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Diagnosis of CTEPH vs. IPAH using capillary to end-tidal CO_2 gradients

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) represents an important differential diagnosis to idiopathic pulmonary arterial hypertension (IPAH). We hypothesized that the capillary to end-tidal CO_2 gradient at rest and during exercise might help differentiate CTEPH from IPAH.

Patients who presented with unequivocal IPAH or CTEPH according to ventilation/perfusion scan, pulmonary angiography, computed tomography and right heart catheterization were included in this retrospective study and compared to healthy controls.

Twenty-one IPAH patients and 16 CTEPH patients fulfilled the inclusion criteria. Hemodynamics and peak oxygen uptake were comparable but respiratory rates at rest and during exercise were significantly higher in CTEPH than in IPAH. End-tidal CO_2 was significantly lower in CTEPH vs. IPAH at rest and during exercise, while capillary CO_2 values were similar. Correspondingly, capillary to end-tidal CO_2 gradients were significantly increased in CTEPH vs. IPAH at rest and during exercise: median (range) [mmHg]: 8.6 (3.0;13.7) vs. 4.4 (0.9;9.0), $p<0.001$, and 9.3 (3.3;13.1) vs. 4.1 (0.0;8.8), $p<0.001$. Although these values were closer to normal in IPAH they were still significantly elevated as compared to healthy controls: 2.3 (-4.8;8.1) and -1.9 (-5.7;6.2).

Capillary to end-tidal CO_2 gradients may help to distinguish CTEPH from IPAH based on resting and exercise values.

Key words

Blood Gas Analysis; Exercise Test; Hypertension, Pulmonary

Introduction

Pulmonary hypertension is a devastating disease that may be caused by thromboembolic events leading to chronic thromboembolic pulmonary hypertension (CTEPH). Among patients referred to a pulmonary hypertension clinic, the majority suffer from two distinct diseases, CTEPH and idiopathic pulmonary arterial hypertension (IPAH) [1]. In our experience scleroderma, congenital heart disease, portal hypertension, human immunodeficiency virus, appetite suppressants and other associated conditions represent a smaller proportion. Although the etiology of CTEPH clearly differs from other forms of pulmonary hypertension, the diagnosis of CTEPH may be challenging. When we consider the rate of CTEPH after symptomatic acute lung embolism, which may amount to 3.6% [2], and that only 50 to 80% of CTEPH patients are aware of a thromboembolic event [3 - 5], we may assume that this disease is dramatically underdiagnosed. This aspect gains even more importance as CTEPH can be prevented by anticoagulation and treated by pulmonary endarterectomy [5, 6], a highly effective but demanding operation that requires special diagnostic measures. Application of methods detecting perfusion heterogeneity might contribute to early identification of these patients and timely initiation of an optimized diagnostic and therapeutic strategy.

In CTEPH, there is heterogeneous blood flow in the lungs. Areas with diminished blood flow and areas with increased blood flow coexist, while ventilation is more or less homogeneously distributed. As a result, there are areas with an increased ventilation/perfusion ratio or even deadspace ventilation and others with low ventilation/perfusion ratio. Deadspace ventilation increases the gradient between arterial and end-tidal CO_2 [7]. The diagnostic value of this consideration has been evaluated for acute thromboembolism and was found to be fairly useful [8, 9].

We hypothesized that the capillary to end-tidal CO_2 gradient at rest and during exercise would provide a distinction between CTEPH and IPAH. We compared two groups of extensively diagnosed patients with comparable hemodynamics who after extensive work-up had unequivocal diagnoses of either CTEPH or IPAH, and found that both resting and maximal exercise capillary to end-tidal CO_2 gradients may help discriminate between these two diseases. Additionally we described a matched control group to demonstrate the physiological range of the evaluated parameters.

Study Objectives

To assess the typical features of ventilatory and gas exchange parameters in patients with CTEPH as compared to IPAH using a cardiopulmonary exercise test with capillary blood gas analysis.

Subjects

For this study, 561 spiroergometry examinations were screened for individuals with a full diagnostic work-up and an unequivocal diagnosis of either CTEPH or IPAH. All investigations were performed in the pulmonary hypertension clinic of the Justus-Liebig University, Giessen.

