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Functional Characterization of Patients with Chronic Thromboembolic Disease

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Key Words
Chronic thromboembolic pulmonary disease · Chronic thromboembolic pulmonary hypertension · Mean pulmonary artery pressure

Abstract
Background: Patients with chronic thromboembolic pulmonary disease (CTED) have persistent pulmonary vascular obstruction and exercise intolerance without pulmonary hypertension at rest and may benefit from pulmonary endarterectomy. However, up to now, CTED has been poorly characterized. ***Objectives:*** This study aimed to analyze the exercise capacity and limiting factors in CTED. ***Methods:*** We compared right heart catheterization and cardiopulmonary exercise test results of patients with CTED [mean pulmonary artery pressure (mPAP) at rest <25 mm Hg, n = 10], chronic thromboembolic pulmonary hypertension (CTEPH, n = 31) and a control group (n = 41) presenting with dyspnea but normal pulmonary vascular imaging and excluded pulmonary hypertension. ***Results:*** Subjects with CTED show a reduced oxygen uptake [median 76/interquartile range (IQR) 22% pred.] and work rate (median 76/IQR 21 W). The work rate was significantly lower compared to control subjects (p = 0.04) but not significantly different from CTEPH patients (p = 0.66). Oxygen pulse and breathing reserve were normal. CTED subjects showed decreased end-tidal CO_2 at anaerobic threshold (28.4/4.3 mm Hg), an elevated V_E/V_{CO_2} slope (42.5/23.5), breathing equivalents (EQ_{O_2} 32.0/8.7, EQ_{CO_2} 39.5/8.8), alveolar-capillary oxygen gradient (34.7/15.5 mm Hg) and capillary end-tidal carbon dioxide gradient (8.8/5.7 mm Hg) compared to control subjects (p < 0.001). The degree of limitation was similar to that in CTEPH. ***Conclusions:*** Despite an mPAP of <25 mm Hg, subjects with CTED show objective functional impairment and similar limitations to patients with CTEPH. Functional limitation is characterized by gas exchange disturbance and ineffective ventilation.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a chronic thromboembolic vascular obstruction along with a mean pulmonary artery pressure (mPAP) of at least 25 mm Hg at rest [1–4]. In untreated patients, prognosis is poor [5, 6]. Due to nonspecific symptoms which include dyspnea on exertion and

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fatigue, the diagnosis of CTEPH after the onset of symptoms is frequently delayed [7]. Clinically, when a final diagnosis of CTEPH is confirmed, most patients show severe functional impairment corresponding to a WHO functional assessment classification for pulmonary hypertension class III – dyspnea on mild exertion [7–9]. The development of modern treatment strategies led to improved outcomes with a 3-year survival of 90–95% in patients following pulmonary endarterectomy (PEA) and of 70–75% in nonoperable patients receiving PH-specific medical treatment [7, 9, 10]. Published data show worse short-term and 1-year survival following PEA in patients with a higher WHO functional class and higher pulmonary vascular resistance [9]. Hence, early detection would most likely improve the outcome.

Chronic thromboembolic vascular disease (CTED) has been described clinically as pulmonary vascular obstruction with an mPAP at rest of <25 mm Hg [7, 11–14]. Recently, successful PEA in patients with CTED has been described [14]. Despite normal PAP at rest, exercise intolerance has been reported in these patients [7, 11, 12, 14]. To date, drivers and limiting factors of exercise intolerance in patients with CTED are not adequately characterized.

It has recently been shown that cardiopulmonary exercise testing (CPET) is able to detect a functional pattern indicating disturbed pulmonary perfusion in subjects with apparent CTEPH [11, 12]. It is not yet known if CPET can detect similar patterns in patients with CTED. Furthermore, it has not yet been studied if gas exchange parameters of CTED patients differ from those of patients with dyspnea but without resting PH and pulmonary vascular obstruction.

This study aimed to characterize the functional capacity in patients with CTED using CPET compared to the functional capacity in patients with CTEPH and patients with dyspnea in whom PH and chronic thromboembolic disease is excluded.

