

Exercise Pulmonary Arterial Pressure during Exercise Stress Echocardiography in Hereditary Hemorrhagic Telangiectasia Rendu-Osler Stress Echocardiography (ROSE) Study

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Abstract

Background

Hereditary hemorrhagic telangiectasia (HHT) is a genetic vascular disorder leading to arteriovenous malformations (AVMs). Liver AVMs can cause high cardiac output (HCO) heart failure (HF), which slowly silently progresses to pulmonary hypertension (PH) and clinical HF. As current options, liver transplantation is limited to patients with PH at rest, when cardiac impairment is already advanced. We aimed to investigate the use of exercise echocardiography to identify earlier signs of HF in HHT patients with severe liver involvement but no PH at rest, by comparing exercise-induced systolic pulmonary arterial pressure (sPAP) between HCO and normal cardiac output (NCO) patients.

Results

We included 40 HHT patients with significant hepatic involvement and no cardiovascular disease or PH at rest, with 35 eligible patients for analysis (17 HCO, 18 NCO). Transthoracic echocardiography (TTE) was performed at rest and during exercise to measure cardiac output and sPAP. Baseline characteristics were not different between HCO and NCO groups. No significant difference was found in sPAP evolution between groups during exercise. However, higher sPAP/cardiac output (CO) slopes values were observed in the HCO group.

Conclusion

Despite the lack of significant differences in exercise-induced sPAP between groups, higher sPAP/CO slopes in HCO patients may indicate early cardiovascular impairment. It could serve as a parameter for identifying HHT patients with severe hepatic involvement at risk of developing PH, patients who may benefit from timely interventions.

Background

Hereditary haemorrhagic telangiectasia (HHT) is a genetic vascular disease caused by loss-of-function pathogenic variants in genes involved in the bone morphogenetic protein 9–10 (BMP9-10) signaling pathway¹: *ENG* and *ACVRL1* genes (> 90%) and rarely in *SMAD4* gene (< 4%). In adults, the most frequent and visible manifestations are related to skin and mucosae telangiectases responsible for recurrent epistaxis, gastrointestinal bleeding, and anemia. Arteriovenous malformations (AVMs) may be present in the lungs, liver and the central nervous system. The diagnosis of HHT is confirmed when a patient fulfills the Curaçao criteria² or by identification of a causative pathogenic variant in HHT genes.

Liver AVMs are responsible for vascular shunting which is mainly left-to-right through systemic AVMs which can lead to high cardiac output (HCO) heart failure (HCO-HF)^{3–6}. These conditions evolve silently

for long-standing period from left ventricular cavities dilation to advanced heart failure with post-capillary pulmonary hypertension (PH), with four successive phases: normal cardiac parameters, isolated high cardiac output, increased left ventricle filling pressures and pulmonary arterial hypertension⁷. Because of its slow and insidious appearance, HHT-related heart failure is often treated at a later stage despite being recognized as a risk factor of mortality^{5,8}. The standard treatment is liver transplantation, although bevacizumab is available for patients not eligible for transplantation⁹⁻¹². These complex treatments cannot be offered to all patients with liver involvement, as the incidence rate of symptomatic HCO is estimated to 3.6 per 100 person-years⁵. Liver transplantation is actually indicated for patients with PH at rest with beneficial effects on pulmonary pressures¹³. However, as PH occurs lately in the course of the disease, cardiac architectural and rhythmic reverse remodeling is less likely to occur as the disease has progressed. It is therefore of the utmost importance to be able to identify patients which could benefit from an earlier treatment (liver transplantation).

We hypothesize that abnormal pulmonary arteries hemodynamics response to exercise is more likely to occur in HHT patients with hepatic involvement and HCO, preceding PH at rest or overt heart failure in the course of the disease. To explore this hypothesis, we aimed in this pilot study at quantifying exercise-induced systolic pulmonary arterial pressure (sPAP) and its relation to cardiac output during exercise (sPAP/CO slopes). The objective was to compare sPAP and sPAP/CO slopes in HHT patients with hepatic involvement between to groups according to the median value of cardiac output: HCO versus “normal” cardiac output (NCO).