The complete work-up consisted of medical history, physical examination, ECG, pulmonary function test including CO diffusion capacity, chest X-ray, blood gas analysis, routine laboratory, antinuclear antibodies, abdominal ultrasonography, echocardiography, ventilation/perfusion scan, pulmonary angiography and computed tomography, cardiopulmonary exercise testing, as well as right heart catheterization. Patients with resting pulmonary arterial pressure < 25 mmHg, pulmonary arterial wedge pressure > 15 mmHg,

forced vital capacity < 70% and forced expiratory 1-second volume < 70% of normal as well as all patients with left to right shunt, portopulmonary hypertension, renal impairment and other associated forms of pulmonary hypertension were excluded. In addition, all patients with any significant left heart or valve disease, lung disease, systemic disease, pulmonary veno-occlusive disease, and all patients in NYHA class IV were excluded from the study. Controls were gender- and age-matched to the patients and were investigated with the same spiroergometry protocol and pulmonary function test. All subjects gave written informed consent to all investigations. The protocol was approved by the local ethics committee.

Radiographic analysis

Pulmonary angiography was performed in 15 of the 16 CTEPH patients and in 13 of the 21 IPAH patients, showing a positive result in terms of pulmonary thromboembolism in all CTEPH patients, and a negative result in all IPAH patients. All patients underwent ventilation-perfusion scan. It showed a high probability of thromboembolism due to typical perfusion defects in all patients with CTEPH, and a negative result, i.e. a low or medium probability, in all patients with IPAH. Spiral and thin-slice computed tomography were performed in 12 of the 16 CTEPH patients, demonstrating mosaic-like ground-glass opacities and pulmonary arterial occlusions in all of the 12 CTEPH patients; none of the IPAH patients showed a mosaic pattern or any occlusion.

Pulmonary Function Test

Spirometry and body plethysmography were performed with a constant volume body plethysmograph (Masterlab Body Pro, Jaeger, Höchberg, Germany). Vital capacity, forced vital capacity, forced expiratory 1-second volume, total lung capacity, residual volume,

airway resistance and lung transfer factor for carbon monoxide were determined by standard procedures. All measurements conformed to the guidelines of the European Coal and Steel Community [10], and for each individual, values are expressed in percent of predicted values or upper limit of normal.

Right Heart Catheterization

All patients underwent diagnostic right heart catheterization within 6 weeks of spiroergometry. Baseline hemodynamic variables including mean pulmonary arterial pressure, mean right atrial pressure, pulmonary capillary wedge pressure, and mean systemic arterial pressure were measured. Cardiac output was measured by thermodilution (Catheter: Baxter Type 95 F 754 H, USA).

Cardiopulmonary Exercise Testing

We applied a stepwise incremental maximal exercise test with continuous monitoring of expiratory gases and repeated blood gas analysis. Exercise was symptom-limited or stopped after objective withdrawal criteria were met. Exercise on a cycle ergometer (Spiroergometer Vmax 2130 V6200, Sensor-Medics BV, Netherlands) was started with no load and stepwise increments of 30Watt/2min up to 150Watt, then with increments of 50Watt/2min. The expiratory fraction of O_2 and CO_2 (F_EO_2, F_ECO_2), minute ventilation, breathing frequency, temperature and air pressure were recorded continuously via mouthpiece. Thirty-second means were calculated for tidal volume, oxygen uptake (VO_2) and carbon dioxide elimination rate (VCO_2). Heart rate was derived from RR intervals and synchronized to ventilatory parameters for calculation of 30-s means. Blood pressure was measured with an arm cuff. The ventilatory equivalent for CO_2 ($EQCO_2$) was continuously calculated and 30-s means were

evaluated. The $EQCO_2$ value at the ventilatory equivalent for O_2 (EQO_2) nadir was considered as $EQCO_2$ at the anaerobic threshold [11].

