

Automated Quantification of Pulmonary Perfused Blood Volume by Dual-Energy CTPA in Chronic Thromboembolic Pulmonary Hypertension

Automatische Quantifizierung des perfundierten Lungenblutvolumens mittels dual-energy CTPA bei chronisch-thromboembolischer pulmonaler Hypertonie

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Zusammenfassung



Zielsetzung: Ziel der Studie war es zu untersuchen, ob die automatisierte Quantifizierung des perfundierten Lungenblutvolumens (PBV) in der dual-energy CT Pulmonalis-Angiografie (DE-CTPA) zur Beurteilung des Schweregrades einer chronisch-thromboembolischen pulmonalen Hypertonie (CTEPH) genutzt werden kann.

Methoden: Die automatisierte Quantifizierung des PBV wurde bei 25 konsekutiven Patienten mit CTEPH durchgeführt, die mittels DE-CTPA untersucht wurden. Die PBV-Werte wurden mit Parametern aus Rechtsherzkatheteruntersuchung (pulmonalarterieller Druck, Herzindex und pulmonalem Gefäßwiderstand) sowie der 6-Minuten-Gehstrecke korreliert. Hierbei wurde der Korrelationskoeffizient nach Pearson verwendet und mittels multivariater linearer Regression für Alter und Geschlecht adjustiert.

Ergebnisse: Die aus der DE-CTPA ermittelten PBV-Werte korrelierten negativ mit dem systolischen ($r = -0,64$, $p = 0,001$) und mittleren ($r = -0,57$, $p = 0,004$) pulmonalarteriellen Blutdruck. Es zeigte sich ein Trend zu einer negativen Korrelation zwischen PBV-Werten und dem pulmonalen Gefäßwiderstand ($r = -0,20$, $p = 0,35$). Zwischen PBV und Herzindex sowie 6-Minuten-Gehstrecke wurden keine signifikanten Korrelationen gefunden. Durch multivariate lineare Regression wurde bestätigt, dass diese Korrelationen von Alter und Geschlecht unabhängig waren.

Schlussfolgerung: Die DE-CTPA kann bei Patienten mit CTEPH für eine automatisierte Quantifizierung des perfundierten Lungenblutvolumens genutzt werden. Deren Ergebnisse korrelieren invers mit systolischem und mittlerem pulmonalarteriellen Druck und können daher den Schweregrad der pulmonalen Hypertonie bei diesen Patienten abschätzen.

Abstract



Objectives: The aim of the study was to determine whether automated quantification of pulmonary perfused blood volume (PBV) in dual-energy computed tomography pulmonary angiography (DE-CTPA) can be used to assess the severity of chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: Automated quantification of PBV was performed in 25 consecutive CTEPH patients undergoing DE-CTPA. PBV values were correlated with cardiac index and pulmonary vascular resistance quantified by right heart catheterization and walking distance in the 6-minute walk test using Pearson's correlation coefficient and multivariate linear regression analysis to control for age and gender.

Results: DE-CTPA derived PBV values inversely correlated with systolic ($r = -0,64$, $p = 0,001$) and mean ($r = -0,57$, $p = 0,004$) pulmonary arterial pressure. There was a trend for PBV values to inversely correlate with pulmonary vascular resistance ($r = -0,20$, $p = 0,35$). No significant correlation was found between PBV values and cardiac index or 6-minute walking distance. These correlations were confirmed to be independent of age and gender on multivariate linear regression analysis.

Conclusion: DE-CTPA can be used for an automated quantification of pulmonary PBV in chronic thromboembolic pulmonary hypertension. PBV values correlate inversely with systolic and mean pulmonary arterial pressure and can thus be used to estimate the severity of pulmonary hypertension in these patients.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a persistent elevation of pulmonary arterial pressure (PAP), which develops in 2–4% of patients after acute pulmonary embolism (PE) [1–3]. Pathophysiologically, CTEPH is characterized by persistent vascular obstruction, small-vessel arteriopathy and vasoconstriction, all contributing to chronic elevation of the PAP [1]. Patients with CTEPH often present with progressively worsening dyspnea and exercise intolerance. The diagnosis is often suspected based on a clinical history of pulmonary embolism and/or signs of right heart dysfunction on echocardiography.