Methods

Patients:

In this exploratory pilot study, HHT patients aged > 18 years old with hepatic involvement as defined by a hepatic artery diameter ≥ 6 mm were included. Hepatic phenotyping also included the assessment of nodular focal hyperplasia, the maximal velocity of hepatic blood flow (m.s^{-1}) and the hepatic artery resistance index ((peak systolic velocity – end-diastolic velocity)/peak systolic velocity). We planned to include 40 patients irrespective to their cardiac output at rest, but without any pulmonary hypertension at rest. Population was categorized in two groups according to the median CO value: patients $\geq$ median CO value (HCO) versus patients < median CO value (NCO).

Exclusion criteria were the presence of other cardiovascular disease, including significant valvular heart disease (severe aortic stenosis, > grade 2 mitral or aortic regurgitation, or rheumatic mitral stenosis), left ventricular ejection fraction (LVEF) < 50%, known significant (> 50% stenosis) coronary artery disease, and pulmonary hypertension at rest as defined by a maximal tricuspid regurgitation velocity (TR-V_{max}) > 2.8 m.s^{-1} by transthoracic echocardiography (TTE). Patients were also not included if hemoglobin was < 90 g/L, if they had permanent or persistent atrial fibrillation (AF) and if they were taking betablocker medication. Finally, patients were not included if TR-V_{max} was missing at rest.

Rest and exercise echocardiography:

Transthoracic echocardiography (TTE) was performed in supine position for standard assessment of left ventricular volumes and systolic and diastolic functions as recommended by international guidelines^{14,15}. Left atrial volume and reservoir strain were also assessed, along with right ventricular function. Pulmonary systolic arterial pressure (sPAP) was estimated using the TR-V_{max} according to the simplified Bernoulli formula: $sPAP = TR-V_{max}^2 + \text{right atrial pressure}$ estimated by the vena cava diameter and compliance. Cardiac output (CO) was calculated using the classical formula: $CO (l/min/m^2) = \text{left ventricular outflow tract (LVOT)ref area (cm}^2) \times \text{sub-aortic velocity time integral (cm)} \times \text{heart rate (HR) (s}^{-1}) / (1000 \times \text{body surface area (m}^2)$.

Exercise TTE was performed according to guidelines¹⁴, on a bicycle ergometer in a semi-supine position¹⁵. Workload started at 20 watts for 3 minutes, and then power increased by 20W each minute to the maximal achievable power. The criteria for stopping high-intensity effort to 1 min recovery at 20W were exhaustion, or symptom limitation (dyspnea, angina...), or arrhythmia, or systolic blood pressure (SBP) > 240 mmHg. Continuous ECG monitoring was recorded and several echocardiographic parameters were recorded at 20W and peak exercise: HR, systolic blood pressure (SPB), CO, early mitral inflow velocity to early diastolic mitral annulus velocity ratio (E/e'), sPAP. LVEF was measured at peak exercise only.

Statistics:

Categorical variables were reported as percentages and continuous variables as median with [interquartile range]. Categorical variables percentages were compared between HCO and NCO groups using the Chi-Square test and continuous variables were compared using the Mann-Whitney non-parametric test.

A general linear model for repeated measures was used to test the interaction between the group category and exercise for both CO and sPAP.

A $p < 0.05$ was considered as significant.

The SPSS v.21.0 software was used for all statistics. Graphic for CO and sPAP at rest and peak exercise for each group was performed using Python with Matplotlib and Pandas libraries.

Results

We included 40 among 47 screened patients between Aug 2023 and Feb 2025. For statistical analyses, 35 patients were eligible because of the absence of tricuspid regurgitation at peak in 5 patients. The reasons for screen and analyses failures are displayed in Fig. 1.

Clinical and biological characteristics:

Patients were 60 [50–66] years old, mainly women and were paucisymptomatic. Hemoglobin, renal function and NT-ProBNP were in normal ranges and were not different between groups. Hepatic artery diameter and ammoniemia were not different between groups (Table 1).