Capillary to end-tidal CO_2 gradient

The end-tidal CO_2 partial pressure ($P_{ET}CO_2$) was registered breath by breath and 30-s means were used as an estimate of the CO_2 partial pressure of the ventilated alveolar regions. Blood gas analysis was performed from arterialized capillary blood at rest and during maximal exercise. For this purpose blood was obtained from the earlobe at least 5 minutes after lubrication with Finalgon®, an ointment enhancing the local blood flow, and immediately inserted into a blood gas analyser (ABL 510, Radiometer Copenhagen, Radiometer A/S, Emdrupvey 72, DK-2400 Copenhagen NV, Denmark). Capillary blood CO_2 partial pressure was used as an estimate of arterial CO_2 partial pressure. Its difference to $P_{ET}CO_2$ served as an estimate of the arterial to end-tidal CO_2 gradient, a measure introduced into clinical practice by Robin et al. [12]. Deadspace ventilation was calculated from the Bohr formula with $V_D = V_E - V_A$ and $VCO_2 = F_ECO_2 * V_E$ and $VCO_2 = F_ACO_2 * V_A$, where V_D is dead space ventilation, V_E is total ventilation, V_A is alveolar ventilation, VCO_2 is carbon dioxide elimination rate, F_ECO_2 is mixed expiratory CO_2 fraction, and F_ACO_2 is the alveolar CO_2 fraction of the perfused lung regions, estimated from capillary PCO_2 with F_ACO_2 = capillary PCO_2 / barometric pressure.

Statistical Analysis

Data were analyzed using the SPSS statistical package (SPSS version 18.0; SPSS Inc; Chicago, IL). The groups were tested for statistical significance using Kruskal-Wallis ANOVA. Additionally we employed the Mann-Whitney-Wilcoxon test for comparison of the

IPAH and CTEPH group, and of the control group with both patient groups. Bonferroni correction was applied where multiple testing was performed. Anthropometric and spiroergometric data, hemodynamics and pulmonary function tests are given as median and range. Pulmonary function test, hemodynamics and $EQCO_2$ at the anaerobic threshold were correlated with peak VO_2 by linear regression analysis. For assessment of the utility of capillary to end-tidal CO_2 gradients for prediction of CTEPH, receiver operating characteristic (ROC) curves were generated. P-values < 0.05 were considered significant [* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$].

Results

Twenty-one IPAH and 16 CTEPH patients were included in the study. The mean age was similar but the female/male ratio was higher in the IPAH than in the CTEPH group. The control group was age and gender matched (Table 1).

Table 1, Anthropometric data

	IPAH	CTEPH	Control
Patients (n)	21	16	37
Gender (f / m)	15 / 6	7 / 9	22 / 15
Age in years	48 (32 ; 61)	55 (32 ; 71)	51 (32 ; 68)
Height in cm	166 (156 ; 188)	170 (162 ; 197)	170 (150 ; 195)
Weight in kg	75 (45 ; 103)	73 (58 ; 122)	67 (53 ; 95)

Medians and (range).

Right heart catheterization revealed that pulmonary pressure and resistance in IPAH and CTEPH were comparable, while right atrial pressure was significantly higher in the CTEPH group (Table 2).

Table 2, Hemodynamics at rest				
Parameter	IPAH	CTEPH	Correlation coefficient (r) with peak VO_2 (%)	
			IPAH	CTEPH
mPAP (mmHg)	45 (31 ; 71)	48 (33 ; 62)	-0.55 $^{++}$	-0.31
CO (l/min)	3.6 (2.0 ; 5.4)	3.7 (2.3 ; 6.7)	0.37	0.11
PVR (dyn s cm^{-5})	936 (385 ; 2290)	985 (372 ; 1420)	-0.4	0.05
RAP (mmHg)	3 (0 ; 19)	12 (3 ; 22) **	-0.59 $^{++}$	0.11
mSAP (mmHg)	91 (50 ; 116)	95 (66 ; 131)	0.08	0.15
SVR (dyn s cm^{-5})	1828 (1110 ; 2593)	2091 (811 ; 3166)	-0.05	-0.06
SaO_2 (%)	94 (80 ; 99)	93 (84 ; 100)	0.54 $^{+}$	0.27
SvO_2 (%)	68 (34 ; 74)	53 (34 ; 75)	0.62 $^{++}$	0.31
CI (l/min/m^2)	2.0 (1.3 ; 3.1)	1.8 (1.3 ; 3.8)	0.44 $^{+}$	0.43

