest by manually delineating the lung boundary and excluding the large (central) vessels for each section. Differences in ventilation, perfusion, and VQM between IND-GLY and placebo were compared using analysis of variance, with study treatment, patient, and period included as factors.

Results: Fifty patients (mean age, 64.3 years ± 7.65 [SD]; 35 men) were included in this analysis. IND-GLY significantly increased mean correlation as measured with FVL-CM versus that of placebo (least squares [LS] means treatment difference: 0.05 [95% CI: 0.03, 0.07]; P < .0001). Compared with placebo, IND-GLY increased mean Q (LS means treatment difference: 9.27 mL/min/100 mL [95% CI: 0.05, 18.49]; P = .049) and improved both VQMVent (LS means treatment difference: 0.06 [95% CI: 0.03, 0.08]; P < .0001) and VQMCM (LS means treatment difference: 0.05 [95% CI: 0.02, 0.08]; P = .0011, respectively).

Conclusion: Regional ventilation dynamics and VQM measured by PREFUL MRI show treatment response in COPD.

Supplemental material is available for this article.

Clinical trial registration no. NCT02442206

Published under a CC BY 4.0 license.
PREFUL MRI Depicts Dual Bronchodilator Changes in COPD

Abbreviations
COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, FVL-CM = flow-volume loop correlation map, IND-GLY = indacaterol-glycopyrronium, LS = least squares, PREFUL = phase-resolved functional lung, Q = perfusion, QDP = perfusion defect percentage, RVent = regional ventilation, TDI = Transition Dyspnea Index, VDP = ventilation defect percentage, VQM = ventilation-perfusion match, VQM CM = ventilation-perfusion match with Q and FVL-CM, VQM RVent = ventilation-perfusion match with Q and RVent

Summary
Indacaterol-glycopyrronium improves ventilation, perfusion, and ventilation-perfusion match in patients with chronic obstructive pulmonary disease measured by phase-resolved functional lung (PREFUL) MRI; therefore, PREFUL could provide end points in future cardiopulmonary trials.

Key Points
- Compared with placebo, indacaterol-glycopyrronium (IND-GLY) increased mean flow-volume loop correlation (least squares [LS] mean treatment difference: 0.05 [95% CI: 0.03, 0.07]; P < .0001) and reduced ventilation heterogeneity (LS means treatment difference: −0.05 [95% CI: −0.07, −0.03]; P < .0001).
- Compared with placebo, IND-GLY increased mean perfusion (Q) (LS means treatment difference: 9 mL/min/100 mL [95% CI: 0.1, 18.5]; P = .049).
- Compared with placebo, IND-GLY increased ventilation-perfusion match (VQM) with Q and regional ventilation (VQM QRVent)(LS means treatment difference: 0.05 [95% CI: 0.02, 0.08]; P = .001) and VQM with Q and flow-volume loop correlation map (VQM CM) (LS means treatment difference: 0.06 [95% CI: 0.03, 0.08]; P < .0001).

Keywords
MRI, COPD, Perfusion, Ventilation, Lung, Pulmonary

this problem, the postprocessing algorithm phase-resolved functional lung (PREFUL) MRI was recently developed to quantify perfusion and ventilation dynamics (5,6). The concept of ventilation- and perfusion-phase sorting as an addition to Fourier decomposition analysis was previously introduced as SELF-gated Non–Contrast-Enhanced Functional Lung imaging (SENCE-FUL) (7). Although this approach can sort each phase-encoding step, a special sequence with non–phase-encoded direct current signal acquisition is mandatory. On the contrary, the phase sorting used in PREFUL can be used in conjunction with default sequences (spoiled gradient-echo or balanced steady-state free precession). Preliminary results in patients with COPD confirm improved correlation of spirometric lung function (forced expiratory volume in 1 second [FEV1] percent predicted) with the dynamic regional flow-volume parameters compared to the static regional ventilation (RVent) parameter (8). Similarly, analysis of dynamic regional flow-volume loop parameters was shown to be sufficiently sensitive for the detection of early chronic lung allograft dysfunction (9).

PREFUL MRI–derived perfusion defect percentages have been shown to correlate with dynamic contrast-enhanced–derived pulmonary microvascular blood flow perfusion defect percentages in a prospective study in patients with COPD (10). Both ventilation and perfusion PREFUL MRI parameters were repeatable over two scan sessions in both healthy controls and patients with COPD (11).

In the cardiac left ventricular function in COPD (CLAIM) study, the RVent parameter showed a significant treatment response to 14-day therapy with the dual bronchodilator indacaterol-glycopyrronium (IND-GLY) (12). Posttreatment metrics of pulmonary microvascular blood flow and RVent correlated with posttreatment left ventricular end-diastolic volume and Transition Dyspnea Index (TDI) values but were not correlated with treatment change (12). It is unknown whether IND-GLY also improves regional VQM and RVent dynamics. The PREFUL MRI parameters in this work were not available at the time of the original CLAIM study, and this retrospective analysis should evaluate if these promising PREFUL ventilation-perfusion parameters are suited as reliable markers in future trials.

