Background: The translation of phase-resolved functional lung (PREFUL)-MRI to routine practice in monitoring chronic thromboembolic pulmonary hypertension (CTEPH) still requires clinical corresponding imaging biomarkers of pulmonary vascular disease.

Purpose: To evaluate successful pulmonary endarterectomy (PEA) via PREFUL-MRI with pulmonary pulse wave transit time (pPTT).

Study Type: Retrospective.

Population: Thirty CTEPH patients and 12 healthy controls were included.

Field Strength/Sequence: For PREFUL-MRI a 2D spoiled gradient echo sequence and for DCE-MRI a 3D time-resolved angiography with stochastic trajectories (TWIST) sequence were performed on 1.5T.

Assessment: Eight coronal slices of PREFUL-MRI were obtained on consecutive 13 days before and 14 days after PEA. PREFUL quantitative lung perfusion (PREFULQ) phases over the whole cardiac cycle were calculated to quantify pPTT, the time the pulmonary pulse wave travels from the central pulmonary arteries to the pulmonary capillaries. Also, perfusion defect percentage based on pPTT (QDPpPTT), PREFULQ (QDPPREFUL), and V/Q match were calculated. For DCE-MRI, pulmonary blood flow (PBF) and QDPPBF were computed as reference. For clinical correlation, mean pulmonary arterial pressure (mPAP) and 6-minute walking distance were evaluated preoperatively and after PEA.

Statistical Tests: The Shapiro-Wilk test, paired two-sided Wilcoxon rank sum test, Dice coefficient, and Spearman’s correlation coefficient (\( \rho \)) were applied.

Results: Median pPTT was significantly lower post PEA (139 msec) compared to pre PEA (193 msec), \( P = 0.0002 \). Median pPTT correlated significantly with the mPAP post PEA (\( r = 0.52, P < 0.008 \)). Median pPTT was distributed more homogeneously after PEA: IQR pPTT decreased from 336 to 281 msec (\( P < 0.004 \)). Median PREFULQ (\( P < 0.0002 \)), QDPpPTT (\( P < 0.0478 \)), QDPPREFUL (\( P < 0.0001 \)) and V/Q match (\( P < 0.0001 \)) improved significantly after PEA. Percentage change of PREFULQ correlated significantly with percentage change of 6-minute walking distance (\( \rho = 0.61; P = 0.0031 \)) 5 months post PEA.

Data Conclusion: Perioperative perfusion changes in CTEPH can be detected and quantified by PREFUL-MRI. Normalization of pPTT reflects surgical success and improvement of PREFULQ predicts 6-minute walking distance changes.

Level of Evidence: 3

Technical Efficacy Stage: 2
C hronic thromboembolic pulmonary hypertension (CTEPH), classified as World Health Organization (WHO) group 4 pulmonary hypertension, is known as a life-threatening complication of acute pulmonary embolism with incomplete solution of the thrombotic material. CTEPH is potentially curable by pulmonary endarterectomy (PEA). Therefore, pre-operative selection of appropriate patients is of fundamental importance. Further, peri/post operative changes and response to therapy have an essential role in assessing the efficacy of the PEA treatment and clinical improvement. Diagnostic management and evaluation of treatment success in CTEPH are widely determined invasively by right heart catheterization (RHC). However, non-invasive diagnostic methods such as echocardiography and MRI in pulmonary hypertension are emerging. For example, the 6-minute walking distance test objectively evaluates changes in functional exercise capacity and improvement in 6-minute walking distance correlates with survival in patients with pulmonary arterial hypertension.

Dynamic contrast enhanced MR-imaging (DCE-MRI) has been shown to be a reliable, non-invasive tool to detect and quantify regional improvement in pulmonary blood flow (PBF) to assess treatment response after PEA. Interestingly, DCE-MRI PBF changes in the lower lobes predicted post-operative changes of the 6-minute walking distance test. This was explained by the resection of the hemodynamically highest relevant thrombus burden in the lower lobe that might result in an improvement in exercise capacity due to increase in vascular reserve.