Table 1
baseline characteristics of the population

Age	All patients (n = 35)	High CO (n = 17)	Normal CO (n = 18)	p
	60 [50–66]	63 [55–67]	57 [44–64]	0.11
Gender (F: n, %)	32 (91%)	15 (88%)	17 (94%)	0.6
BMI (kg/m ²)	22 [20–26]	22 [20–26]	23 [20–27]	0.49
NYHA I/II/III	18/15/2	7/9/1	11/6/1	0.48
Haemoglobin (g/L)	131 [122–144]	131 [113–141]	132 [123–147]	0.56
CKD no/stage 1/ stage 2	24/7/1	11/3/0	13/4/1	0.66
NT-ProBNP (pmol/L)	66 [42–102]	54 [46–108]	73 [36–95]	0.91
Hepatic artery (mm)	7 [6–8]	8 [6–10]	6 [6–8]	0.18
Hepatic artery Vmax (cm.s ⁻¹)	82 [64–141]	119 [64–150]	80 [64–100]	0.37
Resistance index	0.7 [0.6–0.7]	0.65 [0.55–0.71]	0.67 [0.62–0.69]	0.55
HHT mutated gene (ALK1: n, %)	30 (86%)	17 (100%)	13 (72%)	0.05
Ammoniemia (μmol/L)	37 [32–44]	36 [32–45]	41 [33–45]	0.5

Echocardiography at rest:

Median cardiac output was 3.8 L.min⁻¹.m⁻², and by definition higher in the HCO group. Systolic pulmonary arterial pressure (sPAP) was slightly but significantly higher in the HCO group. Both LA and LV volumes were significantly greater in the HCO group versus the NCO group, at 41 [32–53] *versus* 29 [25–33] ml.m⁻² for the left atrium (p < 0.05) and 57 [52–69] *versus* 47 [41–55] ml.m⁻² for the left ventricle (p < 0.05). Except for LA volume, diastolic function as assessed by E/e' and LA reservoir strain was not different between groups (Table 2).

Table 2
echocardiography at rest

SBP (mmHg)	All patients (n = 35)	High CO (n = 17)	Normal CO (n = 18)	p
	124 [108–135]	124 [111–138]	125 [105–132]	0.93
HR (min ⁻¹)	75 [70–82]	75 [74–85]	75 [69–81]	0.35
CO (L.min ⁻¹ .m ⁻²)	3.8 [3.2–4.5]	4.4 [3.9–4.9]	3.3 [2.9–3.4]	< 0.001
LAVol (mL.m ⁻²)	32 [28–42]	41 [32–53]	29 [25–33]	0.002
LA strain (%)	32 [28–39]	35 [30–40]	30 [18–37]	0.49
TR velocity (m.s ⁻¹)	2.4 [2.2–2.6]	2.5 [2.3–2.7]	2.4 [2.1–2.4]	0.01
sPAP (mmHg)	26 [23–29]	28 [25–34]	23 [22–27]	0.02
Mitral E/e'	7.2 [5.8–8.8]	7.6 [6.9–8.6]	6.4 [5.3–8.6]	0.18
LVEDV (mL.m ⁻²)	53 [45–63]	57 [52–69]	47 [41–55]	0.01
LVEF (%)	69 [64–74]	71 [66–76]	66 [63–73]	0.1

Stress echocardiography:

General characteristics:

All tests were well tolerated without any adverse event. The median power, METS and duration were 100 [80–120] watts, 6.7 [5.2–7.8] and 596 [429–625] seconds respectively, and not significantly different between groups (Table 3).

