



Abnormal levels of apolipoprotein A-I in chronic thromboembolic pulmonary hypertension

Ghaleb Khirfan¹ , Manshi Li², Xiaofeng Wang², Joseph A. DiDonato³, Raed A. Dweik⁴ and Gustavo A. Heresi⁴ 

¹Department of Pulmonary and Critical Care Medicine, Cleveland Clinic, Cleveland, OH, USA; ²Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA; ³Department of Cellular and Molecular Medicine, Cleveland Clinic, Cleveland, OH, USA; ⁴Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract

Recent studies have shown low high-density lipoprotein cholesterol (HDL-C) and dysregulated lipid metabolism in chronic thromboembolic pulmonary hypertension (CTEPH). Apolipoprotein A-I (ApoA-I) is the major protein component of HDL-C and mediates most of its functions. We hypothesize that ApoA-I and its oxidative state might be more sensitive biomarkers in CTEPH. Plasma levels of HDL-C, ApoA-I, paraoxonase-I enzyme activity (PON1), and the oxidized dysfunctional ApoA-I (oxTrp72-ApoA-I) were measured in patients with CTEPH and compared to those in healthy controls. Association with markers of disease severity in CTEPH was assessed. We included a total of 61 patients with CTEPH (age: 61.2 ± 15 years; male 52.5%) and 28 control subjects (age: 60.1 ± 8 years; male 59.3%). When adjusting for age, sex, body mass index, and statin use, ApoA-I was lower in CTEPH compared to controls (CTEPH: 125.2 ± 27 mg/dl; control: 158.3 ± 29.4 mg/dl; $p < 0.001$), but HDL-C levels were not statistically different. There were no significant differences in PON and oxTrp72-ApoA-I/ApoA-I ratio. In exploratory analyses, ApoA-I was associated with mean right atrial pressure ($r_s = -0.32$, $p = 0.013$) and N-terminal pro B-type natriuretic peptide ($r_s = -0.31$, $p = 0.038$). There were no significant associations between HDL-C, PON1, or oxTrp72-ApoA-I/ApoA-I ratio and markers of disease severity. We conclude that ApoA-I is a more sensitive biomarker than HDL-C in CTEPH, and may be associated with right heart dysfunction.

Keywords

apolipoprotein A-I, biomarkers, chronic thromboembolic pulmonary hypertension, high density lipoprotein cholesterol, lipoproteins

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in 0.57% to 3.8% of patients after an episode of acute pulmonary embolism.^{1,2} Obstruction of large pulmonary arteries by thromboembolic material and the concomitant small vessel vasculopathy leads to progressive increase in pulmonary artery pressure and pulmonary vascular resistance (PVR), and ultimately right heart failure and death if left untreated.^{3,4} The hemodynamic changes,⁵ pathological findings of small vessel vasculopathy,⁶ and dismal prognosis with eventual development of right heart failure are very similar in CTEPH patients with small vessel

vasculopathy to what is seen in patients with idiopathic pulmonary arterial hypertension (IPAH).⁷

Over the last decade, several studies highlighted the metabolic dysregulations, derangements in glucose metabolism^{8,9} and alterations in lipids profile^{10–13} that occur in IPAH patients and their association with disease severity and outcomes. Given the fact that some degree of similarity

Corresponding author:

Gustavo A. Heresi, Respiratory Institute Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA.