Imaging is commonly performed in CTEPH to confirm the diagnosis and exclude other causes of pulmonary hypertension, to localize the extent of disease and to determine whether a patient is a suitable candidate for pulmonary thromboendarterectomy. [1] Ventilation-perfusion (V/Q) scintigraphy typically demonstrates peripheral wedge-shaped perfusion defects without matching ventilation defects [4]. Characteristic findings of CTEPH on CT pulmonary angiography (CTPA) include mosaic attenuation pattern, dilatation of the proximal pulmonary arteries and vascular stenosis and vascular obstruction [2, 5]. Contrast-enhanced MR angiography can also demonstrate vascular abnormalities associated with CTEPH but has been shown to be inferior to CTPA in this indication [6, 7]. It has been shown that V/Q scintigraphy has a higher sensitivity and negative predictive value for CTEPH than CTPA [4]. However, V/Q scintigraphy is inferior to CTPA in assessing the exact anatomical extent of disease, in differentiating CTEPH from recurrent acute PE and in excluding abnormalities of the pulmonary parenchyma such as emphysema or interstitial lung disease as alternative causes of pulmonary hypertension. Therefore, in many centers CTEPH patients routinely undergo both V/Q scanning and CTPA. Additionally, invasive pulmonary angiography is often performed in the preoperative work-up of patients considered for pulmonary thromboendarterectomy to determine the extent of thrombotic material and assess its surgical accessibility [1, 2, 8]. In most patients with CTEPH, the diagnostic work-up is complemented by functional assessment including right heart catheterization with direct quantification of pulmonary artery pressure and other hemodynamic parameters. The six-minute walk test, quantifying the achievable walking distance, is commonly used as a measure of a patient's global functional impairment in CTEPH [9].

Among many other applications [10–13], dual-energy CTPA (DE-CTPA) can be used to generate iodine distribution maps of pulmonary parenchyma [14–16] which correspond well with pulmonary perfusion on scintigraphy [17] and SPECT [18] in acute PE. A good correlation of DE-CTPA iodine distribution maps with lung perfusion scintigraphy has been specifically demonstrated in patients with CTEPH [19]. Dual-energy CT thus simultaneously provides high-resolution morphological images of pulmonary parenchyma and functional information on pulmonary perfusion. DE-CTPA therefore represents a very promising imaging modality for patients with CTEPH since it allows simultaneous morphological assessment of pulmonary vasculature and parenchyma and functional assessment of pulmonary perfusion [20, 21]. Therefore, the dual-energy technique is likely to increase the sensitivity of CTPA for CTEPH, although this has not yet been demonstrated conclusively.

Recently developed software allows automated quantification of pulmonary perfused blood volume (PBV) based on DE-CTPA iodine distribution maps, thus providing a quick, reader-indepen-

dent tool for the assessment of global and regional pulmonary perfusion. A pilot study has found automated pulmonary PBV values to be decreased in patients with acute PE and to correlate with thrombus load [22].

The purpose of this study was to determine the diagnostic value of PBV quantification in DE-CTPA in patients with chronic thromboembolic pulmonary hypertension (CTEPH) by correlating the quantified perfused blood volume with the results of right heart catheterization and a six-minute walk test.

Materials and Methods

Ethical approval and informed consent were waived by the responsible ethics committee for this retrospective analysis. All patients provided written informed consent to the CTPA examination.

Patient selection

We defined the following inclusion criteria:

1. Diagnosis of CTEPH definitely confirmed by pooled data from clinical history and examination, imaging studies (including CT, scintigraphy or SPECT and conventional pulmonary angiography), right heart catheterization and clinical follow-up
2. Clinically indicated DE-CTPA performed

We defined the following exclusion criteria:

1. DE-CTPA with severe artifacts, inadequate vascular enhancement or timing
2. Any cardiopulmonary comorbidities

All DE-CTPAs performed between May 2009 and November 2011 in patients with CTEPH were assessed for any cardiopulmonary comorbidities which might influence pulmonary PBV. This was performed by an experienced chest radiologist to exclude even subtle changes such as mild emphysema or airway disease.