Given the recent debate on gadolinium deposition in the brain parenchyma, non-contrast MR imaging is a quite desirable test available for freely breathing patients, as it is non-invasive and tolerable. Contrast-free, proton-based lung ventilation (V) and perfusion (Q) MRI, known as Fourier decomposition (FD) MRI was demonstrated as a free-breathing imaging method to detect CTEPH. FD MRI was associated with a sensitivity of 100% and specificity of 95% in a recently published single center study. Conventional FD consists of acquisition of lung images in free-breathing patients with high temporal resolution to assess respiratory and cardiac frequencies. After image acquisition, image post processing is necessary to obtain ventilation- and perfusion-weighted images. Since both maps are generated from one acquisition time-series, exact regional matching of V and Q is achieved, an ideal condition for V/Q mapping.

Recently, phase resolved functional lung (PREFUL)-MRI as a further development of FD, has been presented. PREFUL analysis includes a retrospective sorting, which enables both temporal and spatial mapping of the pulmonary arterial pulse wave during the cardiac cycle. In a recent study, PREFUL perfusion was validated to DCE in patients with several diseases. Nevertheless, no comparison of PREFUL perfusion to 6-minute walking distance test has been shown. This might be beneficial to predict clinical outcome in CTEPH after PEA.

The pulmonary pulse wave transit time (pPTT), the time the systolic pressure pulse wave travels from the pulmonary valve to the pulmonary veins, is a clinically recognized marker of pulmonary vascular disease. In detail, a shorter pPTT was described in WHO groups 1 and 3 pulmonary hypertension and is assumed to indicate loss of pulmonary arterial compliance. This makes echocardiographic pPTT clinically important, as pulmonary arterial stiffness increases mortality in patients with pulmonary hypertension. However, the underlying pathomechanism of pPTT changes and its role in WHO group 4 pulmonary hypertension is still unclear. The standardly echocardiographically measured pPTT is defined as the time interval between the R-wave peak in the electrocardiogram (ECG) and the peak late-systolic pulmonary venous flow velocity. Limitations of the echocardiographic pPTT metric data include lack of standardized measurement as well as operator dependency.

The purpose of this study was to first test PREFUL-MRI on a global and a lobar level to detect pulmonary perfusion changes after successful PEA. Also, we investigate if there is a difference in PREFUL-MRI derived pPTT between patients with CTEPH and healthy volunteers.

Material and Methods

Study Design and Patients / Healthy Volunteers Characteristics

This retrospective single center study was approved by the local ethics committee, and written informed consent was obtained from all patients and healthy volunteers. Thirty CTEPH patients (11 female, 19 males, age range, 20–76 years) were consecutively included between July 2013 and May 2016. Twelve healthy volunteers were included as control group. Inclusion criteria of the CTEPH cohort were confirmed severe CTEPH diagnosis, predominantly proximal web stenosis, clinically stable condition, age >18 years, patients planned for PEA after interdisciplinary decision between pneumology, surgery, and radiology, participation in two conducted MRI’s (2 weeks before and after PEA; 25th–75th percentile range, 10–16 days). Inclusion criteria for the 12 healthy volunteers (6 females, 6 males; age range: 22–29 years) as the PREFUL-MRI control group were absence of known lung /heart disease, >18 years. Exclusion criteria of the CTEPH patients (n = 5) and the healthy control group were:

1. incomplete MRI protocol (n = 4): one patient with technical scanning problems, one clinically unstable patient, one patient with claustrophobia, and one patient with chronic kidney insufficiency,
2. contraindications to MRI (i.e. pregnancy, pacemaker, n = 0), contraindications to contrast agent (n = one patient with chronic kidney insufficiency)
3. unsuccessful surgery in CTEPH patients measured by mean pulmonary arterial pressure (mPAP) (n = 1).
Figure 1 and Table 1 show the patient/healthy volunteers inclusion process and demographic and clinical data.

**PEA, mPAP, 6-Minute Walking Distance Test**

The PEA operability of the patients was decided based on the pre-operative estimate of surgical classification and the pre-operative estimation of probable post-operative pulmonary vascular resistance, accessible clots with degree of pulmonary hypertension, the intensive care facilities for post-operative care, and the skills of the operating surgeon. The PEA technique was performed as follows: median sternotomy, cardiopulmonary bypass, arteriotomy incisions within pericardium, endarterectomy with precise full distal dissection, and deep hypothermic circulatory arrest. mPAP was assessed preoperatively by means of RHC and during the post PEA intensive care unit stay with the Swan-Ganz catheter.