Therefore, we hypothesize that the regional information of PREFUL MRI–derived flow-volume loops, PREFUL perfusion, and the combined ventilation-perfusion metrics make this a sensitive method for monitoring patients with COPD. If proven, PREFUL MRI may have added value compared with lung function testing, dyspnea scores, and anatomic chest CT. The purpose of this retrospective CLAIM substudy was to assess whether dynamic ventilation and perfusion biomarkers derived by PREFUL MRI can measure treatment response to 14-day therapy with IND-GLY and correlate to clinical outcomes including lung function, symptoms, and cardiac function in patients with COPD, as determined by spirometry, body plethysmography, cardiac MRI, and dyspnea score measurements.

Materials and Methods

Participants
This study is a retrospective analysis of data prospectively acquired during the CLAIM study (ClinicalTrials.gov identifier: NCT02442206), which took place between May 18, 2015, and April 20, 2017. All patients included in this study were reported previously: the primary, secondary, and exploratory end points of the CLAIM study are published (12,13). CLAIM study participants were patients aged 40 years or older with a clinical diagnosis of COPD, stable cardiovascular function, and baseline hyperinflation (residual volume > 135% predicted), smoking history ≥ 10 pack-years, and airflow limitation (baseline postbronchodilator FEV1 of less than 80% predicted and a postbronchodilator FEV1 to–forced vital capacity ratio of less than 0.7). Patients with arrhythmias, heart failure (left ventricular ejection fraction < 40%), unstable ischemic heart disease, or uncontrolled hypertension were excluded. Patients who discontinued the study were not replaced. Further details of inclusion and exclusion criteria have been previously described (13). The population was selected by the investigators after completion of the CLAIM study, who stayed blinded to placebo and treatment periods even after completion of the study. Patients were included in this analysis if they had completed the whole MRI examination at all four visits of the CLAIM study and had no protocol deviations or missing data that precluded a precise analysis using this method. Patient race was recorded to
measure potential lack of diversity in a single-center trial in a small population. Race was investigator observed. CLAIM was approved by the ethics committee of Hannover Medical School and the German Federal Institute for Drugs and Medical Devices. All patients provided written informed consent.

**Study Design**

The CLAIM study was a randomized, double-blind, placebo-controlled, crossover study (13) that assessed the effect of 14-day treatment with once-daily IND-GLY in patients with COPD with hyperinflated lungs. Patients received once-daily IND-GLY (110/50 µg) for 14 days followed by placebo for 14 days, or vice versa, with the two treatment periods separated by a 14-day washout.

**MRI Procedure**

Participants underwent PREFUL MRI with a 1.5-T scanner (Magnetom Avanto; Siemens Healthcare) under free breathing for 1 minute per section in a head-first supine position. Three strictly coronal sections (one at the middle of the tracheal level, one anterior to the trachea, and one posterior to the trachea) with a 11.25-mm section gap were acquired. To achieve a high reproducibility of the middle section, a transversal localizer was used to find the tracheal bifurcation. Image acquisition was performed with the following acquisition parameters: spoiled gradient-echo sequence at a temporal resolution of 288 msec with echo time of 0.82 msec, repetition time of 3 msec, flip angle of 5°, matrix size of 128 × 96 interpolated with zero filling to 256 × 256, field of view of 50 × 50 cm², section thickness of 15 mm, gap between sections of 11.25 mm, and pixel bandwidth of 1500 Hz/pixel. See Appendix E1 (supplement) for cardiac MRI and dynamic contrast-enhanced MRI methods and Table E4 (supplement) for MRI protocol.

**Image Analysis**

Image analysis was performed with software (MATLAB 2018b; MathWorks) using self-developed scripts and commercial toolboxes. Except for two segmentation tasks, as described in the next paragraph, all steps of analysis were performed automatically. See Appendix E1 (supplement) for details on registration and basic PREFUL analysis as per Voskrebenzev et al (5).

For image and statistical analysis, the lung parenchyma was segmented as a region of interest by manually delineating the lung boundary and excluding the large (central) vessels for each section. Additionally, a manual segmentation of a large vessel was performed. The segmentation tasks were performed by a scientist (A.V.) with more than 5 years of experience in lung MRI under supervision from a radiologist (J.V.C.) with more than 15 years of MRI experience. The averaged perfusion signal in the vessel region of interest was later used to sort images according to their cardiac phase, as described in the PREFUL perfusion analysis section. Analysis of each patient required approximately 4 hours (including registration, analysis, and segmentation of three sections).

