Circulation: Heart Failure

ORIGINAL ARTICLE

Fatty Acid and Oxylipin Metabolism Differentiate Isolated Postcapillary From Combined Pre- and Postcapillary Pulmonary Hypertension

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BACKGROUND: Pulmonary hypertension (PH) due to left-sided heart disease (Group 2 PH) is the most common type of PH and comprises 2 subtypes with distinct clinical profiles and outcomes: isolated postcapillary PH and combined pre- and postcapillary PH (Cpc-PH). Bioactive lipid derivatives may underlie these divergent subphenotypes. This study aimed to investigate the molecular heterogeneity underlying Group 2 PH subtypes and identify shared pathways between Cpc-PH and pulmonary arterial hypertension (PAH).

METHODS: In a cross-sectional study, we profiled plasma bioactive lipids using liquid chromatography-mass spectrometry in 128 patients with isolated postcapillary PH (n=21), Cpc-PH (n=69), or PAH (n=38), as well as in plasma samples from animal models of severe PH.

RESULTS: Of the 844 profiled metabolites, 158 differed between Cpc-PH and isolated postcapillary PH at a false discovery rate of $q<0.05$. Of those, 28 were higher in Cpc-PH, particularly those in the polyunsaturated fatty acid and fatty acyl esters of hydroxy fatty acid pathways. Notably, 24 of these 28 did not differ from PAH, indicating a PAH-like bioactive lipid signature. Several metabolites, including adrenic acid, linoleic acid, docosatrienoic acid, palmitoleic acid, and fatty acyl esters of hydroxy fatty acids, were associated with increased mortality. These findings were corroborated in the Su/Hx rat model of PAH, where a subset of Cpc-PH-elevated metabolites was similarly increased.

CONCLUSIONS: Cpc-PH exhibits a distinct, PAH-like metabolomic signature characterized by higher polyunsaturated fatty acids and fatty acyl esters of hydroxy fatty acids and lower pro-resolvin/vasodilatory oxylipins compared with isolated postcapillary PH. These findings have implications for PH classification, may inform diagnostic strategies, and nominate lipid pathways for therapeutic targeting.

Key Words: biomarkers ■ fatty acids ■ heart diseases ■ heart failure ■ hypertension, pulmonary ■ metabolomics

Editorial by Garry and Brittain

Pulmonary hypertension (PH) arising from left-sided heart disease, classified as World Symposium on Pulmonary Hypertension Group 2 PH, is by far the most common type of PH accounting for 65% to 80% of all cases.[1–5] Group 2 PH comprises 2 clinically important subtypes, the more common of which is isolated postcapillary PH (Ipc-PH) and is associated with worse outcomes than left heart disease alone.[5–7] The less

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WHAT IS NEW?

- This work provides one of the most comprehensive metabolomics investigations of Group 2 pulmonary hypertension (PH), identifying signatures that distinguish isolated postcapillary PH from combined pre- and postcapillary PH (Cpc-PH). The metabolic architecture of Cpc-PH closely resembles that of pulmonary arterial hypertension, suggesting shared biologic processes.
- We show that bioactive lipid pathways linked to vascular remodeling and inflammation track closely with hemodynamics and clinical risk, revealing molecular features that have not previously been linked to Group 2 PH. These findings refine the molecular understanding of Group 2 PH and highlight the utility of metabolomics for subphenotyping and risk stratification.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The study findings highlight metabolomic profiling as a promising tool to refine risk assessment and molecular subphenotyping in Group 2 PH, particularly for identifying patients with Cpc-PH who may have more aggressive, pulmonary arterial hypertension-like biology. The distinctive metabolic features of Cpc-PH suggest the potential for developing noninvasive diagnostic classifiers that move beyond traditional hemodynamics.
- The shared pathways between Cpc-PH and pulmonary arterial hypertension provide a biologic rationale for exploring pulmonary arterial hypertension-directed therapies or repurposing existing treatments in carefully selected patients with Cpc-PH. Collectively, these insights could help guide future precision-based management strategies.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
Cpc-PH	combined precapillary and postcapillary pulmonary hypertension
FAHFA	fatty acyl esters of hydroxy fatty acid
Ipc-PH	isolated postcapillary pulmonary hypertension
mPAP	mean pulmonary artery pressure
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PH	pulmonary hypertension
PUFA	polyunsaturated fatty acid
PVR	pulmonary vascular resistance
RHC	right heart catheterization
WU	Wood units
WHO FC	WHO functional class
WHO	World Health Organization