The 6-minute walking distance test, an established tool to assess exercise tolerance in patients with pulmonary hypertension, was evaluated at baseline preoperatively, and 145 days after PEA (25th–75th percentile range: 87–233 days after PEA). Technical aspects of the 6-minute walking distance test include: indoor performance in a straight 50-m corridor. The patients are instructed to walk as far as possible back and forth for 6 minutes from a starting point.

**MRI Protocol**

All patients underwent lung MRI at 1.5T (Avanto & Aera, Siemens Healthcare, Erlangen, Germany) in supine position using an eight-channel torso phased array coil. For PREFUL, as an additional sequence in a standard pre/post PEA MRI, a spoiled gradient echo sequence with the following settings was used: Repetition time/echo time 3/0.67 msec, flip angle 8°, matrix size 128 × 96, field of view 50 × 50 cm², bandwidth 1502 Hz/px, slice thickness 15 mm, interslice gap 7.5 mm, eight coronal slices. For each slice, 200 images with a temporal resolution of 288 msec were acquired in 58s. DCE and cardiac MRI as clinical standard for monitoring PEA were acquired as described in detail by Schoenfeld et al.

The healthy controls underwent the same functional lung MRI except for DCE-MRI.

**Image Post-Processing of Cardiac Cycle**

The Advanced Normalization Tools open source software library was used for registration, as recently described in detail by Voskrebzenz and colleagues to correct the images for diaphragm and heart movement and enable a voxel-wise analysis.
Next, a high-pass filter (cutoff frequency at 0.8 Hz) was applied to the registered voxel-wise time series. The filter eliminated signal variations caused by respiration. One standardized cardiac cycle was constructed by estimation of cardiac phase for each individual image. For this, a strong perfusion signal from a central lung vessel or the heart was used. The voxel time-series of all lung images was sorted and interpolated to 30 cardiac phases on an equidistant time grid (Fig. 2). PREFUL-derived perfusion (PREFULQ) was quantified in mL/min/100 mL by normalizing the signal of every voxel to the signal of a completely blood-filled voxel (SBlood) obtained from a region of interest (ROI) inside the aorta as proposed by Kjørstad et al.:

\[ \text{PREFUL}_Q = \frac{Q}{S_{\text{Blood}}} \times \frac{1}{2} \times t_{\text{exp}}, \]

where Q corresponds to the cardiac frequency dependent signal amplitude \( \Delta \) of the parenchymal signal, \( S_{\text{Blood}} \) is the...
corresponding $\Delta$ of the aorta signal and $t_{exp}$ is the time between two heartbeats.

A pPTT map in milliseconds was computed as follows: First, for every voxel the phase with maximal signal intensity and the corresponding time $t_1$ was determined using the voxel wise time-series of the Q-weighted images sorted to the cardiac cycle. Then, pPTT is the time difference between $t_1$ and the time corresponding to the phase with maximal signal intensity obtained from the ROI in the central lung artery (Fig. 3). This time corresponds to the duration that the pulse wave needs to travel from the main pulmonary artery to the lung capillaries. The signal reaches its peak during inflow of fresh blood into the slice during systole, which travels as a pulmonary arterial blood flow wave front with the pulmonary pulse wave to the capillaries as depicted in a normal volunteer (Movie S1 in the Supplemental Material).

For PBF, DCE slices with an overlap to PREFUL slices were merged to account for different slice thickness. The slices were co-registered to PREFUL$_Q$ maps to adjust for different lung inflation levels.

### Evaluation of Perfusion, Regional Ventilation and V/Q Maps

All perfusion and ventilation parameters of the CTEPH cohort were evaluated on a global and on a lobar level. In the healthy volunteers, PREFUL MRI was evaluated on a global scale. For perfusion defect percentage based on pPTT (QDP$_{pPTT}$), values $>200$ msec were rated as perfusion defects based on the values of the 95th percentile of the healthy volunteers and previously acquired volunteer data.$^{12}$

The same manually segmented lung parenchyma ROI was applied to the PREFUL$_Q$ and the PBF maps to obtain median values. Then, QDP maps of PREFUL$_Q$ and the PBF (QDP$_{PBF}$) were calculated with a threshold defined as the 75th percentile of all Q values multiplied by a factor of 0.6. This threshold was used according to Kaireit et al, who determined this threshold to reach the best agreement between PREFUL-MRI and DCE-MRI.$^{24}$ Binary PREFUL V/Q maps were generated to visualize V/Q match (%). Left ventricular cardiac output (L/min) was assessed by short-axis cine MR images.