**Quantification of RVent dynamics.**— To perform PREFUL ventilation analysis, a low-pass filter with cutoff at 0.6 Hz was applied to the registered images to remove signal variations due to perfusion. Images were sorted according to their phase by analyzing a spatially averaged lung signal with a cosine model function to create one respiratory cycle with increased temporal resolution. The sorted images were interpolated to an equidistant time grid with 60 phases, which corresponds to a nominal resolution of 55 msec considering an arbitrarily chosen respiratory rate of 0.3 Hz. The static RVent and RVent time series were calculated for each phase according to the RVent definition in Zapke et al (14).

RVent slopes, which act as an MRI surrogate for airflow, were calculated for each voxel in the lung parenchyma by applying the symmetric difference quotient (first derivative) to the RVent time series. The segmentation of the flow-volume reference region of interest was performed automatically inside the lung parenchyma region of interest based on the RVent values. Values inside the 80–90 percentile range were considered healthy. This procedure was performed for each section and each participant separately. Therefore, spatial averaging led to a reference flow-volume curve in each individual for each section. The remaining flow-volume loops covering the complete respiratory cycle in the rest of the lung parenchyma were correlated (using cross-correlation as measurement of similarity with fixed time displacement of zero) to the reference flow-volume loop to measure the similarity of the time course, creating a two-dimensional flow-volume loop correlation map (FVL-CM). A high correlation was interpreted as normal ventilation cycle and a low correlation as abnormal ventilation cycle.

**PREFUL perfusion analysis.**— Using the same registered images as in the ventilation analysis, a high-pass filter with cutoff at 0.8 Hz was applied to remove signal variations due to respiration. The cardiac phase of each image was estimated by analysis of the average signal time series in a large vessel segmentation using a piecewise sine fit, creating a retrospectively sorted cardiac cycle with increased temporal resolution. The sorted images were interpolated to an equidistant time grid with 30 phases, which corresponds to a nominal resolution of 33 msec for a heart rate of 60 beats per minute (1 Hz). The averaged signal in a large vessel segmentation of the coronal section at the middle of the tracheal level and average heart frequency of the respective acquisition were used to quantify perfusion in mL/min/100 mL according to Kjøstad et al (15).

**Ventilation-perfusion match.**— Ventilation defect percentage (VDP) and perfusion defect percentage (QDP) were calculated as outlined in Appendix E1 (supplement). VDP was calculated by applying a 90% threshold to the FVL-CM as per Moher Alsady et al (9). Areas below this threshold were considered as a ventilation defect, and by calculating the relative regions with ventilation below this threshold, the VDP could be derived. QDP was calculated by applying a 20 mL/min/100 mL threshold to Q as discussed in Appendix E1 (supplement). VQM was defined as the relative area where perfusion and ventilation threshold maps show the same value. See Appendix E1 (supplement) for further details. A voxel with ventilation and perfusion defect or a voxel with no ventilation and no perfu-
FEV\textsubscript{1} and forced vital capacity were measured by spirometry.

Pulmonary Function Testing

combination with Q, VQM \textsubscript{RVent} and VQM \textsubscript{CM} were obtained, respectively. Thereby, in a ventilation defect was considered a match. Two ventilation parameters were used for VQM: RV\textsubscript{Vent} and FVL-CM. Thereby, in combination with Q, VQM \textsubscript{RVent} and VQM \textsubscript{CM} were obtained, respectively.

Pulmonary Function Testing

FEV\textsubscript{1} and forced vital capacity were measured by spirometry in accordance with American Thoracic Society/European Respiratory Society recommendations (16) and as described previously (13). Further details are available in Appendix E1 (supplement).

Statistical Analysis

Differences in ventilation, perfusion, and VQM between IND-GLY and placebo were compared using an analysis of variance statistical model, with study treatment, patient, and period included as factors. Patient was included as a random effect.

Table 1: Baseline Patient Characteristics and Demographics

| Characteristic                | Value                  |
|------------------------------|------------------------|
| Total no. of patients        | 50                     |
| Mean age (y)*                | 64.3 (46–78)           |
| Men                          | 35 (70.0)              |
| BMI (kg/m\textsuperscript{2})| 26.9 ± 4.40            |
| Race                         | White                  |
|                              | 50 (100.0)             |
| Duration of COPD (y)         | 9.3 ± 7.19             |
| No. of exacerbations in the past 12 months |                      |
| 0                            | 41 (82.0)              |
| 1                            | 9 (18.0)               |
| ≥2                           | 0 (0.0)                |
| Smoking status               |                        |
| Patients who do not smoke    | 0 (0.0)                |
| Patients with smoking history| 20 (40.0)              |
| Patients who smoke           | 30 (60.0)              |
| Estimated no. of pack-years\textsuperscript{1} | 52.4 ± 21.86         |
| Postbronchodilator FEV\textsubscript{1} (% predicted) | 55.96 ± 14.51         |
| Postbronchodilator FEV\textsubscript{1}/FVC (%) | 42.84 ± 12.18          |
| Baseline Dyspnea Index score | 14.7 ± 4.18            |
| COPD Assessment Test score   | 16.4 ± 4.81            |
| GOLD status                  |                        |
| Mild (GOLD 1)                | 0 (0)                  |
| Moderate (GOLD 2)            | 33 (66)                |
| Severe (GOLD 3)              | 15 (30)                |
| Very severe (GOLD 4)         | 2 (4)                  |