CT image acquisition

All DE-CTPAs were performed on a dual source CT scanner (Somatom Definition Flash, Siemens Medical, Forchheim, Germany). 85 mL of contrast material (Iopromide, Ultravist 370, Bayer Healthcare, Berlin, Germany) were administered via an antecubital vein at a flow rate of 5 mL/s, followed by 50 mL of saline, injected at the same flow rate. Scans were started using a bolus-tracking technique with a threshold of 100 HU in the pulmonary trunk and an additional delay of 7 s. To reduce streak artifacts caused by dense contrast material in the superior vena cava, scans were performed in a caudocranial direction. A combination of a tin-filtered (Sn) 140 kVp and a 100 kVp spectrum was used. Collimation was set to 32 × 0.6 mm. Pitch was 0.5 at a rotation time of 0.28 s/rot. The mean CTDI and DLP were 9.1 ± 3.0 mGy and 291 ± 91 mGy × cm, corresponding to an effective radiation dose of 4.2 ± 1.3 mSv (using a standard conversion factor for chest CT of 0.0145 mSv/mGy × cm (23)).

CT image reconstruction

CTPA images were reconstructed in axial orientation using a specific medium soft convolution kernel optimized for DE images (D30) at a 1.5-mm slice thickness with a 1-mm increment. To obtain axial images similar to standard 120-kVp reconstructions with low image noise, average images were generated with equal contributions from the Sn140 kVp and the 100 kVp dataset. DECT imaging allows for material differentiation based on the different

absorption characteristics of different types of tissue. Iodine is known to produce a higher attenuation at lower tube voltage settings [24]. Thus, the spectral information obtained at different voltage settings allows for a three-material decomposition differentiating soft tissue, air, and iodine. This algorithm assigns a ratio of air and soft tissue to each voxel and uses CT attenuation values at both energies to derive the additional iodine content [16]. Color-coded iodine distribution maps were generated by specific, FDA-approved DE post-processing software (DE lung PBV, Siemens Healthcare) on a dedicated post-processing workstation (syngo MMWP, Somaris Version CT2008G, Siemens Healthcare). Iodine distribution (“PBV”) maps were superimposed onto CTPA images at a slice thickness of 3 mm with a 1-mm increment in axial, sagittal and coronal orientations.

Image quality control

To ensure valid assessment of pulmonary PBV, we excluded all examinations with severe artifacts, inadequate enhancement of the pulmonary vasculature and/or inadequate timing. For this purpose, all images considered for the study were reviewed. The degree of artifacts in iodine distribution maps (from cardiac motion, breathing or concentrated contrast material) was visually rated on a 4-point scale (0 = no artifacts, 1 = mild artifacts, 2 = moderate artifacts, 3 = severe artifacts). Rating was performed by two radiologists in consensus. Rating was performed for upper, middle and lower lung zones. The zone with the worst rating determined the overall rating for the examination. All studies with severe artifacts were excluded from the study. Additionally, we measured enhancement in the pulmonary trunk and ascending aorta. Since lung PBV values are quantified by measuring the enhancement of the pulmonary parenchyma relative to the enhancement of the pulmonary trunk, PBV values may become unreliable with inadequate enhancement of the pulmonary vasculature and inadequate timing of the examination relative to the contrast bolus. Therefore, all examinations with enhancement of the pulmonary trunk of <200 HU were excluded. Since this study was performed on a second-generation dual-source scanner with an extended field of view of 32 cm for dual-energy applications, the dual-energy analysis fully covered the pulmonary parenchyma in all patients.

CT data analysis

Automated quantification of pulmonary PBV was performed using the DE lung PBV application of the Syngo Dual Energy software (Siemens Healthcare, version VE32B). This analysis quantifies pulmonary PBV by measuring the enhancement of the pulmonary parenchyma in relation to the enhancement of a reference vessel. The reference vessel was defined by placing a standardized region of interest (ROI) sized 0.5 cm² in the pulmonary trunk on axial images. The software calculates pulmonary PBV as (mean enhancement of the pulmonary parenchyma in HU/mean enhancement of the pulmonary trunk in HU)/calibration factor 0.15. For example, for a vascular enhancement of 400 HU, a mean enhancement of the pulmonary parenchyma of 400 HU * 0.15 = 60 HU would represent a PBV of 100%. Lung isolation, lung partitioning (in upper, middle and lower zones) and enhancement analysis are performed automatically. The software then displays PBV for the entire pulmonary parenchyma, right and left lungs separately as well as lower, middle and upper zones of each lung separately.