Similarly, ventilation defect percentage (VDP$_{PREFUL}$) maps were calculated with ventilation defects defined as

### Table 2. Comparison of pPTT Pre and Post PEA of the Whole Lung and the Different Lung Lobes

| Lobe of Lung       | pPTT Pre PEA (msec) | pPTT Post PEA (msec) | Absolute Mean Difference (95% CI) | Median Percentage Change (%) | $P$ Value (Paired Wilcoxon Test) |
|--------------------|---------------------|----------------------|-----------------------------------|------------------------------|---------------------------------|
| Whole lung         | [166–277]           | [119–169]            | 120 [210; 30]                     | −28                          | 0.0002                          |
| Left lower lobe    | [221–316]           | [159–321]            | 44 [138; 49]                      | −12                          | 0.5557                          |
| Middle lobe        | [160–325]           | [92–169]             | 165 [259; 70]                     | −48                          | 0.0001                          |
| Right lower lobe   | [133–235]           | [96–149]             | 114 [210; 19]                     | −26                          | 0.0028                          |
| Left upper lobe    | [144–301]           | [130–214]            | 66 [160; 27]                      | −17                          | 0.0727                          |
| Right upper lobe   | [155–354]           | [103–176]            | 143 [239;47]                      | −46                          | 0.0012                          |

Unless otherwise indicated, data presents as median with 25th and 75th percentile range in parentheses. Significant $P$ values are colored red.

pPTT = pulmonary pulse wave transit time; CI = confidence interval; PEA = pulmonary endarterectomy.
regional ventilation below the 75th percentile of all V values multiplied by a factor of 0.7.\textsuperscript{24}

**Statistical Analysis**
Statistical analysis was performed with JMP Pro 14 (SAS Institute, Cary, NC). According to the Shapiro–Wilk test, the parameters are not normally distributed. Accordingly, non-parametric tests were applied. Unless otherwise indicated, data are provided as median values with 25th and 75th percentiles in parentheses. A paired two-sided Wilcoxon rank sum test was performed to compare Q and V data pre and post PEA and healthy controls. To assess the agreement of QDP maps of PREFUL\textsubscript{Q} and PBF, spatial overlap of the maps and the Dice coefficient for the defect label were calculated on a voxel level. The Spearman $\rho$ correlation was applied to the QDP obtained by PREFUL\textsubscript{Q} and PBF and lung function parameters (mPAP, 6-minute walking distance test, left ventricular cardiac output). A $P$ value of less than 0.05 was defined as statistically significant.

**Results**
**pPTT**
The pPTT of the whole lung and of all lobes in CTEPH can be found in Table 2. See Movies S2 and S3 in the Supplemental Material for exemplary cardiac cycles pre and post PEA derived by PREFUL. pPTT was more homogeneously distributed post PEA.
distributed after PEA; pre interquartile range (IQR) pPTT was 336 msec, and post IQR pPTT was 281 msec ($P = 0.004$) (Fig. 4). Median pPTT whole lung post PEA correlated significantly with mPAP post PEA ($P < 0.008, r = 0.52$). The whole lung QDP$_{pPTT}$ decreased significantly after PEA ($36\%$ to $19\%$ after PEA in this patient. V/Q match of the whole lung increased from $63\%$ to $80\%$ after PEA. Visually, areas of reduced perfusion match with both MR techniques (overlap = $58\%$, Dice coefficient for defect voxels = $0.57$).

**TABLE 3. pPTT Inside and Outside the Perfusion Defects of PREFULQ Before and After PEA**

| Location and Time Point | pPTT (msec) | $P$ Value (Paired Wilcoxon Test) |
|-------------------------|-------------|----------------------------------|
| In the perfusion defects pre PEA | 328 [296–403] | $<0.0001$ |
| Outside the perfusion defects pre PEA | 108 [60–136] | |
| In the perfusion defects post PEA | 312 [298–349] | $<0.0001$ |
| Outside the perfusion defects post PEA | 90 [69–120] | |

In CTEPH, pPTT outside the perfusion defects before and after PEA was stable ($P > 0.595$). Unless otherwise indicated, data presents as median with 25th and 75th percentile range in parentheses. Significant $P$ values are colored red.

pPTT = pulmonary pulse wave transit time; PEA = pulmonary endarterectomy.