Note.—Values given are mean ± SD or number with percentage in parentheses, unless otherwise indicated. BMI = body mass index, COPD = chronic obstructive pulmonary disease, FEV\textsubscript{1} = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease.

* Age range in parentheses.

\textsuperscript{1}For patients who smoke or have a smoking history only.

Table 2: Perfusion–Ventrilation Mismatch (VQM) Parameters

| Parameter                      | Value                      |
|-------------------------------|----------------------------|
| Estimated no. of pack-years\textsuperscript{1} | 52.4 ± 21.86         |
| Postbronchodilator FEV\textsubscript{1} (% predicted) | 55.96 ± 14.51         |
| Postbronchodilator FEV\textsubscript{1}/FVC (%) | 42.84 ± 12.18          |
| Baseline Dyspnea Index score | 14.7 ± 4.18              |
| COPD Assessment Test score    | 16.4 ± 4.81              |
| GOLD status                   |                           |
| Mild (GOLD 1)                 | 0 (0)                     |
| Moderate (GOLD 2)             | 33 (66)                   |
| Severe (GOLD 3)               | 15 (30)                   |
| Very severe (GOLD 4)          | 2 (4)                     |

Note.—Values given are mean ± SD or number with percentage in parentheses, unless otherwise indicated. BMI = body mass index, COPD = chronic obstructive pulmonary disease, FEV\textsubscript{1} = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease.

* Age range in parentheses.

\textsuperscript{1}For patients who smoke or have a smoking history only.

As shown in Table 2, in the IND-GLY treatment period, mean correlation as measured by FVL-CM changed from 0.77 ± 0.11 (SD) at baseline to 0.83 ± 0.11 after treatment, while in the placebo period this parameter changed from 0.77 ± 0.11 after treatment, respectively.

Results

Participants

A total of 421 patients were screened, and 62 eligible participants were randomly assigned to treatment: 30 to IND-GLY followed by placebo and 32 to placebo followed by IND-GLY. In total, 57 patients completed both treatment periods (13). Of these, 50 patients (35 men: mean age, 64.8 years [range, 46–78 years]; 15 women: mean age, 62.3 years [range, 51–73 years]) had fully complete cardiac and lung MRI data sets and are included here. In total, 359 patients were excluded from the original CLAIM study (screening failures), and 12 were excluded from this retrospective analysis, either due to early trial discontinuation (n = 3), protocol deviations (n = 2), or an incomplete MRI data set (n = 7) (see Fig E1 [supplement]). The incomplete protocol of the seven patients can be explained by the fact that PREFUL was an exploratory endpoint that required a longer measurement protocol. Therefore, seven patients either chose individually or were physically (as a result of dyspnea) unable to complete the whole protocol. Table 1 shows patient demographics and characteristics.

Ventilation Dynamics

Figure 1 shows the ventilation cycle for one patient (67-year-old man, postbronchodilator FEV\textsubscript{1} at baseline of 31.6%, FEV\textsubscript{1} postbronchodilator treatment of 36.7%, Global Initiative for Chronic Obstructive Lung Disease stage 3) following treatment with placebo and IND-GLY obtained with PREFUL MRI. Movies 1 and 2 demonstrate this ventilation cycle.

Figures 2 and 3 show the flow-volume loops derived from the ventilation cycle and further parameter maps calculated with PREFUL MRI for the same patient following treatment with placebo and IND-GLY. Postbronchodilator treatment values were consistently improved compared with placebo (see Fig 3 for details).}

As shown in Table 2, in the IND-GLY treatment period, mean correlation as measured by FVL-CM changed from 0.77 ± 0.11 (SD) at baseline to 0.83 ± 0.11 after treatment, while in the placebo period this parameter changed from 0.77 ± 0.11 (SD) at baseline to 0.83 ± 0.11 after treatment.
Dispersion) was reduced with IND-GLY treatment compared with placebo (LS means treatment difference: –0.05 [95% CI: –0.07, –0.03]; \( P \leq 0.0001 \)) (Table 2).