common subtype is combined pre- and postcapillary PH (Cpc-PH) and is marked by increased pulmonary vascular disease compared with Ipc-PH.[6,7] Cpc-PH is clinically differentiated by a pulmonary vascular resistance (PVR) of >2 Wood units (WU), compared with a PVR ≤2 WU for Ipc-PH.[5] Cpc-PH carries a worse prognosis than Ipc-PH[8] and has been proposed to lie on a continuum with pulmonary arterial hypertension (PAH).[9,10] However, the pathophysiology underlying Cpc-PH remains poorly understood, and the molecular features distinguishing Ipc-PH, Cpc-PH, and PAH have not been delineated.

Why some patients with left heart disease develop Cpc-PH while others develop Ipc-PH is unclear. Evidence implicates a role for heightened activity of inflammatory mediators, including bioactive lipid molecules with systemic and pulmonary vascular effects.[11–14] Of particular interest are oxylipins, a class of bioactive lipid mediators derived from polyunsaturated fatty acids (eg, arachidonic acid, linoleic acid, and omega-3 fatty acids). These pathways generate a diverse set of metabolites that regulate pulmonary vascular tone, inflammation, endothelial function, and remodeling both in PH[14–18] and in systemic cardiovascular disease.[19,20] In PH, distinct metabolomic and lipid profiles have been linked to disease severity[21] and mortality risk.[22] Compared with broader metabolic intermediates, oxylipins are closely linked to vascular and endothelial signaling pathways, making them particularly relevant to the hemodynamic and pathobiological differences observed across PH subtypes. Therefore, we hypothesized that Cpc-PH and Ipc-PH exhibit distinct molecular signatures reflecting divergent pathophysiology, and that Cpc-PH shares molecular features with PAH, suggesting overlapping mechanisms. Understanding these similarities and differences could identify common therapeutic targets and inform treatment strategies.

METHODS

Data Availability

All data sets generated and analyzed during the current study are available to researchers through requests made directly to the primary invetigators. All liquid chromatography-mass spectrometry (LC-MS) data have been deposited in the public UCSD massIVE data repository (https://massive.ucsd.edu/) under data set identifier MSV000101426 and can be directly accessed at ftp://massive-ftp.ucsd.edu/v12/MSV000101426/.

Study Cohorts

In this cross-sectional observational study, we studied patients enrolled in the Tufts Medical Center Pulmonary Hypertension Database and Biobank, a prospective registry of adult patients with a diagnosis of PH confirmed by right heart catheterization (RHC) between June 1, 2006, and March 31, 2012. The study was conducted in accordance with the Declaration of Helsinki, V edition (2000), and approved by the Tufts Medical Center

institutional review board, and informed consent was obtained from all subjects.