**FIGURE 6:** Three exemplary slices of QDP$_{pPTT}$ maps (A), V/Q maps (B), and QDP$_{PBF}$ maps (C) for a male CTEPH patient (Fig. 4) before (left) and after PEA (right). Defects of QDP maps are marked in red and V/Q maps in black. The QDP$_{pPTT}$ decreased from $36\%$ to $19\%$ after PEA in this patient. V/Q match of the whole lung increased from $63\%$ to $80\%$ after PEA. Visually, areas of reduced perfusion match with both MR techniques (overlap = $58\%$, Dice coefficient for defect voxels = $0.57$).

**PREFULQ, PBF**

See Table 4 and 5 for detailed analysis of PREFULQ and PBF of each patient before and after PEA. Except for PREFULQ in the left upper lobe, pulmonary perfusion values increased after PEA using both MRI techniques. However, there was no significant correlation of whole lung PREFULQ and PBF ($r = 0.07, P = 0.76$).

**QDP$_{pPTT}$, QDP$_{PBF}$, V/Q Match**

The median QDP$_{pPTT}$ of the whole lung decreased from $43\%$ [35–48%] to $31\%$ [24–35%] after PEA ($P < 0.0001$). The median QDP$_{pPTT}$ in the right lower lobe (pre 35% [30–50%] to post 17% [12–30%], $P < 0.0001$), the right upper lobe (pre 53% [38–61%] to post 25% [18–32%], $P < 0.0005$) and in the middle lobe (pre 46% [38–54%] to post 25% [17–29%], $P < 0.0002$) decreased significantly after PEA. No significant difference of QDP$_{pPTT}$ was observed in the left lower lobes (pre 48% [36–64%] to post 52% [37–72%], $P = 0.48$) and the left upper lobes (pre 35% [25–35%] to post 42% [33–50%], $P = 0.13$).

Spatial overlap of QDP defect voxels of PREFUL and DCE, showed a moderate agreement of 56.5% before and 57.7% after PEA for the whole lung with a related Dice coefficient of 0.61 [0.579–0.650] for the QDP$_{pPTT}$ and QDP$_{DCE}$ defect voxels before PEA and 0.602 [0.579–0.646] for the QDP defect voxels after PEA.

The V/Q match increased from $53\%$ [50–63%] to $64\%$ [57–79%] after PEA ($P < 0.0001$). (Fig. 6).
**Regional Ventilation and VDPPREFUL**

Median PREFUL regional ventilation (pre 0.22 mL/mL [0.20–0.29 mL/mL] and post 0.22 mL/mL [0.20–0.25 mL/mL]) and median VDPPREFUL (pre & post 1% [0–2%], [0–3%]) of the whole lung of all patients did not change after PEA (P = 0.23, P = 0.35).

### Table 4. Results of PREFULQ and PBF of the Whole Lung and the Lobes of the Lung Are Presented

| Lobe of Lung       | Perfusion Parameter (mL/min/100 mL) | Pre PEA | Post PEA | Healthy Volunteers | Absolute Mean Difference (95% CI) | Median Percentage Change (%) | P Value Pre vs. Post PEA |
|--------------------|-------------------------------------|---------|----------|--------------------|----------------------------------|-------------------------------|--------------------------|
| Whole lung         | PREFULQ                             | 23 [21–27] | 26 [22–36] | 51 [40–53]         | -4 [12; −20]                     | 13 <0.0002                   |                          |
|                    | PBF                                 | 30 [25–50] | 55 [45–71] | -                  | -21 [24; −66]                    | 83 <0.0001                   |                          |
| Left lower lobe    | PREFULQ                             | 22 [21–26] | 27 [23–35] | -                  | -7 [64; −78]                    | 14 0.0062                   |                          |
|                    | PBF                                 | 40 [32–52] | 58 [45–80] | -                  | -18 [23; −60]                    | 45 0.0001                   |                          |
| Middle lobe        | PREFULQ                             | 22 [19–25] | 27 [24–37] | -                  | -8 [27; −44]                    | 13 0.0022                   |                          |
|                    | PBF                                 | 25 [18–38] | 47 [39–69] | -                  | -22 [25; −70]                    | 88 0.0001                   |                          |
| Right lower lobe   | PREFULQ                             | 21 [20–26] | 28 [24–42] | -                  | -7 [27; −42]                    | 13 0.0001                   |                          |
|                    | PBF                                 | 33 [27–50] | 68 [54–86] | -                  | -28 [26; −82]                    | 106 <0.0001                 |                          |
| Left upper lobe    | PREFULQ                             | 22 [20–30] | 24 [21–33] | -                  | -0.4 [17; −18]                  | 1.4 0.39                    |                          |
|                    | PBF                                 | 42 [28–51] | 47 [33–66] | -                  | -9 [30; −47]                    | 12 0.021                    |                          |
| Right upper lobe   | PREFULQ                             | 21 [19–26] | 29 [21–34] | -                  | -4 [12; −20]                    | 18 0.001                    |                          |
|                    | PBF                                 | 28 [20–41] | 49 [37–59] | -                  | -15 [25; −55]                    | 75 0.0025                   |                          |