IND-GLY also reduced FVL-CM–derived VDP compared with placebo (LS means treatment difference: –8.9% [95% CI: 6.01 at baseline to 0.78 ± 0.12 after placebo treatment, representing a LS means treatment difference of 0.05 (95% CI: 0.03, 0.07; \( P < .0001 \)) (Fig 4).

Similar effects were observed at a regional level. Ventilation heterogeneity (as measured by quartile coefficient of dispersion) was reduced with IND-GLY treatment compared with placebo (LS means treatment difference: –0.05 [95% CI: –0.07, –0.03]; \( P < .0001 \)) (Table 2).

IND-GLY also reduced FVL-CM–derived VDP compared with placebo (LS means treatment difference: –8.9% [95% CI: –11.0, –6.8]; \( P < .0001 \)).
PREFUL MRI Depicts Dual Bronchodilator Changes in COPD

CI: –11.5, –6.3; P < .0001), which is a relative change of –28.6%. While reductions in VDP were observed with IND-GLY (40.9% at baseline to 31.1% after 14 days of treatment), results for this parameter remained largely unchanged following placebo (41.1% at baseline to 40.0% after 14 days) (Table 2). A comparatively smaller change in the measurement of hypoventilated and nonventilated regions of the lung was previously reported using static regional ventilation metrics, which included only the inspiratory and expiratory respiratory phases during free tidal volume breathing: The area of hypoventilated and nonventilated regions of the lung was decreased by 5% in response to IND-GLY (relative change of −14.3% vs placebo) (12).

Perfusion

In the IND-GLY group, pulmonary perfusion in the parenchyma was 97 mL/min/100 mL at baseline, rising to 122 mL/min/100 mL following IND-GLY treatment. Negligible changes were observed between baseline (108 mL/min/100 mL) and placebo treatment (113 mL/min/100 mL). Patients receiving 14-day IND-GLY treatment experienced a 9 mL/min/100 mL (8.2% relative) increase in mean Q compared with placebo (LS means treatment difference: 9 mL/min/100 mL [95% CI: 0.1, 18.5]; P = .049) (Fig 4).

Furthermore, Table 2 shows that IND-GLY decreased quartile coefficient of dispersion of perfusion by 0.04 compared with placebo (95% CI: –0.07, –0.01; P = .013), indicating improved perfusion heterogeneity throughout the lung with IND-GLY treatment.

Finally, a change of 2.4% QDP was observed with IND-GLY compared with placebo (95% CI: –4.0, –0.8; P = .005) (Table 2).

**Ventilation-Perfusion Match**

VQM\textsubscript{RVent} was improved with IND-GLY treatment compared with placebo: IND-GLY increased VQM\textsubscript{RVent} from 0.64 at baseline to 0.70 after treatment, whereas placebo increased VQM\textsubscript{RVent} from 0.64 at baseline to 0.65 only (LS means treatment difference: 0.05 [95% CI: 0.02, 0.08]; P = .001) (see Table 2 and Fig 4).

More significant results were obtained for VQM\textsubscript{CM}. IND-GLY increased VQM\textsubscript{CM} from 0.60 at baseline to 0.66 after treatment, whereas placebo only increased VQM\textsubscript{CM} from 0.59 at baseline to 0.60 (Table 2) (LS means treatment difference: 0.06 [95% CI: 0.03, 0.08]; P < .0001) (see Table 2 and Fig 4).

**Correlation of PREFUL MRI–derived Measurements with Traditional Measurements of Lung Function and Other Cardiac and Clinical Outcomes**

Posttreatment correlation and treatment change analyses demonstrated significant relationships between ventilation and perfusion measures with spirometry, body plethysmography, left ventricular filling, and dyspnea score measurements (Tables E1, E2 [supplement]). In particular, there were posttreatment correlations (Table E1) between FVL-CM and FE\textsubscript{V1} (r = 0.65, P < .0001), which were stronger compared with RVent and FE\textsubscript{V1} (r = 0.33, P = .001). Additionally, treatment changes in VQM\textsubscript{CM} were correlated with left ventricular end-diastolic volume (r = 0.34, P = .015) (Fig 5; Table E2), and treatment changes in QDP were correlated with TDI (r = −0.31, P = .026; Table E2). For more details, see Appendix E2 (supplement).

**Discussion**

PREFUL MRI–derived regional flow-volume loop and pulmonary perfusion measures are correlated to treatment response in patients with COPD before and after IND-GLY treatment in...
this retrospective analysis of the CLAIM study. The PREFUL technique identified significant treatment changes for various ventilation and perfusion parameters, as well as significant decreases in VDP and QDP, leading to increased ventilation-perfusion matching in response to IND-GLY compared with placebo. This study demonstrated that diverse patterns of flow-volume curves can be visualized in patients with COPD using PREFUL MRI, and these can be further evaluated with a correlation metric, measuring the similarity to an individualized reference flow-volume loop.