Table 3
exercise echocardiography

	All patients (n = 35)	High CO (n = 17)	Normal CO (n = 18)	p
20W exercise				
SBP (mmHg)	121 [110–134]	124 [113–135]	120 [109–131]	0.6
HR (min⁻¹)	96 [86–105]	96 [85–105]	97 [91–106]	0.49
CO (L.min⁻¹.m⁻²)	5.1 [4.4–5.9]	5.9 [4.8–6.7]	4.7 [4.2–5.2]	0.007
TR velocity (m.s⁻¹)	2.9 [2.7–3.1]	3.0 [2.8–3.2]	2.7 [2.6–3.0]	0.21
sPAP (mmHg)	36 [28–41]	40 [32–43]	35 [28–38]	0.25
Mitral E/e'	7.4 [6.4–9.0]	7.5 [6.5–9.0]	7.4 [6.2–10.1]	0.68
Peak exercise				
SBP (mmHg)	187 [172–201]	182 [173–206]	188 [160–195]	0.47
HR (min⁻¹)	145 [131–160]	139 [127–159]	146 [131–162]	0.49
CO (L.min⁻¹.m⁻²)	6.8 [6.2–7.7]	7.0 [6.8–8.2]	6.5 [6.1–7.4]	0.01
TR velocity (m.s⁻¹)	3.3 [3.0–3.5]	3.4 [3.2–3.6]	3.1 [2.8–3.4]	0.06
sPAP (mmHg)	46 [36–52]	50 [41–54]	44 [34–51]	0.07
Mitral E/e'	7.9 [6.6–9.3]	7.3 [6.4–8.6]	8.5 [7.1–10.4]	0.18
LVEF (%)	75 [70–79]	76 [70–80]	75 [70–79]	0.82
sPAP/CO 20W	6.2 [3.2–12.3]	8.9 [2.6–16.0]	5.2 [3.7–6.8]	0.21
sPAP/CO Peak	5.5 [4.3–7.5]	7.5 [5.6–12.7]	4.6 [4.1–6.3]	0.02
Watts	100 [80–120]	100 [60–140]	100 [80–120]	0.77
METS	6.7 [5.2–7.8]	6.4 [5.0–7.8]	6.8 [5.5–7.7]	0.84
Duration (sec)	596 [429–625]	480 [411–623]	600 [510–652]	0.38

Between rest and peak exercise:

Both CO and sPAP increased from rest to peak exercise in both groups (Table 3). CO remained significantly higher in the HCO group at peak as compared to the NCO group (7.0 [6.8–8.2] vs 6.5 [6.1–7.4] L.min⁻¹.m⁻² p = 0.01), whereas the difference of sPAP between group at peak was less significant (50 [41–54] vs 44 [34–51], p = 0.07). Linear regression for repeated measures was not statistically significant, without any interaction between sPAP increase and the group (F = 0.97, p = 0.33).

Between rest and 20W:

No early interaction was found in the evolution between rest and 20W exercise. Cardiac output and sPAP increased in both group (Table 3). Similarly to the aforementioned analysis, no significant interaction was found between 20W sPAP increase and the group ($F = 0.26$, $p = 0.61$).

sPAP/CO slopes:

We found a significant difference in sPAP/CO slopes between rest and peak exercise, those of the HCO group being higher values (7.5 [5.6–12.7 vs 4.6 [4.1–6.3], $p = 0.02$, Fig. 2), and individual plots are displayed in Fig. 3.

Discussion

The ROSE study was designed to assess the evolution of systolic pulmonary arterial pressure during exercise in relation to baseline cardiac output in a subset of HHT patients with hepatic involvement. Our findings indicate no significant difference in sPAP evolution between high cardiac output (HCO) and normal cardiac output (NCO) patients, although a notable trend was observed. Importantly, the exploratory analysis of sPAP/CO slopes between rest and peak exercise showed a statistically significant difference, with HCO patients exhibiting higher slopes values compared to NCO patients.

Despite excluding patients with resting pulmonary hypertension, HCO patients displayed higher sPAP than NCO patients. This finding aligns with the well-established relationship between cardiac output and pulmonary arterial pressure, mediated by vascular resistances¹⁶. This lack of significant difference in exercise-induced sPAP may be attributed to confounding factors such as exercise power or exercise duration, age or gender, anemia or renal insufficiency, none of which differed significantly between groups.

We hypothesized that the sPAP/CO slope, a diagnostic criterion reintroduced in the ESC 2022 guidelines, could serve as a valuable surrogate marker¹⁷. Given that mean pulmonary arterial pressure (mPAP) is typically inaccessible via transthoracic echocardiography (TTE) without pulmonary regurgitation, we utilized the sPAP/CO ratio. When analyzing the results of this parameter, beyond the significant difference between groups, we noticed a remarkable difference in the distribution of values, especially in the HCO group, the 4th quartile being skewed (Figs. 2 and 3). By transforming the ESC mPAP/CO slope cutoff value of $3 \text{ mmHg.L}^{-1}.\text{min}^{-1}$ into a systolic pulmonary pressure divided by the cardiac output indexed to the BSA, we identified a potential threshold for sPAP/CO slope at $10 \text{ mmHg.L.min}^{-1}.\text{m}^{-2}$. Only 3 patients of the ROSE cohort exceeded this value, all within the HCO group, suggesting these 3 patients may have the highest risk of further developing pulmonary hypertension at rest.