Email: heresig@ccf.org



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exists between CTEPH and IPAH, there is a growing interest to study these metabolic dysregulations in CTEPH. In a previous study, we showed that levels of high-density lipoprotein cholesterol (HDL-C) are lower in CTEPH patients compared to controls, and are associated with some markers of disease severity.¹⁴ More recently, our group also characterized the plasma metabolomic profile in CTEPH, which suggested altered lipid metabolism in multiple tissues and organs.¹⁵

Apolipoprotein A-I (ApoA-I) is the major protein component of HDL-C and contributes to its major vascular protective properties.¹⁶ Levels of ApoA-I can predict future risk of cardiovascular diseases and were shown to be inversely related to risk of major cardiovascular events.^{16–18} Yuditskaya et al. showed that sickle cell disease patients with pulmonary hypertension had lower levels of ApoA-I. The oxidized dysfunctional ApoA-I containing an oxindolyl alanine moiety at Trp72 (oxTrp72-ApoA-I) has proinflammatory properties¹⁹ and paroxanase-1 enzyme (PON1) protects against HDL-C oxidation.²⁰ To our knowledge, the presence of derangements of ApoA-I, PON1, and oxTrp72-ApoA-I has not been studied in CTEPH patients.

Given these observations, we hypothesized that ApoA-I and its oxidative state might be more sensitive biomarkers in CTEPH. The objectives of our study were to: (a) measure levels of ApoA-I, HDL-C, PON1, and oxTrp72-ApoA-I in CTEPH patients and compare those to control subjects, and (b) perform an exploratory analysis to assess the association between these variables and markers of disease severity in CTEPH.

Materials and methods

Study subjects

This retrospective study was approved by our Institutional Review Board (study numbers: IRB 8097 and IRB 11-444). Written informed consent was waived. Patients with CTEPH were identified from our Pulmonary Hypertension Registry. CTEPH patients had right heart catheterization (RHC) consistent with the diagnosis of pre-capillary pulmonary hypertension²¹ and imaging studies and ventilation perfusion scans with mismatched perfusion defects consistent with the diagnosis of CTEPH. Two pulmonary hypertension experts reviewed the information available and agreed on the pulmonary hypertension etiology based on pulmonary hypertension guidelines.²¹ A group of healthy subjects from our biobank were included to be part of the control group. Based on the interview conducted, they did not have symptoms or prior diagnosis of cardiac or pulmonary diseases.

Laboratory and clinical data

Previously collected and frozen blood samples from the CTEPH and control group were used to measure HDL-C, ApoA-I, PON1 enzyme activity, and oxTrp72-ApoA-I. As oxTrp72-ApoA-I represents an oxidized version of ApoA-I and its level varies according to the level of ApoA-I, we calculated the ratio between oxTrp72-ApoA-I and ApoA-I (oxTrp72-ApoA-I/ApoA-I ratio) to provide a meaningful comparison of this variable across the groups.

For patients with CTEPH, we reviewed the medical records and collected data regarding demographics, comorbidities, body mass index (BMI), smoking status, use of statin therapy, functional class as determined by the New York Heart Association (NYHA) functional classification, laboratory data (N-terminal pro-B type natriuretic peptide (NT-proBNP)), six-minute walk test (6MWT), pulmonary function tests, diffusion lung capacity for carbon monoxide (DLCO), echocardiography, and hemodynamic measures from RHC. Data in closest proximity to the time of blood sample collection were recorded.

Statistical analysis

Patients' information was summarized as mean and standard deviation for continuous variables, and as counts and percentage for all categorical variables. Normality was checked for the tested variables. ANOVA was performed to compare the levels of HDL-C, ApoA-I, and oxTrp72-ApoA-I/ApoA-I ratio between the two groups (CTEPH and control). ANCOVA was used to compare these variables between the groups while taking into account the influence of age, sex, BMI, and use of statin therapy. Kruskal–Wallis test was conducted to compare the levels of PON1 and proportional odds ordinal logistic model was used to adjust for covariates because its levels were not normally distributed. To assess the association between HDL-C, ApoA-I, PON1 and oxTrp72-ApoA-I/ApoA-I ratio and continuous markers of disease severity in CTEPH patients, Spearman's Rank test was used and Spearman's correlation coefficients and the corresponding *p* values were calculated; we corrected for multiple testing by using Bonferroni correction method. All analyses were performed by using SAS 9.4 software (SAS Institute, Cary, NC). The level of statistical significance was set at $p < 0.05$ (two tailed).