Analysis of clinical data

Chart review was performed to obtain results from right heart catheterization (systolic and mean pulmonary arterial pressure, cardiac index and pulmonary vascular resistance) and walking distance in the 6-minute walk test. The cardiac index is defined as the cardiac output (in L/min) divided by the body surface area (in m²) and is a commonly used parameter of global circulatory function. The 6-minute walk test quantifies the distance a patient can walk during a 6-minute interval and is commonly used as a measure of a patient’s global functional impairment in CTEPH [9]. Only studies performed within 6 months before or after the CTPA examination were included. If multiple studies were available within this time frame, the study closest in time to the CTPA examination was chosen.

Statistical analysis

Statistical analysis was performed using Microsoft Excel for Mac 2011 (version 14.1.3) and IBM SPSS Statistics for Mac (version 20.0.0.1). Global PBV values were correlated with parameters of right heart catheterization and the 6-minute walk test using Pearson’s correlation coefficient *r*. Multivariate linear regression analysis was performed to determine whether possible correlations of global PBV values with parameters of right heart catheterization and the 6-minute walk test were independent of age and gender. A two-sided *p*-value of <0.05 was considered to indicate statistical significance.

Results

Patient selection and characteristics

32 patients with a definite diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) underwent DE-CTPA at our institution between May 2009 and November 2011. Four patients were excluded because of thoracic comorbidities that could potentially confound pulmonary perfusion, including pneumonia (*n* = 2) and large pleural effusions (*n* = 2). Two patients were excluded because iodine distribution maps showed severe artifacts from concentrated contrast material. One patient was excluded because of inadequate contrast timing with inadequate enhance-

Table 1 Patient characteristics.

number of patients	25	
clinical diagnosis	chronic thromboembolic pulmonary hypertension (CTEPH)	
cardiopulmonary comorbidities	none	
% females	52% (<i>n</i> = 13)	
median age (range)	65 (25 – 83) years	
prior therapy	treatment naïve (<i>n</i> = 10) phosphodiesterase 5 inhibitors (<i>n</i> = 12) calcium channel blockers (<i>n</i> = 2), endothelin receptor antagonist (<i>n</i> = 1)	
	median	range
pulmonary PBV (%)	42	31 – 67
PAP _{sys} (mmHg)	79	54 – 109
PAP _m (mmHg)	45	34 – 66
cardiac index (L/min/m ²)	2.2	1.5 – 3.6
pulmonary vascular resistance (mmHg/L/min)	8.9	4.2 – 15.9
6-minute walking distance (m)	330	100 – 510