These results underscore the potential of the sPAP/CO slope as a prognostic indicator. While exercise-induced sPAP appears less informative, the sPAP/CO slope may reflect early cardiovascular impairment during exercise and serve as a predictive marker for adverse outcomes in HHT patients. It has been

reported as a prognostic factor in other contexts¹⁸. It could therefore be a predictive parameter of an unfavorable cardiological trajectory in HHT patients, more precocious than elevation of PAPs or NT-pro BNP. Further prospective studies with larger cohorts are essential to validate these findings and explore their clinical implications.

Limitations:

ROSE was a single-center small pilot study that included a small sample of patients. Lack of power is the main limitation. Any comparison with other parameters for diagnosis or prognosis purposes was not feasible and requires further investigations with more patients and follow-up. Despite a very careful evaluation of selected patients by trained physicians, we also cannot exclude some measurement error bias, especially for sPAP quantification at peak exercise. Moreover, patients with persistent or permanent atrial fibrillation as well as patients treated with betablockers were not included in the study even though these patients were possibly the most severe ones.

Conclusions

Evaluation of systolic pulmonary pressure (sPAP) evolution during exercise in HHT patients with severe hepatic involvement is promising, especially by the assessment of the relationships between sPAP and cardiac index changes during exercise. Follow-up of this cohort and more studies are needed to confirm this approach.

Abbreviations

AVMs

arteriovenous malformations

BMI

body mass index

CO

cardiac output

CKD

chronic kidney disease

E/e'

early mitral inflow velocity to early diastolic mitral annulus velocity ratio

HCO

high cardiac output

HF

heart failure

HR

heart rate

HHT

hereditary hemorrhagic telangiectasia

IQR

interquartile range

LA

left atrium

LAVol

left atrial volume

LV

left ventricle

LVEDV

left ventricular end-diastolic volume

LVEF

left ventricular ejection fraction

METS

metabolic equivalents

mPAP

mean pulmonary arterial pressure

NCO

normal cardiac output

NYHA

New York Heart Association

PH

pulmonary hypertension

sPAP

systolic pulmonary arterial pressure

SBP

systolic blood pressure

TTE

transthoracic echocardiography

TR-Vmax

tricuspid regurgitation maximum velocity

LVOT

left ventricular outflow tract

SA

body surface area

AF

atrial fibrillation

Declarations

Ethics approval and consent to participate:

The study was approved by the Southern Mediterranean Ethics Committee on July 22, 2024 (registration number 2022-A02671-42) in accordance with French regulations and the Declaration of Helsinki. All patients signed a informed consent.

Clinical Trial Registry details:

This study was registered on July 13, 2023, on the “clinicaltrials.gov” registry under number NCT05954481.

Consent for publication:

Not applicable.

Availability of data and materials:

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

CB, SDG, AG and AEF contributed to the conception and design of the study. CB, TB, QB and HT participated to the acquisition of data. CB, SDG and AG interpreted the data. CB drafted the work and all the authors revised it.

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Not applicable.