Methods

The study data were obtained from a project aiming to evaluate diagnostic tools in CTEPH. This study was approved by the local Ethics Committee of the Julius Maximilian University of Würzburg, Würzburg, Germany, and was conducted in accordance with the Declaration of Helsinki. All patients gave their written informed consent. For this retrospective analysis, the data of 79 consecutive subjects diagnosed with CTEPH and CTED between January 2010 and September 2013 were involved. Of these subjects, 31 patients with CTEPH and 10 patients with CTED had available cardiopulmonary exercise test data. All patients were treatment naïve. Forty-one simultaneously presented control subjects consisting of patients presenting with dyspnea, normal imaging of the pulmonary vasculature, and an mPAP of <25 mm Hg at rest were also included in the study. Comparisons were made based on hemodynamic parameters and data from CPET. All patients with CTEPH, CTED and the control group received a diagnostic workup according to international guidelines in order to confirm or rule out a diagnosis of CTED or CTEPH as described above [1–3].

Echocardiography (Vivid7®, GE Medical Systems, Solingen, Germany) was performed according to current guidelines [1]. A ventilation-perfusion scan (Technegas-Generator®, Tetley Medical Limited, Australia; E Cam Variable®, Siemens Medical Solutions Inc., Hoffman Estates, Ill., USA) and a computed tomography (Activion 16®, Toshiba Medical Systems, Neuss, Germany) were performed to exclude or detect chronic thromboembolism. Right heart catheterization was conducted according to the guidelines using a Swan-Ganz catheter (Smith Medical, Grasbrunn, Germany) [1, 15, 16]. Measurements were conducted with the monitor system IntelliVue MP70 (M8007A®, Philips Medizinsysteme, Böblingen, Germany). In patients with an mPAP at rest of <25 mm Hg, the measurement was repeated under incremental exercise (25 W/2 min) at 50 W. To confirm the diagnosis and to assess the operability, a pulmonary angiography (Integris Allura; Philips Medical Systems, Best, The Netherlands; films stored digitally) was conducted. Diagnosis and treatment strategies were discussed by an interdisciplinary CTEPH team. Capillary blood samples were gathered from the ear, and blood gases were measured at rest and at peak exercise (ABL 800 Basic®, Radiometer, Cadolzburg, Germany).

CPET was performed at the time of diagnosis according to the ATS and American College of Chest Physicians statement [17], as described previously using an E-bike basic PC plus (GE Medical Systems) and a Masterscreen CPX® (CareFusion, Hoechberg, Germany) [11, 18–21]. CPET consisted of a 2-min registration at rest followed by 2 min of unloaded pedaling. For the following exercise protocol, work load was increased by 25 W every 2 min per ramp. Exercise was terminated by symptom limitations or when predetermined withdrawal criteria were met. We measured minute ventilation, breathing rate and expiratory gas fractions of O_2 and CO_2 breath by breath. An average number of 8 breaths were used for analysis. Temperature and air pressure were measured continuously. Anaerobic threshold (AT) was determined at the equivalents for oxygen (EQO_2) nadir. Statistical analysis was performed using Microsoft Excel® and SSPS® IBM, version 21.0.

The anthropometric data are expressed as mean ± SD. Significance was calculated with the χ^2 test/Fisher's exact test for WHO functional class and sex distribution and by a t test for age and BMI. Since most functional data were not normally distributed, we show the functional data as median and interquartile range (IQR) and calculated the significance with the Mann-Whitney U test. Significance was attained if the p value was <0.05.

Results

Anthropometric data for all 3 groups are shown in table 1. Within all 3 groups, there were more women. Sex, BMI and age did not differ significantly across the groups.

Table 1. Anthropometric data

	CTEPH (n = 31)	CTED (n = 10)	Control (n = 41)	p
Mean age ± SD, years	66.4±14.4	62.0±13.9	62.5±12.5	n.s.
Mean BMI ± SD	27.6±4.8	27.6±5.9	28.5±5.2	n.s.
Male/female	12/19	1/9	12/29	n.s.
WHO functional class I/II/III/IV	0/10/20/1	0/1/9/0	1/15/25/0	n.s.

n.s. = Not significant.