Results

We included a total of 61 patients with CTEPH (age: 61.2 ± 15 years; male 52.5%), and 28 control subjects (age: 60.1 ± 8 years; male 59.3%). Table 1 shows baseline patient characteristics. Levels of ApoA-I and HDL-C were lower in CTEPH patients compared to controls ($p < 0.001$ for ApoA-I and $p = 0.011$ for HDL-C). There were no statistically significant differences in PON1 and oxTrp72-ApoA-I/ApoA-I ratio between the two groups. After adjusting for

Table 1. Baseline patient characteristics.

Variable	CTEPH (n = 61)	Control (n = 28)
Age, years	61.2 ± 14.9	60.1 ± 8.0
Male gender, n (%)	32 (52.5)	16/27 (59.3)
BMI (kg/m ²)	32.1 ± 8.5	29 ± 5.4
Smoking history		
Current, n (%)	4/60 (6.7)	0 (0)
Former, n (%)	27/60 (45.0)	6/21 (28.6)
Never, n (%)	29/60 (48.3)	15/21 (71.4)
Statin therapy, n (%)	21 (34.4)	1/22 (4.5)
Diabetes mellitus, n (%)	15 (24.6)	—
Hypertension, n (%)	41 (67.2)	—
Dyslipidemia, n (%)	25 (41.0)	—
OSA, n (%)	16 (26.2)	—
CAD, n (%)	14 (23)	—
PAH specific therapy, n (%)	25 (41)	—
NYHA class, n (%)		
Class I	2/45 (4.4)	—
Class II	12/45 (26.7)	—
Class III	26/45 (57.8)	—
Class IV	5/45 (11.1)	—
6MWT		
Distance walked (m)	301.9 ± 122.8	—
Distance walked (% predicted)	82.4 ± 18.8	—
PFT		
FVC (% predicted)	80.6 ± 19.9	—
FEV ₁ (% predicted)	75.0 ± 21.1	—
FEV ₁ /FVC (%)	71.4 ± 13.6	—
TLC (% predicted)	89.5 ± 13.3	—
DLCO (% predicted)	65.3 ± 15.5	—
Echocardiogram		
RVSP (mmHg)	71.2 ± 23.4	—
NT-pro BNP (pg/ml)	1542.2 ± 2959.3	—
RHC		
RA pressure (mmHg)	9.5 ± 6.9	—
Mean PAP (mmHg)	41.5 ± 10.6	—
PAWP (mmHg)	13.6 ± 8.0	—
CI (L/min/m ²) by thermodilution	2.7 ± 0.72	—
PVR (Wood units)	6.2 ± 3.3	—
SvO ₂ (%)	63.7 ± 8.7	—

BMI: body mass index; CAD: coronary artery disease; CI: cardiac index; DLCO: diffusion lung capacity for carbon monoxide; DM: diabetes mellitus; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; NT-pro BNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association functional class; OSA: obstructive sleep apnea; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PFT: pulmonary function test; PVR: pulmonary vascular resistance; RA: right atrial; RHC: right heart catheterization; RVSP: right ventricular systolic pressure; SvO₂: mixed venous oxygen saturation; TLC: total lung capacity; 6MWT: six-minute walk test.
Note: Data expressed as mean ± SD unless otherwise indicated.

age, sex, BMI and statin use, levels of ApoA-I ($p < 0.001$) but not HDL-C ($p = 0.054$) remained significantly lower in CTEPH compared to controls. No significant differences were noted in PON1 and oxTrp72-ApoA-I/ApoA-I ratio in the adjusted analysis. Table 2 shows the results of adjusted and unadjusted analysis comparing the levels of these

variables between the groups. Fig. 1 shows violin plots to demonstrate the distribution of these variables in the CTEPH and control group.