Medians and (range); mPAP = mean pulmonary arterial pressure; CO = cardiac output; PVR = pulmonary vascular resistance; RAP = right atrial pressure; mSAP = mean systemic arterial pressure; SVR = systemic vascular resistance; SaO_2 = systemic arterial oxygen saturation; SvO_2 = pulmonary arterial oxygen saturation; CI = Cardiac Index; **: $p < 0.01$ for difference between IPAH and CTEPH; +: $p < 0.05$ and ++: $p < 0.01$ for correlation with peak VO_2 (%).

Both IPAH and CTEPH patients presented with reduced FEV_1 and reduced vital capacity as compared to the control group, and CTEPH was significantly more affected than IPAH. The lung transfer factor for carbon monoxide (DLCO) was not significantly reduced in IPAH and CTEPH (Table 3).

Table 3, Pulmonary function test, Capillary PO_2 and Peak VO_2				
Parameter	Control	IPAH	CTEPH	ANOVA
FEV_1 (% predicted)	100 (85 ; 127)	94 (70 ; 108) * $^+$	77 (56 ; 107) *	$p < 0.001$
VC (% predicted)	99 (85 ; 120)	94 (70 ; 114) $^+$	81 (56 ; 110) ***	$p < 0.001$
TLC (% predicted)	113 (95 ; 130)	101 (82 ; 120) **	96 (69 ; 134)	$p = 0.01$
Resistance (% ULN)	71 (41 ; 100)	93 (45 ; 159) *	88 (46 ; 149) *	$p = 0.002$
DLCO (% predicted)	99 (67 ; 113)	73 (28 ; 111) **	67 (52 ; 114) **	$p < 0.001$
P_cO_2 (mmHg)	80 (66 ; 105)	69 (46 ; 93) **	62 (49 ; 86) **	$p < 0.001$
Peak VO_2 (% predicted)	97 (75 ; 169)	52 (27 ; 88) ***	42 (28 ; 65) ***	$p < 0.001$

Medians and (range); control (n = 37) vs. IPAH (n = 21) and CTEPH (n = 16); FEV1, forced expiratory volume in 1 second; VC, vital capacity; TLC, total lung capacity; R, airway resistance, ULN, upper limit of normal; DLCO, CO transfer factor corrected for actual haemoglobin level; P_cO_2, capillary oxygen partial pressure; Peak VO_2, peak oxygen consumption during exercise; *: $p < 0.05$, **: $p < 0.01$, and ***: $p < 0.001$ for difference to control; $^+$: $p < 0.05$ for difference between IPAH and CTEPH.

Breathing frequency was significantly increased in CTEPH vs. IPAH at rest and during exercise (range): 20 min^{-1} (10 ; 27) vs. 16 min^{-1} (8 ; 26), $p < 0.05$, and 31 min^{-1} (27 ; 44) vs. 26 min^{-1} (18 ; 37), $p < 0.001$. Ventilation was slightly increased in CTEPH at rest and during exercise (range): 15 l/min (4 ; 21) vs. 11 l/min (7 ; 18), and 58 l/min (29 ; 78) vs. 50 l/min (29 ; 82), yet with no significant difference between the two groups. There were no significant differences between CTEPH and IPAH in oxygen uptake upon maximal exercise (Table 3), and tidal volume at rest and at maximal exercise (range): 0.7 l (0.4 ; 1.3) vs. 0.7 l (0.5 ; 1.4), and 1.9 l (0.7 ; 2.3) vs. 1.9 l (1.3 ; 3.1). $EQCO_2$ at the anaerobic threshold was significantly correlated with peak VO_2 in IPAH patients, while there was no such correlation in the CTEPH group (Figure 1). When CTEPH patients were compared to IPAH patients, expiratory gas analysis and capillary blood gas analysis at rest and upon maximal exercise demonstrated significantly lower end-tidal CO_2 partial pressure ($P_{ET}CO_2$), and correspondingly, both patient

groups showed significantly decreased capillary to end-tidal CO_2 gradients. Alveolar dead spaces were lowest in controls compared with patients, and they were significantly increased in CTEPH vs. IPAH at rest and during exercise (Table 4).

