METHODOLOGY:

MR perfusion: MRI was performed on a 1.5 Tesla GE HDx Scanner (GE Healthcare, Milwaukee, USA). An 8 channel cardiac receive array RF coil was used. Contrast enhanced 3D MR lung perfusion images were acquired using a time resolved 3D spoiled gradient echo sequence with view sharing (TRICKS)[1]. The sequence parameters were: coronal orientation, TE 1.1ms, TR 2.5 ms, flip angle of 30°, FOV=48x48cm, matrix 200 x 80, SENSE R=2, 250 kHz bandwidth, slice thickness of 10mm. This sequence was acquired during full inspiratory breathhold after intravenous administration of 0.05 ml/kg of Gadovist (Schering, Berlin) injected at 4 ml/s followed by a 20ml saline flush. 40 3D image volumes were acquired consecutively depicting the passage of contrast bolus at an effective frame rate of two 3D volumes per second. To obtain full lung coverage, an average of 24 slices was obtained with a total breath hold time of 25 seconds. The perfusion images were generated by pixel-by-pixel subtraction of the pre-contrast data time point from the pixel which showed peak enhancement in the post contrast time course.

MR image analysis: The MR images were independently analysed by two radiologists who were blinded to the results of other imaging studies and clinical information. Images were analysed in the coronal plane and the image quality was graded on a three-point scale [2]: 1) un-interpretable 2) interpretable but of marginal image quality, or 3) of sufficient image quality to obtain a confident diagnosis. Two observers then independently evaluated the perfusion images for perfusion defects. A perfusion defect was defined as a lung region with decreased or no visible contrast enhancement. A diagnosis of CTEPH was made when there were one or more segmental and / or circumscribed perfusion defects, based on evidence from previous studies [3-4]. The distribution of perfusion defects was also recorded as upper, middle or lower zone in the right lung and upper and lower in the left lung. If the observers disagreed, a separate consensus reading took place and the consensus report was used in all further analysis. MR perfusion images were

evaluated without referring to other MRI techniques as the purpose was to evaluate the standalone value of perfusion MRI.

Perfusion scintigraphy: The perfusion scintigraphy images were obtained with the patient in the supine position following intravenous administration of technetium 99m labelled macro-aggregated albumin (dose of 100-MBq; MAASOL; Amersham Health, Vienna, Austria). Scanning was performed on a gamma camera system (GE Millennium, GE Infinia, or Siemens Symbia gamma camera systems) with a 256 x 256 matrix using a 20% window centered over the 140-keV energy peak. Four standard images (anterior, posterior, right posterior oblique and left posterior oblique) were obtained for 500,000 to 750,000 counts each. Images were interpreted according to the modified PIOPED criteria [5] and a high-probability scan was suggestive of chronic thromboembolic pulmonary disease [5-6].

CT pulmonary angiography: CTPA was performed on a 64 slice MDCT scanner (Light-Speed General Electric Medical Systems, Milwaukee, WI). Standard acquisition parameters were used: 100 mA with automated dose reduction, 120 kV, pitch 1, rotation time 0.5 s and 0.625mm collimation. The field of view was 400 x 400mm with an acquisition matrix of 512 x 512. 100ml of intravenous contrast agent (Ultravist 300; Bayer Schering, Berlin, Germany) was administered at a rate of 5ml/sec. CT findings of lack of contrast filling in the arterial vessel, intraluminal or eccentric contrast filling defects, calcified filling defects, recanalization, abrupt change in vessel calibre, strictures, post-stenotic dilatation, webs and parenchymal heterogeneity typical of perfusion abnormalities were considered suggestive of chronic thrombotic disease [7].

Final reference diagnosis: The final diagnosis of CTEPH or non-CTEPH was made at a multi-disciplinary meeting. This decision was based on clinical assessment, imaging findings and right heart catheter haemodynamics. The patients with a diagnosis of CTEPH were then referred to the national centre for pulmonary endarterectomy and a final diagnosis of surgically accessible or inaccessible disease was made. Appropriate patients with surgically

accessible disease were offered pulmonary endarterectomy. Follow-up data was retrieved on outcome following pulmonary endarterectomy.