The table gives an overview of the perfusion parameter’s median, absolute mean difference, median percentage change and P values of the Wilcoxon rank sum test. Significant values are colored in red. Unless otherwise indicated, data presented as median with 25th and 75th percentile range in parentheses.

PREFULQ = quantitative perfusion derived by phase-resolved functional lung MRI; PBF = pulmonary blood flow; CI = confidence interval; PEA = pulmonary endarterectomy.

**Discussion**

In this explorative study, we showed that the contrast-free PREFUL-MRI method detects and quantifies perfusion changes in CTEPH patients after successful PEA: pPTT was more homogeneous and normalized after PEA and correlated directly with mPAP after PEA. Moreover, reduction of perfusion defects correlated with the improvement in 6-minute walking distance test.

The observed healthy volunteers pPTT values were around 100 msec, which are clearly shorter when compared to the echocardiography data of Dogan et al (180 msec) and others.25,26 This difference is likely due to the defined pPTT reference points. While we measured the arterial part of the pulmonary circulation starting from the main pulmonary artery to the capillaries, Dogan et al and others assessed echocardiographic pPTT as the time interval between the R-wave peak in the ECG and the corresponding peak late systolic pulmonary vein flow velocity.14,25

pPTT has been shown to be shortened in patients with pulmonary hypertension WHO groups 1 and 3, likely due to increased pulmonary pressure and stiffening of the pulmonary vasculature.14,27 Interestingly, in our cohort, the pPTT is prolonged and normalized post-operatively. The exact reason for this is unclear. One possible reason for the pulse wave

**mPAP, 6-Minute Walking Distance, Left Ventricular Cardiac Output**

After PEA, median mPAP decreased significantly from 46 mmHg (35–53 mmHg) to a median of 25 mmHg (16–32 mmHg), P < 0.0001. The percentage change in mPAP and the percentage change in QDPREFUL of the whole lung revealed a significant correlation (Spearman’s ρ = 0.45; P = 0.021). Six-minute walking distance increased significantly after PEA, P < 0.0005 (Table 1). Left ventricular cardiac output increased significantly after PEA from 4.7 L/min [4–6 L/min] to 6.3 L/min [5–8 L/min], P = 0.0001. Percentage change of PREFULQ of the whole lung showed good agreement with the percentage change of 6-minute walking distance (ρ = 0.61; P = 0.0031). PREFULQ and the left ventricular cardiac output before surgery showed moderate agreement (Spearman’s ρ = 0.44; P = 0.027).

In this explorative study, we showed that the contrast-free PREFUL-MRI method detects and quantifies perfusion changes in CTEPH patients after successful PEA: pPTT was more homogeneous and normalized after PEA and correlated directly with mPAP after PEA. Moreover, reduction of perfusion defects correlated with the improvement in 6-minute walking distance test.

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pPTT has been shown to be shortened in patients with pulmonary hypertension WHO groups 1 and 3, likely due to increased pulmonary pressure and stiffening of the pulmonary vasculature.14,27 Interestingly, in our cohort, the pPTT is prolonged and normalized post-operatively. The exact reason for this is unclear. One possible reason for the pulse wave
includes a small associated risk of morbidity and mortality.31

According to Schoenfeld et al, the left upper lobe might be
This is in concordance with Schoenfeld et al, who reported
may be also useful for patient assessment after balloon pulmo-
walking distance test) make PREFUL-MRI a promising tool
pPTT with clinical outcome parameters (mPAP and 6-minute
was a direct correlation of pPTT with mPAP post PEA. Addi-
recovery from surgery must be considered in time. Also, there
used for early evaluation of surgical success, because physical
the regional lobe wise analysis of the left lung and only the
No significant change of median pPTT was detected in
the least affected lobe of thromboembolic load.8 A possible
The low correlation of the PREFUL-Q and PBF is in
agreement with previously reported results for COPD
patients.24 One reason of low correlation between PREFUL-Q
and PBF is a correct and repeatable blood volume determina-
tion, which is needed for perfusion quantification and which
is prone to uncertainties (eg, coil sensitivity, assumption of
orthogonal flow).