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Figures

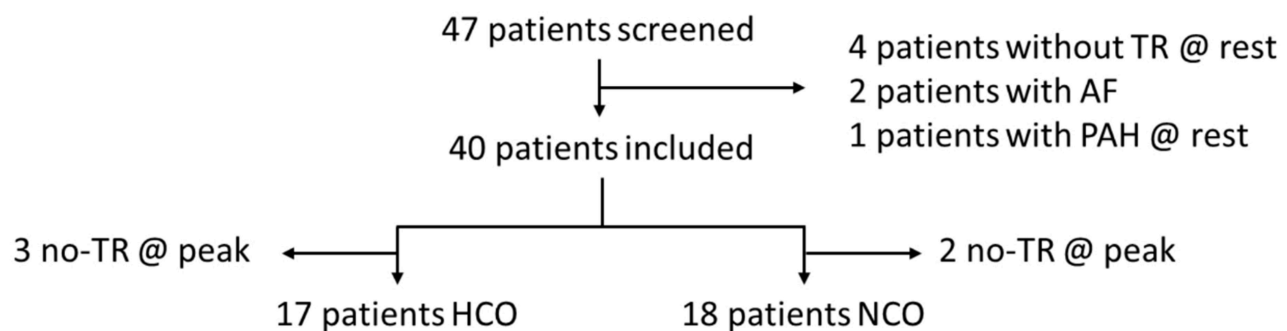


Figure 1

flow chart of the study

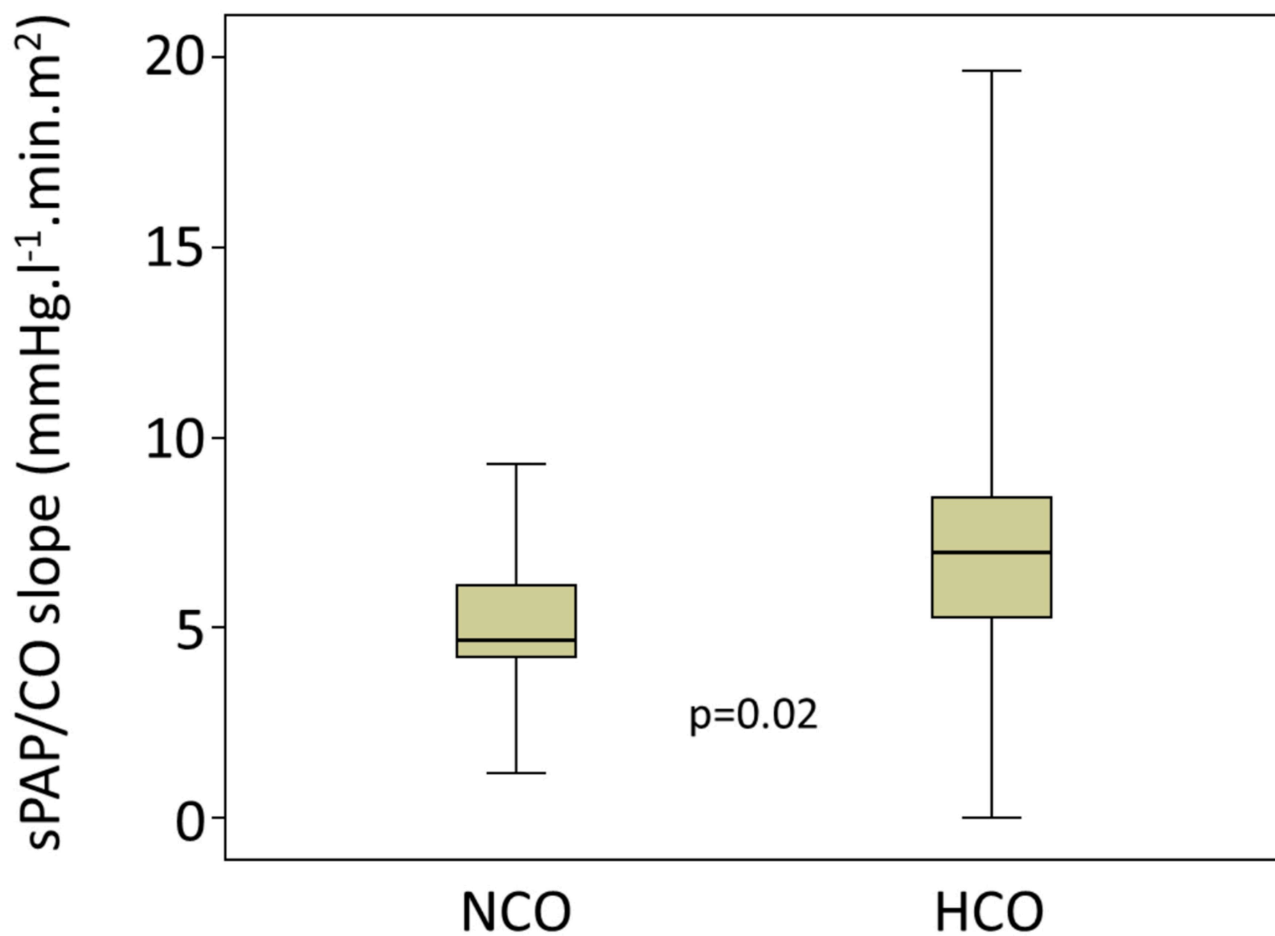