In addition, we divided the CTEPH group into two subgroups based on ApoA-I levels above and below the median of 123 mg/dl and compared the patients' characteristics between the two groups. This analysis showed that patients with ApoA-I < 123 mg/dl had significantly higher percentage of NYHA functional class III/IV, higher mean RAP, and lower CI (Table 3).

In exploratory analyses, we tested the association between HDL-C, ApoA-I, PON1 and oxTrp72-ApoA-I/ApoA-I ratio and several markers of CTEPH severity including: NT-proBNP, distance walked during 6MWT (absolute value and percentage predicted), NYHA functional class, echocardiography (right ventricular systolic pressure, severity of tricuspid regurgitation, right ventricular dilation, right atrial dilation and the presence of pericardial effusion), and hemodynamic measures obtained during RHC (mean pulmonary artery pressure, right atrial pressure, cardiac index, PVR, total pulmonary resistance and pulmonary artery compliance). ApoA-I was associated with mean right atrial pressure ($r_s = -0.32$, $p = 0.013$) and NT-proBNP ($r_s = -0.31$, $p = 0.038$). There were no significant associations between HDL-C, PON1 or oxTrp72-ApoA-I/ApoA-I ratio, and markers of disease severity. When corrected for multiple testing (significant Bonferroni $p < 0.0056$), none of these associations met the threshold of statistical significance. The correlations between these variables and markers of disease severity are shown in Table 4.

Discussion

In a cohort of patients with CTEPH, we found that levels of HDL-C and ApoA-I are lower in CTEPH patients compared to controls. Adjusting for age, sex, BMI and statin use, we noticed that differences in ApoA-I but not in HDL-C remained statistically significant. We found no significant differences in PON1 and oxTrp72-ApoA-I/ApoA-I ratio between the groups. There was an association between ApoA-I and some markers of disease severity in CTEPH but no association with HDL-C, PON1, or oxTrp72-ApoA-I/ApoA-I.

Our observation of lower HDL-C in CTEPH group is consistent with previous studies.^{10,11,13,14} These findings could be explained by the fact that HDL-C has anti-inflammatory^{22,23} properties, protects against endothelial dysfunction,^{24,25} increases available prostacyclin,^{26–28} and promotes nitric oxide synthase.^{29,30} Our finding of lower levels of ApoA-I in CTEPH patients compared to controls is novel and these differences persisted even after adjusting for age, sex, BMI, and statin use. Since ApoA-I is the major protein component of HDL-C and contributes to its major vascular protective properties,¹⁶ levels of ApoA-I are expected to be lower in CTEPH patients compared to

Table 2. Comparison of HDL-C, ApoA-I, PON1 and oxTrp72-ApoA-I/ApoA-I ratio between CTEPH and control group.

Variable	CTEPH (n = 61)	Control (n = 28)	Unadjusted p-value	Adjusted p-value †
ApoA-I (mg/dl)	125.2 ± 26.8	158.3 ± 29.4	<0.001 ^a	<0.001 ^c
HDL-C (mg/dl)	45.6 ± 15.3	54.8 ± 15.8	0.011 ^a	0.054 ^c
PON1 (nm/min/ml) ^a	724 [364,941]	851.5 [347,1058]	0.48 ^b	0.71 ^d
oxTrp72-ApoA-I/ApoA-I ratio (nM/mg/dl)	0.10 ± 0.03	0.11 ± 0.04	0.43 ^a	0.18 ^c

ApoA-I: apolipoprotein A-I; CTEPH: chronic thromboembolic pulmonary hypertension; HDL-C: high density lipoprotein cholesterol; nM: nanomolar; oxTrp72-ApoA-I: ApoA-I containing an oxindolyl alanine moiety at Trp72; PON1: paraoxonase-I enzyme activity.

^aData presented as mean ± SD except for PON1 which was not normally distributed and as such we reported the median [Q1, Q3].

†Analysis adjusted for age, sex, BMI and use of statin therapy.

p-values: a = ANOVA, b = Kruskal-Wallis test, c = ANCOVA, d = Proportional odds ordinal logistic model.