Table 4, Capillary CO_2 partial pressure and Expiratory gases at rest and during maximal exercise

	Rest				Maximal exercise			
Parameter	Control	IPAH	CTEPH	ANOVA	Control	IPAH	CTEPH	ANOVA
P_cCO_2 (mmHg)	38.1 (32.0 ; 42.1)	31.7 *** (24.1 ; 37.6)	32.8 *** (27.1 ; 38.2)	$p < 0.001$	37.5 (27.4 ; 44.2)	31.6 *** (22.8 ; 39.0)	29.5 *** (22.8 ; 40.7)	$p < 0.001$
$P_{ET}CO_2$ (mmHg)	35.8 (26.5 ; 44.7)	27.2 *** + (20.4 ; 35.0)	22.7 *** (20.3 ; 35.1)	$p < 0.001$	39.4 (26.3 ; 48.3)	28.3 *** ++ (16.5 ; 38.9)	19.7 *** (13.8 ; 34.0)	$p < 0.001$
P (c-ET) CO_2 (mmHg)	2.3 (-4.8 ; 8.1)	4.4 +++ (0.9 ; 9.0)	8.6 *** (3.0 ; 13.7)	$p < 0.001$	-1.9 (-5.7 ; 6.2)	4.1 *** +++ (0.0 ; 8.8)	9.3 *** (3.3 ; 13.1)	$p < 0.001$
VD/VT (%)	42 (13 ; 64)	46 ++ (29 ; 61)	58 *** (39 ; 66)	$p < 0.001$	23 (5 ; 51)	35 *** +++ (19 ; 52)	49 *** (29 ; 57)	$p < 0.001$

Medians and (range); control (n = 37) vs. IPAH (n = 21) and CTEPH (n = 16); P_cCO_2 = capillary CO_2 partial pressure; $P_{ET}CO_2$ = end-tidal CO_2 partial pressure; P (c-ET) CO_2 = P_cCO_2 - $P_{ET}CO_2$ = capillary to end-tidal CO_2 gradient; VD/VT = alveolar dead space, calculated according to Bohr`s formula; ***: $p < 0.001$ for difference to control; +: $p < 0.05$, ++: $p < 0.01$, and +++: $p < 0.001$ for difference between IPAH and CTEPH.

Within the patient groups, a resting capillary to end-tidal CO_2 gradient > 7.0 mmHg was indicative of CTEPH, with a sensitivity of 75% and a specificity of 95%. A resting capillary to end-tidal CO_2 gradient threshold > 6.3 mmHg would increase the sensitivity to 80% but decrease specificity to 75%. An exercise capillary to end-tidal CO_2 gradient > 7.0 mmHg would indicate CTEPH with a specificity of 90% and a sensitivity of 88% (Figure 2).

Discussion

This study showed that markedly increased capillary to end-tidal CO_2 gradients indicating heterogeneous pulmonary perfusion may help to distinguish CTEPH from IPAH. While IPAH is subject to treatment with targeted PAH therapies, the therapy of choice for CTEPH is pulmonary endarterectomy and early anticoagulation may prevent the development of the full disease [4, 13]. Additionally, CTEPH necessitates permanent and aggressive anticoagulation to prevent further embolic events, hence early diagnosis is of utmost importance.

Spiroergometry has a place in the work-up of pulmonary hypertension as it helps to define the exercise-limiting factors of an individual with pulmonary hypertension and quantifies the limitation in comparison to healthy individuals. The most important parameters are considered to be peak VO_2 and $EQCO_2$ at the anaerobic threshold [14], and it has been shown that peak VO_2 has prognostic relevance in IPAH [15]. Our data suggest that spiroergometry also indicates whether pulmonary blood flow is heterogeneous in comparison to ventilation. Heterogeneous pulmonary perfusion is the hallmark of CTEPH. Correspondingly, this investigation indicated that CTEPH patients may be distinguished from IPAH patients based on analysis of capillary and end-tidal CO_2 partial pressures and that a markedly increased capillary to end-tidal CO_2 gradient may predict CTEPH.