Hemodynamics and PH Group Definitions

For all patients, the diagnosis of PH was confirmed from RHC measures, adhering to the updated criteria for PH, that is, a mean pulmonary arterial pressure (mPAP) >20 mm Hg.[5] Of note, data collection occurred before the 2018 World Symposium on Pulmonary Hypertension, which broadened the definition of PH to include mPAP >20 mm Hg.[5,23] Group 2 PH was defined as the presence of PH in addition to a mean pulmonary artery wedge pressure (PAWP) >15 mm Hg. The presence of Group 2 PH was further confirmed in the setting of a known diagnosis of left heart disease based on echocardiographic data reviewed by an expert physician at the time of diagnosis, including: heart failure with preserved ejection fraction, heart failure with reduced or mildly reduced ejection fraction, valvular heart disease, and congenital/acquired cardiovascular conditions leading to post-capillary PH, and expert physician ascertainment. Note that echocardiographic reports were not available for us to review at the time of this study analysis. Group 2 PH subtypes were further defined based on a PVR ≤2 WU for patients categorized as Ipc-PH or a PVR >2 WU for Cpc-PH, based on the updated definition.[5] In addition to patients with Group 2 PH, we also studied contemporaneously assessed patients from the same registry who were specifically identified as having Group 1 PAH. The diagnosis of PAH was based on established criteria: PH with PAWP ≤15 mm Hg and PVR >2 WU while excluding patients with World Health Organization (WHO) Group 3, 4, or 5 PH as confirmed by the treating physician.[23] Patients with missing PH classification data were excluded from the analyses.

Clinical and Outcomes Data

Demographic data, comorbidities, and medications were collected at the time of RHC for all patients. Laboratory data were restricted to within 30 days of RHC. Blood specimens were collected at the time of RHC or within 1 week before or after. Follow-up time was calculated from the date of RHC to the date of death or last known contact, with survivors censored at last follow-up.

Animal Studies

All animal studies were approved by the Division of Laboratory Animal Resources at the University of Pittsburgh. Male Sprague-Dawley rats (12 weeks old; weight, 190–200 g) were divided into 2 groups: the PH rats (N=4) and control rats (N=5). PH rats received a single injection of SU-5416 (Sigma-Aldrich) on day 1 (20 mg/kg) and were then maintained in 10% O_2 for 3 weeks. PH rats were returned to normoxia for an additional 2 weeks. Right ventricular systolic pressure and right ventricular hypertrophy (Fulton index: ratio of right ventricular weight to left ventricular plus septal weight) were measured as described previously in both groups.[24] After death, plasma samples were collected and stored at −80 °C, for oxylipin and bioactive lipid metabolomics analysis. Protocols were conducted under the Animals (Scientific Procedures) Act 1986 (Amendment Regulations 2012) after ethics review by the University of Pittsburgh Animal Welfare and Ethical Review Committe. All animal studies were conducted at the University of Pittsburgh.

Oxylipins and Bioactive Lipids Analysis

For all patients, fasting plasma samples were collected at the time of RHC and stored at −80 °C. All biological specimens subsequently underwent standardized processing and liquid chromatography-mass spectrometry-based oxylipin profiling using methods described previously.[25] Following quality control and quality assurance analysis, data were extracted using image processing and machine learning-based spectral optimization, then normalized, aligned, and filtered for data analyses according to methods previously detailed.[18,26]