Table 2. Right heart catheterization parameters

	CTEPH (n = 31)	p	CTED (n = 10)	p	Control (n = 41)
At rest					
mPAP, mm Hg	40.0 (21.0)	***	20.5 (4.3)	###	15.0 (4.0)
PAWP, mm Hg	11.0 (5.5)	**	7.5 (6.0)	n.s.	7.0 (7.0)
CO, l/min	4.3 (1.9)	n.s.	4.5 (1.4)	n.s.	5.2 (1.5)
CI, l/min/m^2	2.4 (0.7)	n.s.	2.6 (0.8)	n.s.	2.6 (0.7)
PVR, dyn × s × cm^{-5}	474.0 (426.3)	***	243.5 (151.3)	##	132 (121)
RAP, mm Hg	11.0 (7.0)	***	2.0 (4.5)	n.s.	5.0 3.3)
Under exercise					
mPAP, mm Hg	–		44.0 (13.3)	#	28.0 (16.3)
PAWP, mm Hg	–		9.5 (6.0)	n.s.	11.0 (9.5)
CO, l/min	–		8.8 (1.5)	n.s.	9.3 (4.5)
CI, l/min/m^2	–		4.7 (1.0)	n.s.	4.9 (1.9)

Values are given as the median (IQR). CO = Cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance; RAP = right atrial pressure. Differences between CTEPH and CTED: ** $p < 0.01$, *** $p < 0.001$; differences between CTED and controls: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$.

Table 3. Echocardiographic data

	CTEPH (n = 31)	p	CTED (n = 10)	p	Control (n = 41)
TAPSE	19.0 (10.0)	n.s.	23.0 (8.7)	n.s.	24.0 (7.0)
Right atrial area, cm^2	22.1 (12.5)	***	12.5 (5.5)	n.s.	13.8 (9.3)
Left atrial area, cm^2	15.6 (8.0)	n.s.	16.3 (5.3)	n.s.	15.9 (7.6)
Left ventricular ejection fraction, %	66.0 (12.0)	n.s.	64.0 (9.5)	n.s	58.5 (12.7)
E/E′	6.8 (4.6)	n.s.	8.9 (3.7)	n.s.	7.6 (3.5)

Values are given as the median (IQR). TAPSE = Tricuspid plane systolic excursion; n.s. = not significant; E/E′ = ratio of diastolic early mitral blood flow to early diastolic peak of tissue velocity of the basal lateral left ventricular wall. Differences between CTEPH and CTED: *** $p < 0.001$.

Table 2 shows the hemodynamic data for the 3 cohorts. The mPAP and pulmonary vascular resistance differed significantly across the 3 cohorts. The CTEPH patients presented with a median mPAP of 40 mm Hg and a median pulmonary arterial wedge pressure (PAWP) of 11 mm Hg, indicating severe precapillary pulmonary hypertension at rest. CTED subjects showed a median mPAP at rest of 20.5 mm Hg and a PAWP of 7.5 mm Hg. In the CTED subjects, mPAP (44.0 mm Hg) but not PAWP (9.5 mm Hg) increased during exercise. The control cohort showed normal hemodynamic parameters at rest and only a mild but normal increase in mPAP following exer-