While clinical spirometry uses a forced expiratory breathing maneuver, PREFUL MRI spirometry uses resting tidal volume breathing. FVL-CM and VDP derived from FVL-CM correlates strongly with FEV₁ changes after IND-GLY treatment. This correlation is much stronger than that between the static RVent measurement and FEV₁. This suggests that the flow-volume loop analysis at tidal volume breathing is more closely related to FEV₁ than the RVent measurement, which only uses the inspiratory and expiratory phase. Whether full lung coverage instead of regional ventilation, VQM = ventilation-perfusion match, VQM_{RVent} = ventilation-perfusion match with Q and RVent, VQM_{CM} = ventilation-perfusion match with Q and FVL-CM.

Table 2: Analysis of Ventilation and Perfusion in Response to IND-GLY versus Placebo

| Parameter | Treatment | Baseline Mean | Treatment LS Means | LS Means | 95% CI               | P Value |
|-----------|-----------|---------------|--------------------|----------|---------------------|---------|
| FVL-CM    | IND-GLY   | 0.77          | 0.83               | 0.05     | (0.03, 0.07)        | <.0001  |
|           | Placebo   | 0.77          | 0.78               |          |                     |         |
| QCD       | IND-GLY   | 0.15          | 0.10               | −0.05    | (−0.07, −0.03)      | <.0001  |
|           | Placebo   | 0.14          | 0.14               |          |                     |         |
| VDP (%)   | IND-GLY   | 40.9          | 31.1               | −8.9     | (−11.5, −6.3)       | <.0001  |
|           | Placebo   | 41.1          | 40.0               |          |                     |         |

Note.—For all parameters, n = 50 for treatment and placebo groups. IND-GLY fixed dose is 110/50 µg. IND-GLY = indacaterol-glycopyrrolate, FVL-CM = flow-volume loop correlation map, Q = perfusion, QCD = quartile coefficient of dispersion, VDP = ventilation defect percentage, QDP = perfusion defect percentage, VQM = ventilation-perfusion match, VQM_{RVent} = ventilation-perfusion match with Q and RVent, VQM_{CM} = ventilation-perfusion match with Q and FVL-CM.
measures of dyspnea in patients with COPD. Of further interest is the significant correlation between perfusion heterogeneity and TDI. As perfusion heterogeneity improved with IND-GLY treatment (as measured using perfusion quartile coefficient of dispersion and QDP), so too did TDI, suggesting a link between perfusion heterogeneity and patient-reported dyspnea. A number of these correlations were no longer significant when treatment changes were specifically analyzed, such as in the posttreatment correlation for the correlation metric of RVent with left ventricular end-diastolic volume (the primary end point of the CLAIM study [13]). However, the combination of the suggested ventilation and perfusion parameters, as calculated by treatment change in VQM CM, showed a significant treatment correlation with left ventricular end-diastolic volume ($P = .015$). This seems plausible because the measurement of combined positive effects on perfusion and ventilation add up, thus explaining improved ventricular filling likely due to improved oxygenation and microvascular function.

This study carried several limitations. First, identification of a healthy flow-volume curve for reference may be challenging in patients with very severe disease, and the automatic selection relies on the assumption that high RVent corresponds to healthy lung regions. Nevertheless, this approach was shown to deliver very similar results in patients after double lung

Figure 4: Effect of IND-GLY on FVL-CM, perfusion, and VQM ($n = 50$). Analysis of change in (A) FVL-CM as calculated using the mean correlation metric of the coronal sections, (B) Q, (C) VQM RVent, and (D) VQM CM. The ANOVA model calculated the outcome from treatment plus patient plus period with the patient included as a random effect. $\Delta$ denotes least squares means treatment differences compared with placebo. Error bars denote SD. ANOVA = analysis of variance, FVL-CM = flow-volume loop correlation map, IND/GLY = indacaterol-glycopyrronium, RVent = regional ventilation, Q = perfusion, V = ventilation, V/Q = ventilation-perfusion, VQM RVent = ventilation-perfusion match with Q and FVL-CM, VQM CM = ventilation-perfusion match with Q and RVent.