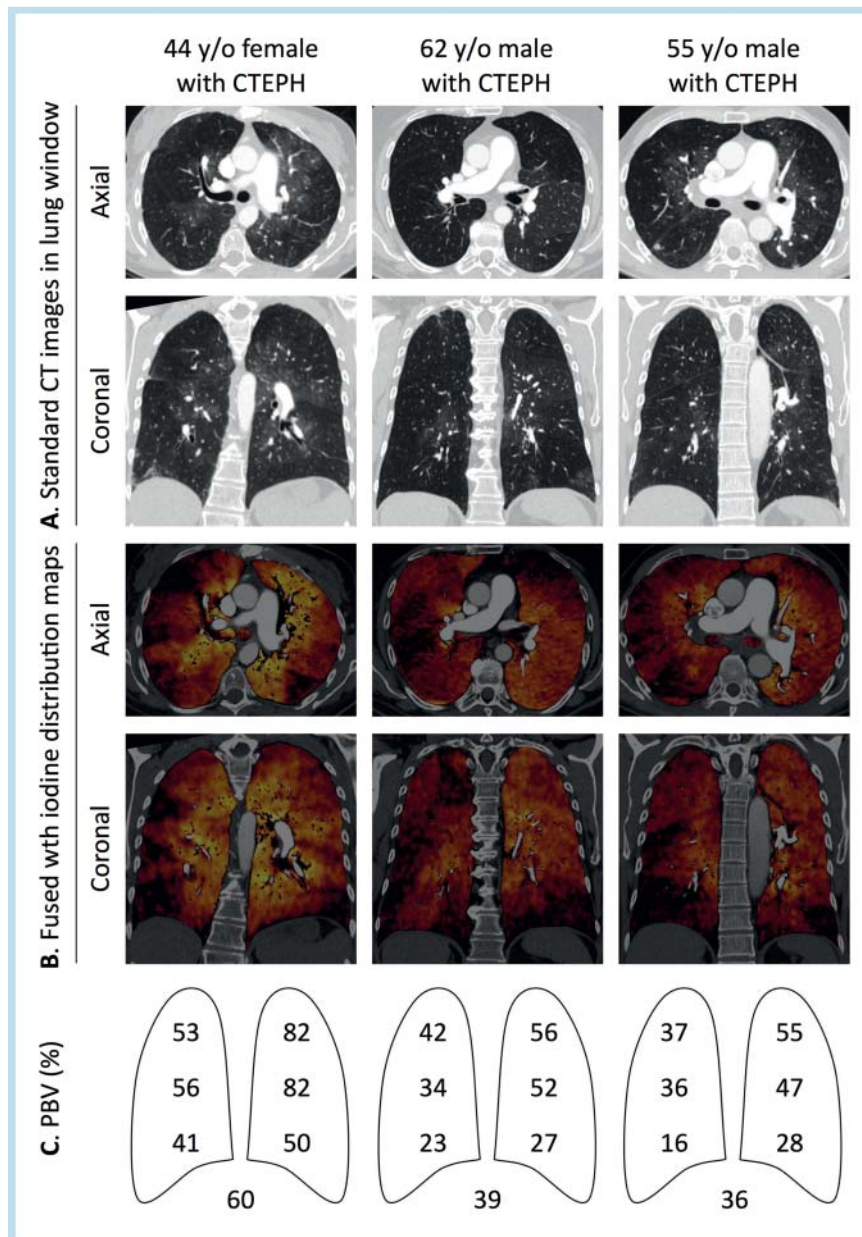


Fig. 1 Representative images. Representative axial and coronal slices are shown in general viewing mode **a** and with superimposed iodine distribution maps **b**. After manual definition of the pulmonary trunk as a reference vessel, lung isolation, partitioning and enhancement analysis are performed automatically. Note the mosaic attenuation pattern in the standard images and the peripheral, wedge-shaped perfusion defects in the fused images. Relative pulmonary parenchymal enhancement is shown for the left and right upper, middle and lower lung zones as well as the entire pulmonary parenchyma **c**.

Abb. 1 Repräsentative Bilder. Repräsentative axiale und koronare Schichten sind in der allgemeinen Ansicht **a** sowie mit darübergelegten Iodverteilungskarten **b** gezeigt. Nach manueller Definition des Truncus pulmonalis als Referenzgefäß werden Isolierung und Unterteilung der Lunge sowie die Analyse der Kontrastmittelanreicherung automatisch durchgeführt. Zu beachten ist die deutliche Mosaikperfusion in den Standardbildern und die peripheren, keilförmigen Perfusionsdefekte in den fusionierten Bildern. Die relative Kontrastmittelanreicherung des Lungenparenchyms ist jeweils für die linke und rechte obere, mittlere und untere Lungenregion sowie als Gesamtwert für das gesamte Lungenparenchym gezeigt.

ment of the pulmonary trunk (<200 HU). The remaining 25 patients met all eligibility criteria and were included in this retrospective analysis. The patient population thus consisted of 25 patients with chronic-thromboembolic pulmonary hypertension (CTEPH) and no cardiopulmonary comorbidities. The median age was 65 years with a range of 25–83 years (Table 1). 24/25 patients had right heart catheterization and 20/25 patients had undergone the 6-minute walk test within 6 months of the CTPA examination. Representative CTPA images are shown in Fig. 1. Of the examinations included in the study, 2 were rated to have no artifacts in the dual-energy iodine distribution maps, 20 were rated to display mild artifacts and 3 were rated to have moderate artifacts.

Bivariate correlation of pulmonary PBV with parameters of CTEPH severity

A highly significant negative correlation was found between pulmonary PBV values and both systolic ($r = -0.64$, $p = 0.001$) and mean ($r = -0.57$, $p = 0.004$) pulmonary arterial pressure (Table 2,

Table 2 Bivariate correlation of pulmonary PBV values with markers of CTEPH severity.