As expected, regional ventilation using PREFUL-MRI
did not change post PEA, which confirms prior results.2,30,35

Limitations
First, one potential confounder may be the PEA procedure
itself by resection of the elastic membrane with the cast of
organized thrombi that may also influence vessel elasticity and
thus pPTT.36 Also, patients with coexistence of other chronic
lung disease were not excluded in the current study, which
might potentially influence PEA outcome. We investigated a
relatively small sample size at a single center. However, the
study provides sufficient single center data to show the moni-
toring potential of PREFUL in CTEPH patients before and
after surgery and serves as basis for larger trials, which need
to further assess the prognostic value of pPTT derived by
PREFUL. Another limitation is the incomplete coverage of
the lung volume by the 2D-acquisition of PREFUL-MRI
compared to the 3D-acquisition of DCE-MRI.

Conclusion
The PREFUL-MRI method may detect and quantify hemo-
dynamic changes in CTEPH after PEA and predicts
6-minute walking distance test changes 5 months after PEA.
Thus, PREFUL-MRI is a promising tool to non-invasively
monitor CTEPH patients after PEA in the future.

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delay could be that pulmonary blood flow is directed toward
preserved and non-obstructed vascular beds in CTEPH
patients.8 Distal of the stenotic web only a relatively small
pulmonary blood volume flows through a highly compliant
and low pressure distal pulmonary arterial and capillary vascu-
lar bed leading to a marked decrease in pulse wave velocity28
and prolonged pPTT. This is supported by the fact, that
there was no significant difference of pPTT in the non-defect
regions in CTEPH patients pre and post surgery compared
with healthy volunteers in our study. Another possible reason
is that the conduction of the pulse wave is impeded by the
obstructed vessel. Thus, the pulse wave continues to move
much slower by means of lung tissue conduction. Tissue con-
duction effects the pulse wave velocity, which is consequently
different from pulse wave movement through the vessels.29
Rather unlikely is that the phase signal is created by the bron-
chial arteries and generates the strong phase delay.

The different severities of the pulmonary arterial web
stenosis and the heterogeneity of disease with predominantly
proximal and quite severe CTEPH likely caused the heteroge-
eous distribution of pPTT pre PEA in our study. Directly
after successful PEA the proximal pulmonary web stenosis was
removed, and pulmonary pressure and resistance improved
resulting in more homogeneous pPTT.

The 6-minute walking distance test and the mPAP are
commonly used to evaluate surgical outcome after PEA and
serve as predictor of mortality in patients with pulmonary
hypertension.30 PREFULQ predicted changes in 6-minute
walking distance test 5 months post PEA. In contrary to
PREFULQ, the 6-minute walking distance test cannot be
used for early evaluation of surgical success, because physical
recovery from surgery must be considered in time. Also, there
was a direct correlation of pPTT with mPAP post PEA. Addi-
tionally, we observed a correlation of the decrease of
QDPpreful and mPAP of the whole lung after PEA. In con-
trast to PREFUL-derived pPTT and QDPpreful, RHC-
derived mPAP is invasive, causes radiation exposure, and
includes a small associated risk of morbidity and mortality.31
The missing correlation of pPTT with mPAP before surgery is
explained by the wide time interval between RHC pre PEA
and the MRI examination in accordance with Kreitner et al.32
Nevertheless, the correlation of PREFULQ, QDPpreful, and
pPTT with clinical outcome parameters (mPAP and 6-minute
walking distance test) make PREFUL-MRI a promising tool
for non-invasive treatment monitoring of CTEPH patients.
It may be also useful for patient assessment after balloon pulmo-

No significant change of median pPTT was detected in
the regional lobe wise analysis of the left lung and only the
left upper lobe showed no significant change of PREFULQ.
This is in concordance with Schoenfeld et al, who reported
the lowest PBF increase in the left upper lobe after PEA.
According to Schoenfeld et al, the left upper lobe might be

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