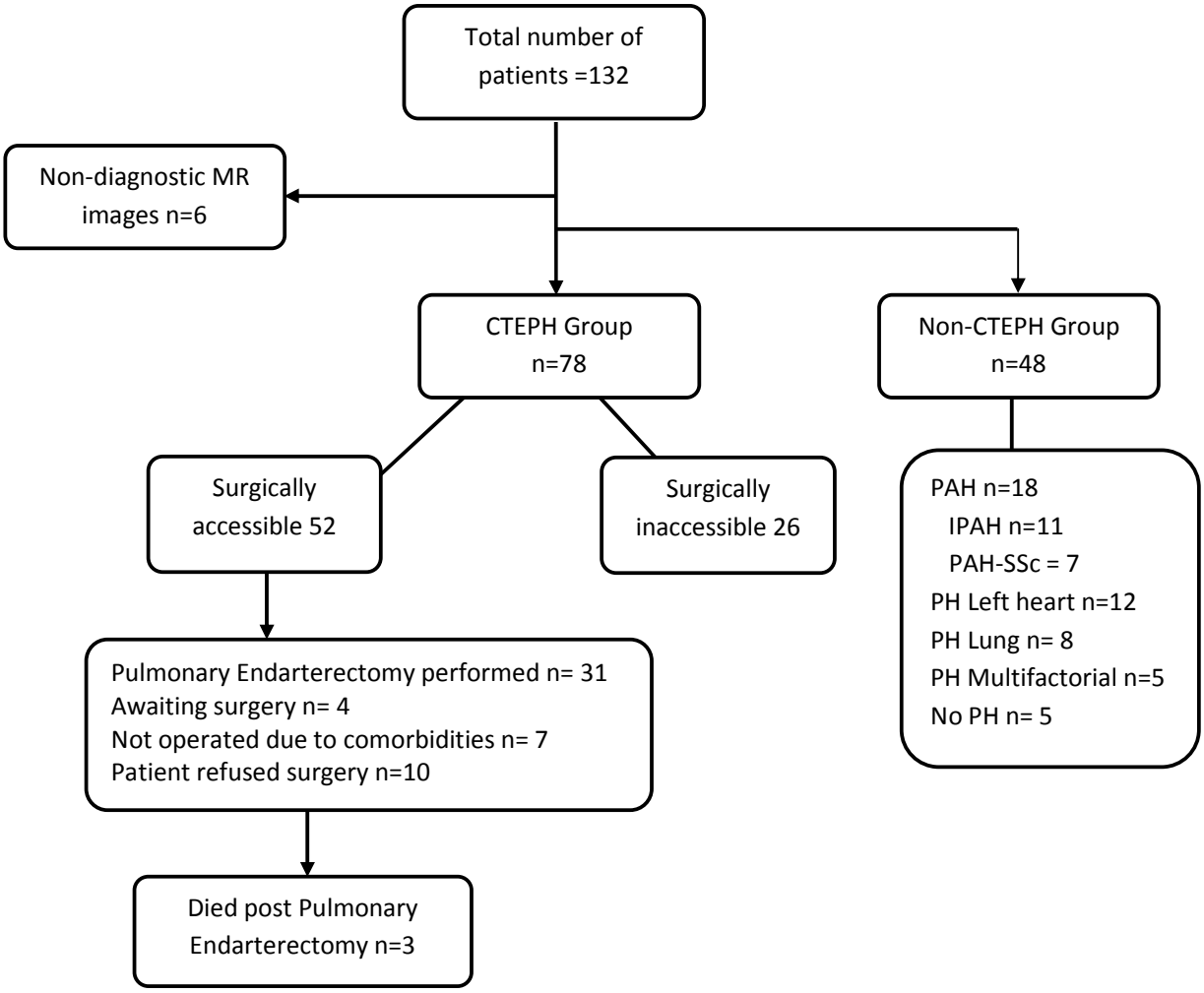
Statistical analysis: Sensitivity, specificity, positive predictive value and negative predictive value were calculated with 95% confidence interval (CI) for detection of CTEPH on MR perfusion images, perfusion scintigraphy and CTPA. Kappa statistics were used to analyze inter-observer agreement and to measure agreement between imaging modalities for the detection and location of perfusion defects. All statistical analysis was performed using commercially available software (SPSS program version 16.0 for Windows, Chicago, IL).

Patient demographics and right heart catheter parameters

	Whole Group n=126	CTEPH n=78	Non-CTEPH n=48	p-value
Age (yrs)	62(14)	59 (16)	64 (17)	0.47
Female (%)	58	56	66	0.9
mRAP (mmHg)	11(5)	11 (5)	10 (4)	0.67
mPAP (mmHg)	42 (13)	43 (11)	40 (14)	0.11
PCWP (mmHg)	12(6)	10(5)	14(6)	0.02
CI (L.min.m2)	2.7 (0.9)	2.9 (1)	2.7(1)	0.11
PVR (dyn.s.cm-5)	435 (365)	599(373)	429(365)	0.04
TPR (dyn.s.cm-5)	792 (267)	801(231)	789 (181)	0.4
mVO2 (%)	63 (8)	61(8)	66 (8)	0.008

Abbreviations: mRAP- mean right atrial pressure; mPAP- mean pulmonary artery pressure; PCWP- pulmonary capillary wedge pressure; CI-cardiac index; PVR –pulmonary vascular resistance; TPR- total pulmonary resistance; mVO2 - mixed venous oxygen saturation (standard deviation in brackets)

Patient classification



Abbreviations: CTEPH-chronic thromboembolic pulmonary hypertension; PH-pulmonary hypertension; IPAH – idiopathic pulmonary arterial hypertension; PAH- pulmonary arterial hypertension; SSc – Systemic Sclerosis

Summary of results for perfusion scintigraphy, 3D MR perfusion and CT images

Groups	Perfusion scintigraphy		3D MR perfusion		CT	
	+	-	+	-	+	-
CTEPH (n=78)	75	3	76	2	73	5
Non-CTEPH (n=48)	5	43	4	44	1	47

Summary of False-Positive perfusion MR, perfusion scintigraphy and CT images

Modality	**Diagnosis**
Perfusion MRI	1. Systemic sclerosis and pulmonary fibrosis (n=2) 2. PAH with background pulmonary emphysema (n=2)
Perfusion Scintigraphy	1. Scleroderma and pulmonary fibrosis (n=2) 2. PAH with background pulmonary emphysema (n=1) 3. PAH associated with congenital heart disease (n=1) 4. Pulmonary hypertension secondary to lung disease (n=1)
CT	1. PH associated with Pulmonary fibrosis (n=1)

PAH-pulmonary arterial hypertension; IPAH-idiopathic pulmonary arterial hypertension. Patients in 1 and 2 were the same for perfusion MRI and perfusion scintigraphy

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