Figure 5: Correlation analysis of FVL-CM with left ventricular end-diastolic volume comparing changes due to treatment response. Post hoc Pearson rank correlation analyses [IND-GLY-placebo] of VQM CM change with left ventricular end-diastolic volume change. Linear regression lines $\pm$ CIs are denoted. The measurement of combined positive effects on perfusion and ventilation [VQM CM] add up, explaining improved ventricular filling that is likely due to improved oxygenation and microvascular function. FVL-CM = flow-volume loop correlation map, IND/GLY = indacaterol-glycopyrronium, LV-EDV = left ventricular end-diastolic volume, VQM CM = ventilation-perfusion match with Q and FVL-CM.
transplantation in comparison with manual segmentation of a healthy region of interest by an experienced radiologist who visually analyzed the whole respiratory cycle (9). Also, although a reference derived from a healthy population would be desirable for FVL-CM calculation, this approach is currently not practicable because the inter- and intrapatient variability (eg, thoracic vs diaphragmatic breathing) of MRI-derived flow-volume curve shapes has not yet been investigated in detail. Therefore, it is difficult to determine a correlation cutoff. Another limitation was the fact that the technique proposed herein relies on only partial acquisition to reflect the whole lung volume. Increasing spatial resolution and achieving full lung volume coverage, as demonstrated by the recently developed three-dimensional PREFUL technique, could potentially enable the measurement of even smaller treatment changes and reduce the problem of partial volume artifacts and the interrelated segmentation inaccuracies (20). Additionally, the correlation of perfusion measured by PREFUL with dynamic contrast-enhanced MRI–derived pulmonary microvascular blood flow may be imperfect because only one coronal section at the level of the trachea for dynamic contrast-enhanced MRI was compared with three coronal sections for the PREFUL analysis. A more detailed analysis was recently published (10). Furthermore, the PREFUL technique depends on a negative signal measure relative to expiratory parenchymal signal; therefore, in low-signal-to-noise ratio conditions such as hyperinflated lung, the dynamic range of this measure is limited. Also, the ventilation and perfusion measurements are conducted indirectly with PREFUL (and other Fourier decomposition–related methods), relying on the MRI signal as a surrogate marker. Nevertheless, more direct measurements with fluorinated gas inhalation (4) and the reference standard SPECT (21) confirm the validity of the signal-based model. As this was a post hoc analysis, \( P \) values were not adjusted and therefore should be interpreted with caution. Finally, although the observed strong treatment effect of dual bronchodilation in the CLAIM study allowed investigation of the link between PREFUL MRI–based measurements with clinical outcomes, CLAIM was not designed primarily to investigate PREFUL functional MRI outcomes.

In conclusion, RVent dynamics and QVM measured by PREFUL MRI show treatment response in COPD. IND-GLY significantly improves RVent dynamics, perfusion, and QVM in patients with COPD. Additionally, the noninvasive, free-breathing PREFUL MRI method could provide important end points in future clinical cardiopulmonary trials in the form of dynamic regional assessment of lung function and information regarding the entire respiratory cycle.

**Acknowledgments:** The authors thank Sorcha Mc Ginty, PhD, Cathy McDonnell, PhD, and Gillian Lavelle, PhD, of Novartis CONEXTS for providing scientific writing support for this article, which was funded by Novartis Pharma in accordance with Good Publication Practice (GPP3) guidelines (http://www.cpp3.org/gpp3).

**Author contributions:** Guarantors of integrity of entire study, A.V., J.V.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.V., T.E.K., F.K., G.H.P., L.B., K.B., J.V.C.; clinical studies, A.V., T.E.K., F.K., L.B., H.B., K.B., T.W., J.M.H., J.V.C.; statistical analysis, A.V., T.E.K., F.K., G.H.P., L.B., K.B., J.V.C.; and manuscript editing, A.V., T.E.K., F.K., G.H.P., L.B., K.B., F.W., T.W., J.M.H., J.V.C.

**Data sharing:** Data generated or analyzed during the study are available from the corresponding author by request.

**Disclosures of conflicts of interest:** A.V. Support from Novartis; issued patent. Method of quantitative magnetic resonance lung imaging (patent number: 10010293). T.E.K. Member of the Clinician Scientist Program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3069/3-1). F.K. No relevant relationships. G.H.P. No relevant relationships. L.B. No relevant relationships. K.B. Employee of Novartis Pharma; owns stock in Novartis Pharma. F.W. Institutional grants from German Centre for Lung Research (DZL). D.O. Unpaid board member in German Society of Interventional Radiology. T.W. Support from Novartis (funding and medical writing); grant from German Ministry of Research and Education; fees for lectures/advisory board from Boehringer, GSK, AstraZeneca, and Berlin-Chemie. J.M.H. Institutional research grant from Novartis Pharma; personal lecture fees from Novartis Pharma. J.V.C. Support from Novartis (funding and medical writing); honoraria for presentations from Novartis; support for attending meetings/travel from Novartis; board member of Thoracic Imaging Section of the German Radiological Society; editorial board member of Radiology: Cardiothoracic Imaging.