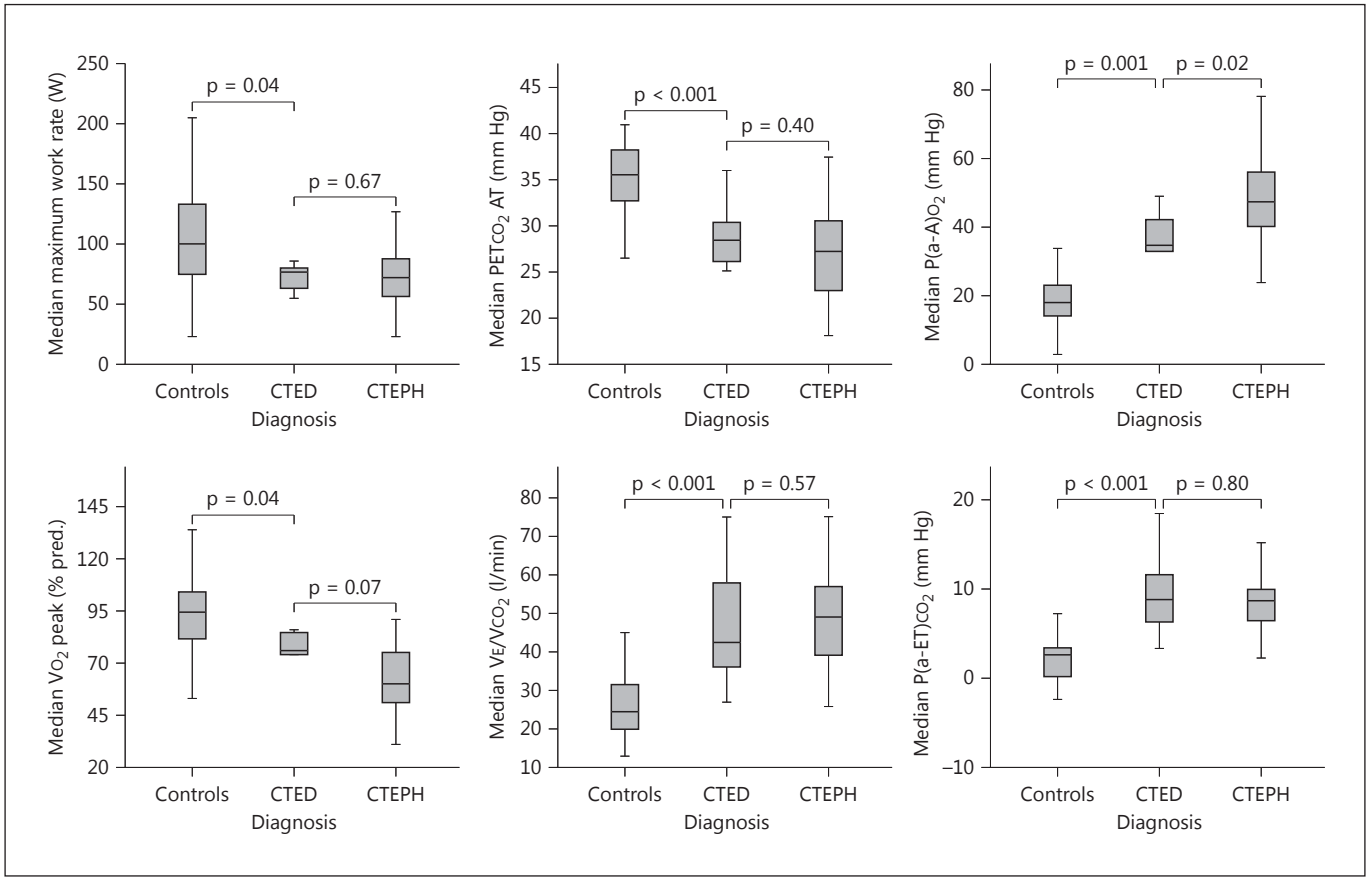

Fig. 1. Cardiopulmonary exercise test parameters of subjects with CTED, CTEPH and controls. Values are presented as the median (IQR). V_{O_2} peak = Oxygen uptake at peak exercise.

cise accompanied by a slight increase in pulmonary arterial occlusion pressure.

Cardiac index at rest was not significantly different across the groups. CTED subjects as well as the control group showed a similar increase in cardiac index under exercise conditions. In patients with CTEPH, PAP was not measured during exercise conditions.

Two thirds of the CTEPH cohort, 9/10 subjects of the CTED group and 25/41 of the control group reported symptoms according to WHO functional class 3.

CTEPH patients showed an increased right atrial area (table 3). This parameter and tricuspid plane systolic excursion, both reflecting echocardiographic parameters of right ventricular function, were normal in the CTED cohort, and these parameters were not significantly different from the control group.

Figure 1 shows data from CPET reflecting the functional capacity. In both the CTED and CTEPH cohorts, we found a functional impairment. CTEPH and CTED patients showed a significantly lower oxygen uptake and maximum work rate than the control subjects. There was no significant difference between the maximum work rate and oxygen uptake across the CTEPH and CTED group highlighting an objective functional impairment in CTED and CTEPH patients.

CTEPH patients presented with a median oxygen pulse of 78.0% predicted (IQR 26.0). This was significantly decreased in comparison to the control group (107.0% pred., IQR 34.0; $p < 0.001$) and the CTED subjects (102.0% pred., IQR 25.0; $p < 0.01$). The oxygen pulse of CTED patients and control subjects did not differ significantly ($p = 0.56$).

Median breathing reserve was 34% (IQR 21.0) in CTEPH patients, 32.5% (IQR 30.0) in the CTED group and 38.5% (IQR 15) in the control subjects, and, by definition, exercise capacity was not limited by ventilation in all cohorts.