The arterial to end-tidal CO_2 gradient has been evaluated as a screening tool for the diagnosis of acute pulmonary thromboembolism. Despite some limitations such as unselected patients, and a study population with considerable comorbidities, the combination of a negative whole blood agglutination D-dimer assay plus a normal gradient was associated with a probability of pulmonary thromboembolism below 1% [8]. To our knowledge, a similar approach has not been taken for CTEPH.

Our study used a highly selected group of patients in whom pulmonary shunting, portal hypertension, lung fibrosis, COPD and left heart disease had been rigorously excluded.

Consequently, our results may not be applicable to an unselected patient population. We were able to show, however, that assessment of capillary to end-tidal CO_2 gradients at rest and during exercise may be a valuable tool to raise the suspicion level for CTEPH, especially if the confounding diseases listed above have been excluded. The study showed that both increased resting and exercise capillary to end-tidal CO_2 gradients indicated CTEPH. The sensitivity and specificity, however, favoured the exercise data for the differentiation from IPAH. With a detection threshold set at a capillary to end-tidal CO_2 gradient of > 7.0 mmHg, the sensitivity for detection of CTEPH was 75% at rest and 88% during exercise. Assessment of capillary to end-tidal CO_2 gradient, which is easy to measure, might therefore allow earlier initiation of further diagnostic tests for thromboembolic disease.

We also analysed the ventilatory equivalent for CO_2 ($EQCO_2$) at the anaerobic threshold. This parameter corresponds closely to the V_E/VCO_2 slope at the anaerobic threshold [12]. We found that in IPAH patients, $EQCO_2$ was inversely correlated with peak VO_2. This can be explained by the fact that reduced pulmonary blood flow results in both a reduced peak VO_2 and an increased V_E/VCO_2 ratio [14, 16]. Interestingly, in the CTEPH group, there was no significant correlation between $EQCO_2$ and peak VO_2. This might be explained by the fact that blood flow heterogeneity through the lung is influenced by two different factors: the extent of vascular occlusion and the tone of the non-occluded vessels. If e.g. 50% of the vessels are occluded and 50% are completely normal, the non-occluded vessels are largely hyperperfused, the pulmonary arterial pressure is normal and the heterogeneous blood flow accounts for a highly increased $EQCO_2$. Indeed, with progressive disease, the non-occluded vessels tend to narrow due to remodeling of the small pulmonary arteries [17]; this reduces the extent of blood flow heterogeneity and thereby decreases $EQCO_2$ but also results in a decrease of peak VO_2 precluding an inverse correlation of these parameters. Resting hemodynamics showed a significant correlation to peak VO_2. This was an expected finding,

because the degree of pulmonary vascular obliteration limits maximal cardiac output. Interestingly, correlation coefficients were generally higher in the IPAH than in the CTEPH group. This could also be due to the heterogeneity of pulmonary blood flow in CTEPH patients that may contribute to exercise limitation apart from pulmonary hemodynamics.

Ventilatory inefficiency in PAH and CTEPH is associated with hyperventilation. This may be due to increased chemosensitivity [18] or an augmented deadspace fraction [19]. Zhai et al. [19] investigated ventilatory efficiency by comparing physiologic deadspace fraction and ventilatory equivalent for CO_2 in PAH and CTEPH patients. These data suggested a greater deadspace in CTEPH as compared to PAH, explaining the pronounced ventilatory inefficiency in CTEPH which is in agreement with our results. In contrast to Zhai et al. we additionally evaluated capillary to end-tidal CO_2 gradients and found that for diagnostic purposes they may be easier to use than calculated deadspace fractions. Because $EQCO_2$ values in both IPAH and CTEPH were in line with capillary pCO_2 and dead spaces were increased in CTEPH and IPAH we conlude that both increased chemosensitivity and increased deadspace fraction contribute to ventilatory inefficiency in IPAH and CTEPH which is in agreement with Naeije & Borne [20].