Figure 2

sPAP/CO slopes according to the CO group

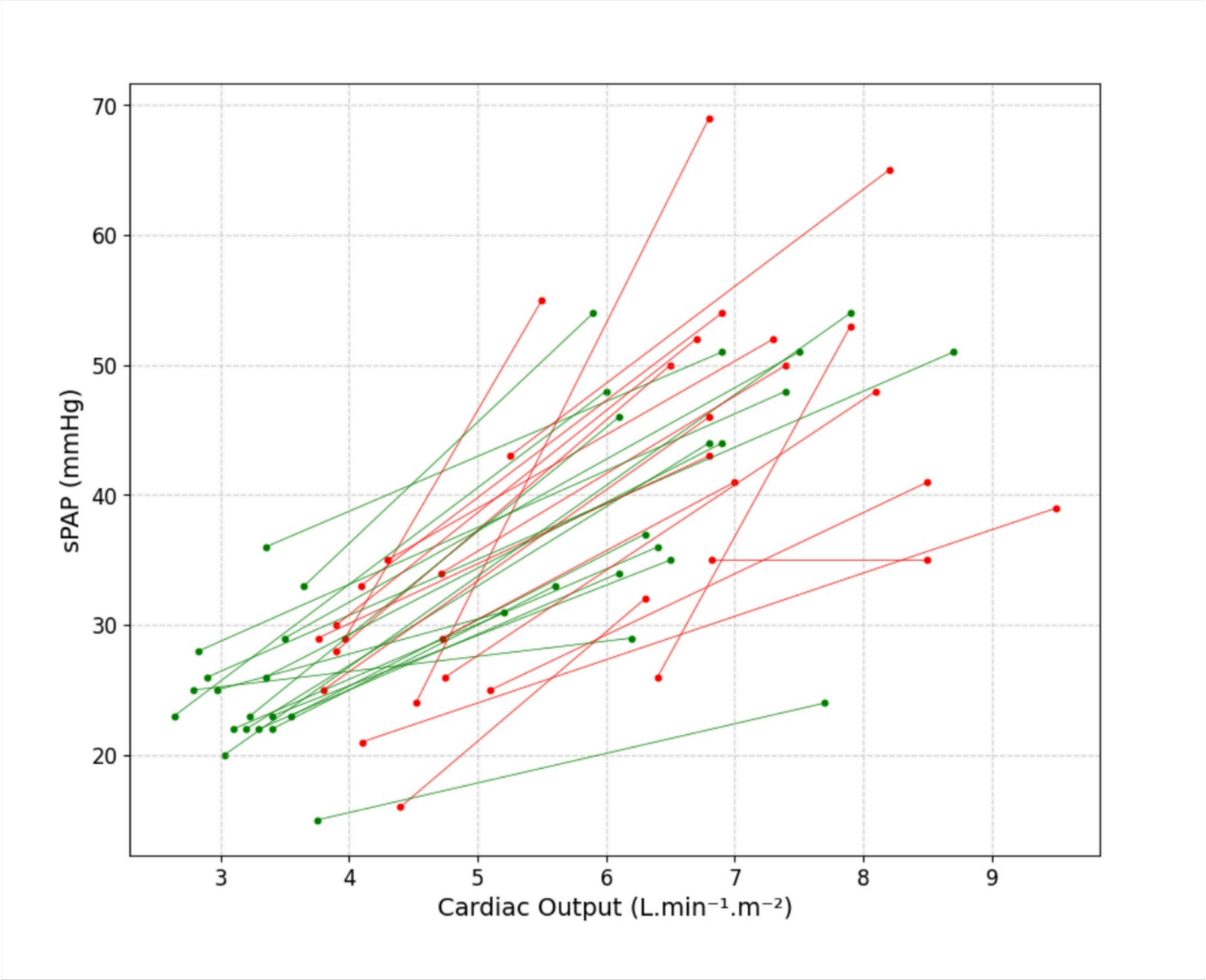


Figure 3

individual sPAP/CO slopes according to the CO group (green=NCO, red=HCO)