	Pearson's correlation coefficient r	p-value
<i>right heart catheterization</i>		
PAP _{sys}	-0.64	0.001
PAP _m	-0.57	0.004
cardiac index	-0.11	0.62
pulmonary vascular resistance	-0.20	0.35
<i>6-minute walk test</i>		
6-minute walking distance	0.13	0.59

Fig. 2). There was a trend for PBV values to inversely correlate with pulmonary vascular resistance ($r = -0.20$, $p = 0.35$). No significant correlation was found between PBV values and cardiac in-

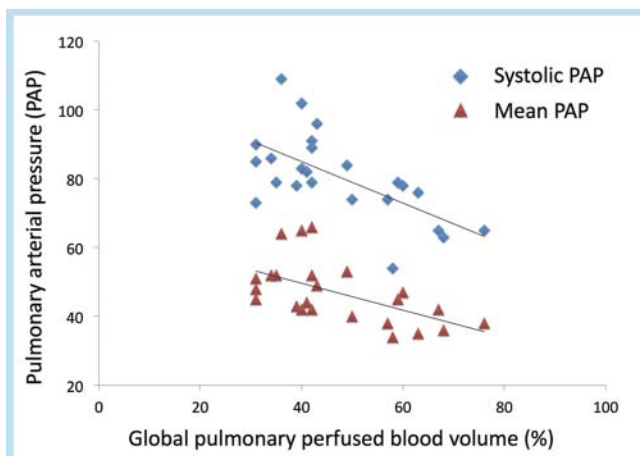


Fig. 2 Correlation of pulmonary PBV with systolic and mean pulmonary arterial pressure. Global pulmonary PBV values are plotted against the systolic and mean pulmonary arterial pressure for all patients with right heart catheterization performed within 6 months before or after the CTPA examination (n = 24).

Abb. 2 Korrelation des pulmonalen PBV mit systolischem und mittlerem pulmonalarteriellen Druck. Die globalen pulmonalen PBV-Werte sind gegen den systolischen und mittleren pulmonalarteriellen Druck aufgetragen. Hierbei wurden alle Patienten berücksichtigt, bei denen innerhalb von 6 Monaten vor oder nach der CTPA eine Rechtsherzkatheteruntersuchung durchgeführt wurde.

Table 3 Multivariate linear regression analysis adjusted for age and gender: correlation of pulmonary PBV values with markers of CTEPH severity.

	standardized regression coefficient β	p-value
<i>right heart catheterization</i>		
PAP _{sys}	-0.66	0.001
PAP _m	-0.61	0.003
cardiac index	-0.04	0.85
pulmonary vascular resistance	-0.29	0.17
<i>6-minute walk test</i>		
6-minute walking distance	0.08	0.74

dex ($r = -0.11$, $p = 0.62$) or 6-minute walking distance ($r = 0.13$, $p = 0.59$).

Covariance of pulmonary PBV with parameters of CTEPH severity on multivariate regression analysis controlling for age and gender

These correlations were confirmed to be independent of age and gender on multivariate linear regression analysis. Again, a highly significant negative covariance was found between pulmonary PBV values and both systolic ($\beta = -0.66$, $p = 0.001$) and mean ($\beta = -0.61$, $p = 0.003$) pulmonary arterial pressure (Table 3). There was a trend for PBV values to inversely co-vary with pulmonary vascular resistance ($\beta = -0.29$, $p = 0.17$). No significant covariance was found between PBV values and cardiac index ($\beta = -0.04$, $p = 0.85$) or 6-minute walking distance ($\beta = 0.08$, $p = 0.74$).

Discussion

This study assessed whether a quantitative analysis of the iodine distribution maps generated by dual-energy CT can be used to estimate the severity of CTEPH. Data from 25 patients with a definite diagnosis of CTEPH and no cardiopulmonary comorbidities were analyzed. We found that global pulmonary perfused blood volume inversely correlates with both systolic and mean pulmonary arterial pressure. There was a trend for PBV values to inversely correlate with pulmonary vascular resistance, but no significant correlation was found between PBV values and cardiac index or 6-minute walking distance.

Our findings go beyond the data published in the literature. Renard and colleagues correlated perfusion defects on iodine distribution maps in 17 CTEPH patients with vascular changes suggestive for CTEPH including stenosis, obstruction by thrombi, webs and bands, and abrupt vessel narrowing [20]. They found that the most severe vascular changes of CTEPH were seen with a higher frequency in segments with perfusion defects on iodine distribution maps [20]. This provided first evidence that perfusion impairment on DE-CTPA iodine perfusion maps may correlate with disease severity in patients with CTEPH, which is confirmed by our results.