Our study has some limitations, including the small number of patients, the retrospective design and the fact that our population was highly selected. This selection let us highlight the specific differences between IPAH and CTEPH promoting earlier detection of patients with CTEPH; the results, however, may not be applicable to an unselected population of pulmonary hypertension patients. Prospective studies and studies in a more general population of patients with pulmonary hypertension are warranted to evaluate the utility of capillary or arterial to end-tidal CO_2 gradients in a diagnostic algorithm.

Without doubt, a CT-angiogram or pulmonary angiogram will always be necessary to determine operability in case of CTEPH. However, noninvasive methods raising the suspicion of CTEPH may be valuable as screening for patients with thromboembolic diseases. Spiroergometry is a widely used method in patients with dyspnea, and the detection of gas-exchange abnormalities indicative of a thromboembolic disease may guide in establishing priorities for further diagnostics and therapy. This might be considered as the true clinical utility of this work.

Conclusion

Spiroergometry with repeated blood gas analysis may identify CTEPH patients among IPAH patients based on increased capillary to end-tidal CO_2 gradients at rest and during exercise.

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Figure 1: Correlation of peak VO_2 with $EQCO_2$ in IPAH and CTEPH patients.

$EQCO_2$ = V_E/VCO_2 at the anaerobic threshold; peak VO_2 = peak oxygen consumption during exercise in % of normal