**References**

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5(9):691–706.
2. Bauman G, Puderbach M, Deimling M, et al. Non-contrast-enhanced perfusion and ventilation assessment of the human lung by means of fourier decomposition in proton MRI. Magn Reson Med 2009;62(3):656–664.
3. Capaldi DP, Sheik K, Guo F, et al. Free-breathing pulmonary 1H and Hyperpolarized 3He MRI: comparison in COPD and bronchiectasis. Acad Radiol 2015;22(3):320–329.
4. Kaireit TF, Guterberl M, Voskrebenzev A, et al. Comparison of quantitative regional ventilation-weighted fourier decomposition MRI with dynamic fluorinated gas washout MRI and lung function testing in COPD patients. J Magn Reson Imaging 2018;47(6):1534–1541.
5. Voskrebenzev A, Kaireit TF, Gutberlet M, et al. Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTETPH, and CF patients. Magn Reson Med 2018;79(4):2306–2314.
6. Ohno Y, Jee SB, Farraga G, et al. Pulmonary Functional Imaging: Part 1-State-of-the-Art Technical and Physiologic Underpinnings. Radiology 2021;299(3):508–523.
7. Fischer A, Weick S, Ritter CO, et al. Self-gated Non-Contrast-Enhanced UnFucntional Lung imaging (SENCEFUL) using a quasi-random fast low-angle shot (FLASH) sequence and proton MRI. NMR Biomed 2014;27(8):907–917.
8. Voskrebenzev A, Klimeš F, Gutberlet M, et al. Imaging-Based Spirometry in Chronic Obstructive Pulmonary Disease (COPD) Patients using Phase Resolved Functional Lung Imaging (PREFUL) [abstr]. In: Proceedings of the Twenty-Sixth Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine, 2018:1079.
9. Moher Alsaydi T, Voskrebenzev A, Greer M, et al. MRI-derived flow-volume loop parameters detect early-stage chronic lung allograft dysfunction. J Magn Reson Imaging 2019;50(6):1873–1882.
10. Kaireit TF, Voskrebenzev A, Guterberl M, et al. Comparison of quantitative regional perfusion-weighted phase resolved functional lung (PREFUL) MRI with dynamic gadolinium-enhanced regional pulmonary perfusion MRI in COPD patients. J Magn Reson Imaging 2019;49(4):1122–1132.
11. Pöhler GH, Klimeš F, Behrendt L, et al. Repeatability of Phase-Resolved Functional Lung (PREFUL)-MRI Ventilation and Perfusion Parameters in Healthy Subjects and COPD Patients. J Magn Reson Imaging 2021;53(3):915–927.
12. Vogel-Claussen J, Schönfeld CO, Kaireit TF, et al. Effect of Indacaterol/Glycopyrronium on Pulmonary Perfusion and Ventilation in Hyperinflated Patients with Chronic Obstructive Pulmonary Disease (CLAIM). A Double-Blind, Randomized, Crossover Trial. Am J Respir Crit Care Med 2019;199(9):1086–1096.
13. Hohlfeld JM, Vogel-Claussen J, Biller H, et al. Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial. Lancet Respir Med 2018;6(5):368–378.
14. Zapke M, Topf HG, Zenker M, et al. Magnetic resonance lung function—a breakthrough for lung imaging and functional assessment? A phantom study and clinical trial. Respir Res 2006;7(1):106.
15. Kjørstad Å, Corteville DM, Fischer A, et al. Quantitative lung perfusion evaluation using Fourier decomposition perfusion MRI. Magn Reson Med 2014;72(2):558–562.
16. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319–338.
17. Voorhees A, An J, Berger KL, Goldring RM, Chen Q. Magnetic resonance imaging-based spirometry for regional assessment of pulmonary function. Magn Reson Med 2005;54(5):1146–1154.
18. Tetzlaff R, Schwarz T, Kauczor HU, Puderbach M, Eichinger M. Lung function measurement of single lungs by lung area segmentation on 2D dynamic MRI. Acad Radiol 2010;17(4):496–505.
19. Boucneau T, Fernandez B, Larson P, Darrasse L, Maitre X. 3D Magnetic Resonance Spirometry (abstr). In: Proceedings of the Twenty-Seventh Meeting of the International Society for Magnetic Resonance in Medicine. Berkeley, Calif: International Society for Magnetic Resonance in Medicine; 2019; 0002.
20. Klimeš F, Voskrebenzev A, Gutberlet M, et al. 3D phase-resolved functional lung ventilation MR imaging in healthy volunteers and patients with chronic pulmonary disease. Magn Reson Med 2021;85(2):912–925.
21. Behrendt L, Voskrebenzev A, Klimeš F, et al. Validation of Automated Perfusion-Weighted Phase-Resolved Functional Lung (PREFUL)-MRI in Patients With Pulmonary Diseases. J Magn Reson Imaging 2020;52(1):103–114.