Overall, the CTED cohort as well as the CTEPH subjects presented with functional signs of ineffective venti-

lation, gas exchange limitation and disturbed pulmonary perfusion reflected by the values of ventilation/carbon dioxide output (V_E/V_{CO_2}), EQ_{O_2} AT, EQ_{CO_2} AT, end-tidal partial pressure of carbon dioxide (PET_{CO_2}) AT and an arterial or capillary to end-tidal carbon dioxide gradient [$P(a\text{-}ET)_{CO_2}$] at maximum exercise (fig. 1; online suppl. table 4; for all online suppl. material, see www.karger.com/doi/10.1159/000447247). As the sex distribution was not equal, it could be speculated that the findings and characteristics of the CTED group might have been influenced by the higher amount of females in comparison to the CTEPH and the control group. A subgroup analysis of the parameters of the females of all 3 cohorts showed the same results across the groups as in the groups containing males and females (data not shown). The results were gender independent. Both, CTED and CTEPH groups showed significantly different values of V_E/V_{CO_2}, PET_{CO_2} AT, alveolar-arterial oxygen gradient [$P(A\text{-}a)_{O_2}$] and $P(a\text{-}ET)_{CO_2}$ at maximum exercise in comparison to the control group (fig. 1). V_E/V_{CO_2}, PET_{CO_2} AT and $P(a\text{-}ET)_{CO_2}$ at maximum exercise were not significantly different between CTEPH and CTED subjects (fig. 1). Only $P(A\text{-}a)_{O_2}$ values at peak exercise were significantly more increased in CTEPH (47.3 mm Hg, IQR 17.3) than in CTED subjects (34.7 mm Hg, IQR 15.5; $p = 0.02$) (fig. 1).

Discussion

The main finding of this study is that patients with CTED show functional limitations comparable to patients with overt CTEPH in contrast to a control group of patients with dyspnea and invasively excluded pulmonary hypertension and no thromboembolic vascular obstruction.

The anthropometric data of all 3 cohorts did not differ significantly. As expected, the CTEPH cohort was characterized by severe precapillary pulmonary hypertension under resting conditions. CTED and control subjects did not show a significant difference in cardiac index at rest and at maximum exercise. Although the CTED subjects presented with a near normal mPAP at rest, these patients were as symptomatic as the CTEPH cohort in terms of WHO functional class.

Oxygen uptake was lower in CTEPH patients compared to patients with CTED during exercise; however, this difference was not significant. In contrast, a markedly reduced oxygen uptake in CTED patients as well as a comparable decrease in maximum work rate in the CTEPH and CTED cohorts indicated an objective functional impairment in the CTED patients comparable to patients with CTEPH.

Despite no significant differences between cardiac output and cardiac index under resting conditions in the CTEPH and CTED patients, CTEPH patients displayed a reduced O_2 pulse at maximum exercise which was normal in CTED patients. This may result from a more disturbed gas exchange in the CTEPH cohort indicated by higher $P(A\text{-}a)_{O_2}$ or by a limited increase in stroke volume and cardiac output in the CTEPH patients under exercise.

The increase in mPAP during exercise in subjects with CTED was not accompanied by an increase in PAWP. This factor, along with a normal oxygen pulse, indicates that the functional limitation of CTED subjects is not driven by a left ventricular limitation. Additionally, echocardiographic analysis of left ventricular function was normal in these patients (table 3). Overall, a normal breathing reserve in CTED and CTEPH cohorts indicates that functional impairment is not a consequence of ventilatory limitation.

Hypocapnia has been described as a typical finding in pulmonary arterial hypertension [22]. Disturbed pulmonary vascular perfusion is characterized by a gas exchange disturbance with an elevated $P(A\text{-}a)_{O_2}$, a relevant hyperventilation indicated by an increased slope of the minute V_E/V_{CO_2} slope. This is accompanied by a decreased partial pressure of end-tidal CO_2 measured at the AT which results in an increased $P(a\text{-}ET)_{CO_2}$ [11, 23]. Overall, it was assumed that these changes are a consequence of decreased pulmonary blood flow and increased dead space ventilation [23]. The changes described above lead to ineffective ventilation, which is indicated by elevated breathing EQ_{O_2} and EQ_{CO_2}. The alterations of the described parameters are more pronounced in CTEPH than in pulmonary arterial hypertension [23] and typical even in CTEPH subjects with normal echocardiographic findings [11].

The CTEPH cohort as well as the CTED patients analyzed in this study showed elevated breathing equivalents (online suppl. table 4). Both cohorts displayed an elevated V_E/V_{CO_2} slope as a sign of pulmonary vascular disease. Surprisingly, these parameters did not differ significantly across both cohorts. PET_{CO_2} AT is decreased dramatically in both groups. Resulting $P(a\text{-}ET)_{CO_2}$ is strikingly elevated at rest as well as at maximum exercise in both cohorts. While it remains stable in the CTEPH patients, there is a further increase under exercise in the CTED subjects.