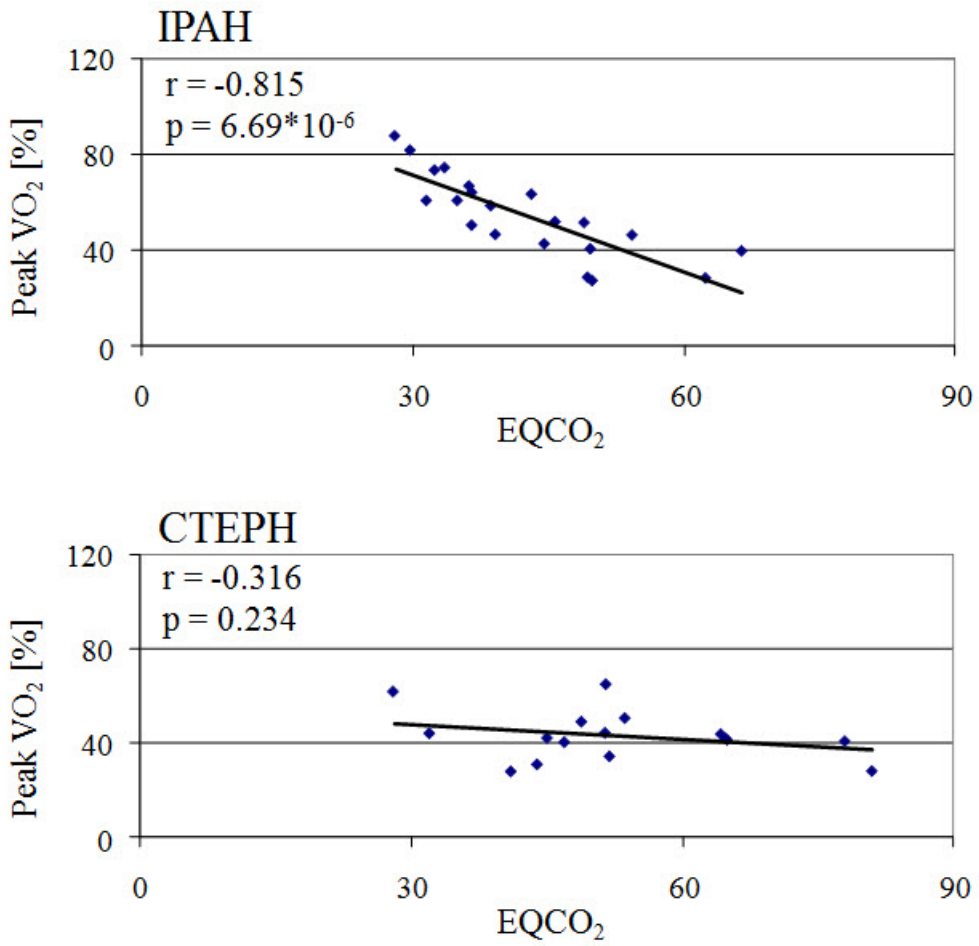
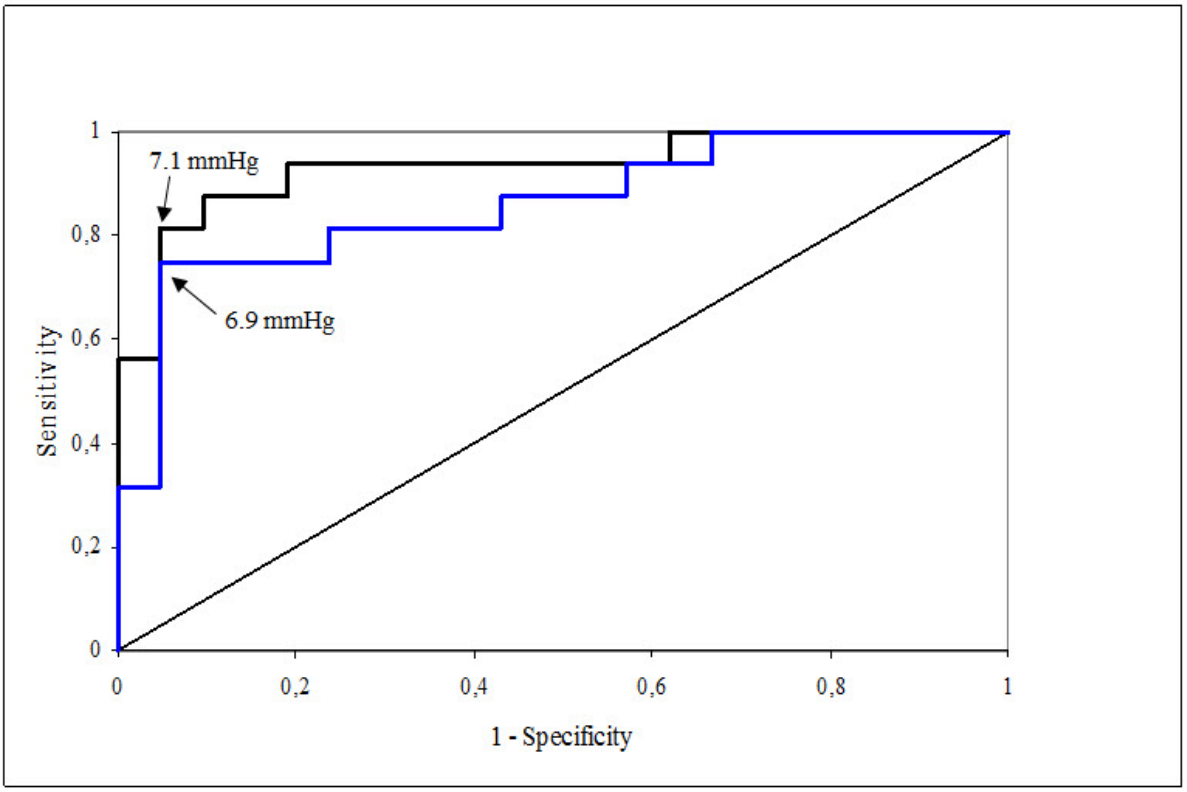


Figure 2: Receiver operating characteristics (ROC) curve for the determination of CTEPH.

P (c-ET) CO_2 = P_cCO_2 - $P_{ET}CO_2$ = capillary to end-tidal CO_2 gradient. Blue line = resting P (c-ET) CO_2; black line = maximal exercise P (c-ET) CO_2


1
0,8
0,6
0,4
0,2
0
Sensitivity
7.1 mmHg
6.9 mmHg
0
0,2
0,4
0,6
0,8
1
1 - Specificity