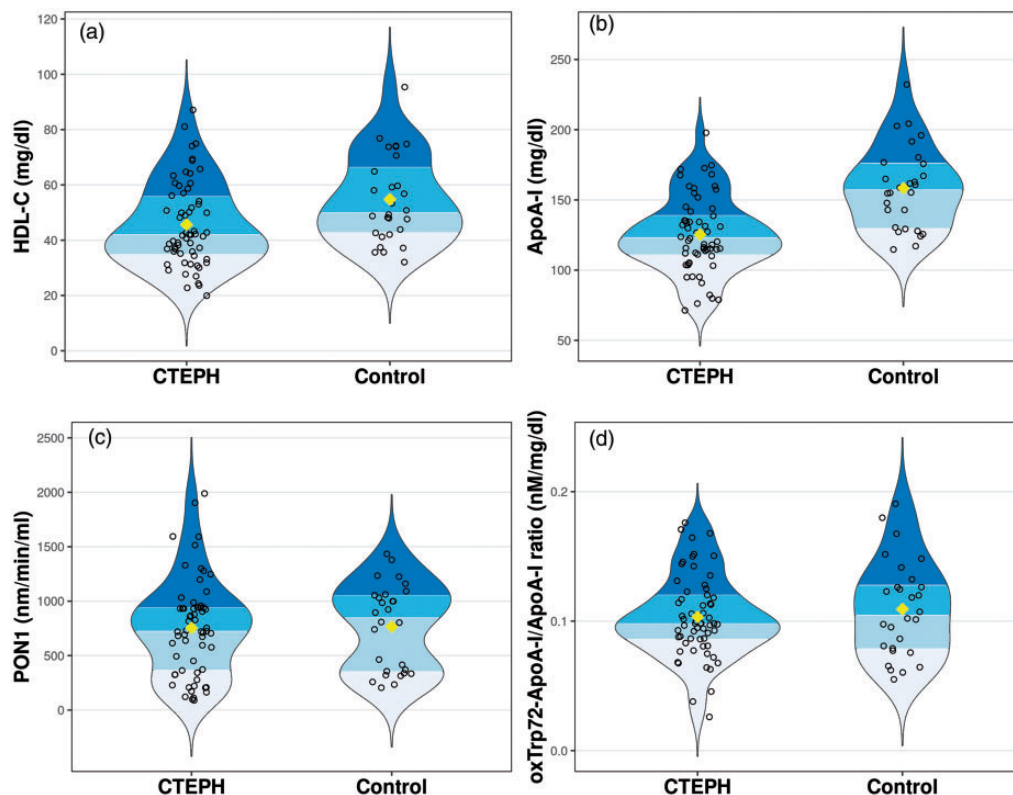


Fig. 1. Violin plots demonstrating the distribution of HDL-C, ApoA-I, PON1 and oxTrp72-ApoA-I/ApoA-I ratio in the CTEPH and control group. Yellow diamonds represent the mean, and the horizontal lines correspond to the first quartile, median, and third quartile, respectively.

controls given the observations of lower HDL-C in these groups. Several studies suggested that ApoA-I may be a stronger predictor of coronary artery disease than HDL-C.^{17,18,31} We noticed that levels of ApoA-I, but not that of HDL-C, remained significantly lower in CTEPH compared to controls after adjusting for several factors that might contribute to variation in the levels among the groups (age, sex, BMI, and statin use), which might suggest that the observed differences in HDL-C could be due to the effect of these factors. This suggests that ApoA-I is a more sensitive biomarker than HDL-C in CTEPH.

We also noticed that ApoA-I was associated with some markers of disease severity in the CTEPH group. ApoA-I correlated with mean right atrial pressure and NT-proBNP.