The only previous study to correlate DE-CTPA iodine distribution maps with clinical parameters of CTEPH severity is a study performed by Hoey and colleagues in 20 patients with CTEPH [21]. In this study, a visual score of perfusion impairment on iodine distribution maps correlated well with the extent of mosaic attenuation pattern on CT [21]. However, the visual perfusion impairment score showed no significant correlation with the degree of vascular obstruction, mean pulmonary artery pressure, or pulmonary vascular resistance [21]. This partly conflicts with our data, since we found a significant negative correlation between global PBV and pulmonary artery pressure. The reason for this disagreement may be imperfections in the visual scoring of perfusion defects on iodine distribution maps. In the technique we propose, quantification of PBV is performed automatically after manual definition of the pulmonary trunk, thus rendering PBV values rater-independent. Furthermore, automated quantification of pulmonary PBV is much faster than visual scoring of perfusion defects on iodine distribution maps, making it much more suitable for an application in routine clinical diagnostic work-up. On the other hand, visual assessment of iodine distribution may be more accurate in the differentiation of pseudodeficits from real perfusion defects than in the automated quantification of pulmonary PBV. However, visual assessment of iodine distribution maps is reader-dependent and more time-consuming.

It is known from MR lung perfusion studies that pulmonary blood flow is doubled in expiration compared to inspiration [25]. This is largely because the ratio of air to tissue per volume is decreased, thus increasing perfusion per volume [26]. Even though all our scans were performed in full inspiration, differences in inspirational effort may account for some of the inter-individual differences in our study, possibly explaining the only moderate correlations with disease severity.

Since there are considerable inter-individual variations in PBV even in the absence of pathology, it is reasonable to hypothesize that the correlation between PBV values and pulmonary arterial pressure may be even stronger for examinations of the same CTEPH patient at different time points. Therefore, DE-CTPA with automated quantification of pulmonary PBV may represent a non-invasive alternative to right heart catheterization for evalu-

ating disease progression, assessing the response to medical therapy or monitoring patients after pulmonary thromboendarterectomy. DE-CTPA lacks the risks associated with the invasive procedure at the expense of exposing the patient to ionizing radiation. The radiation dose associated with DE-CTPA does not exceed the dose of a conventional, single-spectrum CTPA examination [27]. Compared to the average effective radiation dose of 1.4 mSv for combined ventilation/perfusion scintigraphy [28], the radiation dose of one DE-CTPA examination – approximately 4 mSv in our study – is higher by a factor of 3. The incremental life-time risk of malignancy associated with this radiation dose is of only marginal significance compared to the high morbidity and mortality of patients with CTEPH. Nevertheless, the radiation exposure associated with DE-CTPA represents a limitation in patients who require frequent follow-up examinations. The results of this study have to be seen in light of the study design. First, in order to avoid confounding of PBV values, we excluded CTEPH patients with cardiopulmonary comorbidities. The influence of these comorbidities on DE-CTPA pulmonary PBV values in an unselected patient population needs to be addressed in further studies. However, only four patients were excluded from our study because of comorbidities including large pleural effusions and pneumonia. Therefore, the technique presented here is applicable in the majority of CTEPH patients. Second, the majority of patients in our study had – although mostly mild – artifacts in the dual-energy iodine distribution maps. We cannot exclude that subtle pseudoperfusion defects caused by cardiac pulsation or breathing artifacts may have influenced PBV values. Third, limited statistical power may be one reason why we did not find significant correlations between PBV and some clinical parameters of disease severity. This is particularly true for pulmonary vascular resistance where there was at least a trend towards an inverse correlation. Fourth, this was a retrospective study in a relatively small number of patients. Before the technique can be incorporated into the clinical routine, the results should be confirmed in larger, prospective trials. In conclusion, automated quantification of pulmonary PBV in DE-CTPA provides an immediate, reader-independent estimation of global pulmonary perfusion in chronic thromboembolic pulmonary hypertension, which correlates inversely with systolic and mean pulmonary arterial pressure and can thus be used to estimate the severity of pulmonary hypertension in these patients.

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