All previously described parameters were not significantly different in the CTEPH patients compared to the CTED subjects, but both CTED and CTEPH subjects differed significantly from the control group. In fact, only $P(A\text{-}a)O_2$ was significantly higher in the CTEPH cohort than in the CTED group. While $P(A\text{-}a)O_2$ was pathologically increased under resting conditions and exercise in the CTEPH subjects, it was normal under resting conditions in the CTED group. However, during exercise, CTED subjects showed a relevant increase in $P(A\text{-}a)O_2$. McCabe et al. [13] also showed a higher $P(A\text{-}a)O_2$ in CTEPH than in CTED patients; however, these authors did not provide blood gas analysis and therefore no $P(A\text{-}a)O_2$ and $P(a\text{-}ET)CO_2$ data for the control group [13]. Furthermore, McCabe et al. [13] did not perform right heart catheterization under exercise in the CTED group and no right heart catheterization in their control group.

These findings indicate that symptoms and objective functional impairment of patients with CTED results from reduced pulmonary perfusion and pulmonary vascular obstruction. This is of particular concern, as persisting dyspnea after pulmonary embolism is not a rare finding [12]. As echocardiographic parameters were normal in the CTED patients, but the cardiopulmonary exercise test showed objective limitations, this tool may help to distinguish if symptoms and functional impairment are the consequence of comorbidities or a complication of incomplete thrombus resolution [12].

As discussed previously, CTEPH is frequently diagnosed *long after symptoms appear* due to the nonspecific nature of these symptoms [7]. This is critical, as the prognosis of CTEPH is dependent on the degree of hemodynamic impairment [8, 9] that can be worsened by a delayed diagnosis and consecutive progressive remodeling of primarily not obstructed vessels [24]. Early detection of functionally relevant incomplete thrombus resolution and vascular obstruction, as found in the CTED cohort, would therefore be favorable and could help to achieve an earlier diagnosis and treatment. Four of the CTED patients underwent pulmonary thromboendarterectomy. One of these patients improved WHO functional class from III to II. The other CTED patients were asymptomatic after PEA. This is in line with previously reported results [14]. In the future, cardiopulmonary exercise test data before and after PEA of patients with CTED should be analyzed.

This study has several limitations: the sample size is relatively small, the analysis is retrospective, and the data come from a single center. Further, our control cohort did not only consist of healthy individuals. All patients of the control group had dyspnea and some presented with comorbidities (data not shown). However, in all control subjects, PH and vascular obstruction have been excluded. Showing the differences between patients with CTED and controls is therefore of even larger value. All described cohorts are well characterized, and the robustness of the data is reinforced through complete hemodynamic and functional evaluation of all subjects as well as through complete pulmonary vascular imaging. This allows a reliable analysis of functional characteristics and a comparison of cardiopulmonary limitations in CTED and CTEPH patients.

Conclusion

Symptomatic CTED subjects with dyspnea and chronic thromboembolic pulmonary vascular abnormalities but near-normal PAP at rest show similar functional limitations and severe hyperventilation and ineffective ventilation to CTEPH patients. CPET as a noninvasive method can help to identify patients with objective functional impairment despite normal resting hemodynamics.

Financial Disclosure and Conflicts of Interest

Dr. Held reports grants from Actelion, honoraria for lectures from Actelion, Bayer HealthCare, Berlin Chemie, Boehringer Ingelheim, GSK, Novartis and Pfizer, honoraria for advisory board activities from Actelion, Bayer HealthCare and GSK, and participation in clinical trials of Actelion, Bayer HealthCare, GSK, Pfizer and United Therapeutics outside the submitted work. Philipp Kolb has nothing to disclose. Dr. Grün has nothing to disclose. Dr. Jany has nothing to disclose. Gudrun Hübner has nothing to disclose. Dr. Grgic has nothing to disclose. Dr. Holl reports personal fees and nonfinancial support from Actelion, personal fees from Boehringer Ingelheim, personal fees and nonfinancial support from Bayer Vital, nonfinancial support from Pfizer, personal fees from Novartis, and nonfinancial support from OMT outside the submitted work. Dr. Schäfers has nothing to disclose. Dr. Wilkens reports grants and personal fees from Actelion, Bayer Vital, Glaxo Smith Kline, Pfizer, Biotest, Boehringer Ingelheim and Roche outside the submitted work.

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