This might suggest that derangements in ApoA-I could be reflective of right ventricular dysfunction in these patients. While prior studies reported^{10,11,13} association between HDL-C and markers of disease severity and survival in PAH patients, we did not observe an association between HDL-C and markers of disease severity in our CTEPH group. One potential explanation for this observation is that despite the similarities between PAH and CTEPH that are more applicable in CTEPH patients with small vessel vasculopathy,³² they remain separate disease entities with different underlying mechanisms for development of pulmonary vascular pathology, and PAH patients could have more pronounced derangements in lipid metabolism than CTEPH patients.

Table 3. Patients' characteristics of CTEPH subgroups based on ApoA-I levels.

Variable	ApoA-I < 123 mg/dl (n = 30)	ApoA-I ≥ 123 mg/dl (n = 31)	p-value*
Age, years	61.6 ± 16.9	60.7 ± 13.0	0.82 ^a
Male gender, n (%)	17 (56.7)	15 (48.4)	0.52 ^c
BMI (kg/m ²) ^a	28.6 [26.6,35]	31.4 [26.2,39.1]	0.50 ^b
Statin therapy, n (%)	12 (40.0)	9 (29.0)	0.37 ^c
NYHA class, n (%)			0.022^d
Class I	0 (0.0)	2/24 (8.3)	
Class II	3/21 (14.3)	9/24 (37.5)	
Class III	17/21 (81.0)	9/24 (37.5)	
Class IV	1/21 (4.8)	4/24 (16.7)	
6MWT			
Distance walked (m)	280.7 ± 117.3	323.2 ± 126.6	0.21 ^a
Distance walked (% predicted)	51.9 ± 21.7	61.7 ± 22.8	0.11 ^a
Echocardiogram			
RVSP (mmHg)	69.6 ± 20.1	72.6 ± 26.2	0.65 ^a
NT-pro BNP (pg/ml) ^a	623 [255, 2189]	342 [85.5,987]	0.11 ^b
RHC			
RA pressure (mmHg) ^a	11 [6,16]	7 [5,10]	0.048^b
Mean PAP (mmHg)	42.5 ± 10.2	40.5 ± 11.0	0.48 ^b
PAWP (mmHg)	13.9 ± 5.5	13.4 ± 9.9	0.82 ^a
CI (L/min/m ²) by thermodilution	2.5 ± 0.7	2.9 ± 0.7	0.044^a
PVR (Wood units) ^a	6.0 [4.0,9.8]	5.0 [4.0,7.6]	0.38 ^b
SvO ₂ (%)	61.5 ± 10.6	65.8 ± 5.9	0.17 ^a

BMI: body mass index; CI: cardiac index; NT-pro BNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association functional class; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; RA: right atrial; RHC: right heart catheterization; RVSP: right ventricular systolic pressure; SvO₂: mixed venous oxygen saturation; 6MWT: six-minute walk test.

Note: Data presented as mean ± SD unless otherwise indicated.

^aThese variables were not normally distributed and as such were presented as median [Q1, Q3].

*p-values: a = two sample t test, b = Kruskal-Wallis test, c = Pearson's chi square test, d = Fisher's exact test.

Table 4. Correlation between HDL-C, ApoA-I, PON1 and oxTrp72-ApoA-I/ApoA-I ratio and markers of disease severity in CTEPH. Spearman's Correlation Coefficients and p values are shown.

Disease severity marker	N	HDL-C		ApoA-I		PON1		oxTrp72-ApoA-I/ ApoA-I ratio	
		Spearman's CC	p	Spearman's CC	p	Spearman's CC	p	Spearman's CC	p
6MWD (% predicted)	53	0.20	0.15	0.25	0.075	-0.12	0.39	-0.038	0.79
RVSP	54	0.15	0.27	0.032	0.82	-0.11	0.43	-0.042	0.76
NT-proBNP	45	-0.11	0.47	-0.31	0.038[†]	-0.16	0.28	-0.12	0.44
Mean RAP	58	-0.19	0.16	-0.32	0.013[†]	0.099	0.46	0.059	0.66
mPAP	60	-0.061	0.64	-0.19	0.15	-0.057	0.67	-0.009	0.95
CI	57	-0.032	0.82	0.21	0.11	0.12	0.37	0.10	0.46
PVR	55	-0.036	0.79	-0.17	0.20	-0.16	0.25	-0.12	0.38
PA compliance	50	-0.13	0.37	0.094	0.52	-0.0027	0.99	0.15	0.28
TPR	57	-0.023	0.86	-0.22	0.11	-0.11	0.41	-0.099	0.46

ApoA-I: apolipoprotein A1; CI: cardiac index; HDL-C: high density lipoprotein cholesterol; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro b-type natriuretic peptide; oxTrp72-ApoA-I: ApoA-I containing an oxindolyl alanine moiety at Trp72; PA: pulmonary artery; PAP: pulmonary artery pressure; PON1: Paraoxanase-1 enzyme activity; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RVSP: right ventricular systolic pressure; TPR: total pulmonary resistance; 6MWD: distance walked during six-minute walk test.

[†]Using Bonferroni correction method for multiple testing, p values <0.0056 would be considered statistically significant.

Paroxanase-1 enzyme protects against HDL-C oxidation.²⁰ Although we expected to find lower PON1 enzymatic activity in CTEPH compared to controls, there were no significant differences in PON1 among the groups and it

was not associated with any marker of disease severity. These results could possibly be due to lack of derangements in this enzyme in CTEPH or due to the small sample size of our study that limited identification of these differences.

oxTrp72-ApoA-I is an oxidized dysfunctional ApoA-I containing an oxindolyl alanine moiety at Trp72, it is lipid poor, has proinflammatory properties, and impaired HDL-C biogenesis.¹⁹ In one study, elevated levels of oxTrp72-ApoA-I in human subjects were associated with increased risk of cardiovascular diseases.¹⁹ In our study, we did not find significant differences in oxTrp72-ApoA-I/ApoA-I ratio between the CTEPH and control group. While this could be due to the small sample size, it is also possible that low ApoA-I levels mediate worsened pulmonary vascular disease independent of the oxidized state of the lipoprotein in CTEPH.

Our study has several limitations including the retrospective design, single center setting, and small sample size. Despite these limitations, our study is the first to assess the alterations of ApoA-I in CTEPH patients and investigate the derangements in oxTrp72-ApoA-I and PON1 enzymatic activity in CTEPH. Significant differences were noted in ApoA-I in CTEPH patients compared to controls and association with some markers of disease severity was observed. Future studies on larger scale are needed to investigate the association of ApoA-I with markers of disease severity and survival in CTEPH.

Conclusions

ApoA-I is lower in CTEPH patients compared to controls and may be associated with right heart dysfunction. Contrary to HDL-C, differences in ApoA-I in CTEPH remained significant after adjusting for confounders. These data suggest that ApoA-I is a more sensitive biomarker than HDL-C in these patients.

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None

Authors' contributions

Ghaleb Khirfan: Participated in the design of the study, data collection, statistical analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Manshi Li: Participated in the statistical analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Xiaofeng Wang: Participated in the statistical analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

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Raed A. Dweik: Participated in the interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Gustavo A. Heresi: Participated in the design of the study, data collection, statistical analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted. Dr. Heresi is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Conflict of interest

The authors declare that there is no conflicts interest except for Gustavo A. Heresi who received personal fees for being a member in Bayer Healthcare – Advisory Board and Speaking.

Ethical approval

This study was approved by the Cleveland Clinic Institutional Review Board (study numbers: IRB 8097 and IRB 11-444).

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Guarantor

Gustavo A Heresi.

ORCID iDs

Ghaleb Khirfan  <https://orcid.org/0000-0001-8506-4676>

Gustavo A. Heresi  <https://orcid.org/0000-0002-9797-2599>

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