Statistical Analyses

Before statistical analysis, missing metabolite values indicative of levels below the detection limit were imputed as random uniform values between one-sixth of the minimum observed value and the minimum observed value for that metabolite. Metabolite values were then natural log-transformed, and standardized (mean=0, SD=1) to facilitate interanalyte comparisons. Between-group comparisons were performed using the *t* test or the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Principal component analysis was utilized as an unsupervised clustering tool to assess differences and identify clustering patterns between the groups using metabolomics data. Processed, normalized (*Z* scored) data were used. The principal component analysis was performed using the prcomp package, with calculations based on singular value decomposition. Group separation was further evaluated using permutational multivariate ANOVA with Euclidean distance. The first few principal components, which capture the most variance in the data, were used to project the data into a lower-dimensional space. A multivariable logistic regression model was used to identify metabolites associated with Cpc-PH versus Ipc-PH in models adjusting for age, sex, body mass index (BMI), as well as aspirin and statin use (primary model). These variables were selected based on their clinical relevance, their potential to confound the relationship between metabolites, and the outcome and their established effect on eicosanoids.[27,28] For significant metabolites from the primary model, further adjustments were made for use of PH-specific medication, including phosphodiesterase type 5 inhibitors, endothelin receptor blockers, prostaglandin therapy, and calcium channel blockers, in addition to comorbidities such as dyslipidemia, hypertension, diabetes, and disease severity as reflected by mPAP. These factors were chosen due to their significant prevalence and potential impact on PH outcomes as well as the eicosanoid profile. Additional confounders such as renal insufficiency, autoimmune disease, cirrhosis, and history of malignancy were not included in the primary analyses due to their lower prevalence in our cohort. To account for multiple testing in the primary model, a false discovery rate *q* value <0.05 was considered significant, and a *P* value of <0.05 in the secondary analysis was considered significant. Analyses were repeated to compare oxylipin levels in Cpc-PH versus Group 1 PAH. Linear regression was used to determine associations between the selected metabolites and hemodynamic variables, including PVR, mPAP, right atrial pressure, cardiac output, and PAWP. A Cox proportional hazards model was used to examine associations between the selected metabolites and mortality, adjusting for age, sex, and BMI. Associations with clinical metrics of disease severity, such as 6-minute walk distance, brain

natriuretic peptide levels, and WHO functional class (WHO FC), were also examined using regression analyses. WHO FC was assessed as a categorical variable using a cutoff of WHO FC ≥3. For animal studies, metabolites reaching the significance threshold from the human studies were tested using Student *t* test. All statistical analyses were performed using R, v3.5.1.

RESULTS

Cohort Characteristics

An overview of the study design and procedures is provided in Figure 1. Of the 128 patients with PH included in our study, 90 participants had Group 2 PH, including 21 (16%) with Ipc-PH and 69 (53%) with Cpc-PH. The remaining 38 (29.6%) patients had PAH (Group 1) and served as the referent PH sample. The distribution of patients in the Group 1 PAH comparator group mirrored what is typically seen in clinical studies of this group and included idiopathic PAH (38%), connective tissue disease-related PAH (18%), drug- and toxin-associated PAH (10%), and others. During follow-up, 42 patients died, with a median follow-up time of ≈31 months.

Baseline characteristics were differed across the 3 groups (Tables 1 through 3). When compared with Group 2 PH (both Ipc-PH and Cpc-PH), patients with PAH were significantly younger, had a lower BMI, and had a lower prevalence of hyperlipidemia and hypertension. On the other hand, Cpc-PH and Ipc-PH had similar baseline characteristics, including age, BMI, and comorbidities. Brain natriuretic peptide levels were elevated in all 3 cohorts, but were not significantly different. Patients with Group 2 PH had a higher prevalence of hypertension, hyperlipidemia, and atrial fibrillation.

As expected, PAWP was higher in patients with Group 2 PH compared with those with PAH, and PVR was lower. Mean PAP was highest in Cpc-PH, slightly higher than that in PAH, and both were substantially higher than that in Ipc-PH. Right atrial pressure was considerably higher in Cpc-PH compared with Ipc-PH and PAH ($P<0.001$; Table 2).

Differential Oxylipin and Bioactive Lipid Profiles in Cpc-PH Compared With Ipc-PH and PAH

A total of 844 bioactive lipid metabolites were identified after excluding xenobiotics. In initial analyses of all patients with PH, hierarchical clustering and principal component analysis revealed clear separation between Ipc-PH and the other 2 groups, with the first principal component and second principal component explaining 32.6% and 8.7% of the variance, respectively (PERMANOVA between Cpc-PH and Ipc-PH, $F=9.8$, $P=0.006$; and between PAH and Ipc-PH, $F=15.9$, $P=0.003$; Figure 2A).

For the primary analysis prespecified to focus on comparing Ipc-PH patients with Cpc-PH patients, we found that 158 of the 844 bioactive lipid metabolite analytes assayed differed significantly between groups (false discovery rate q value <0.05 for the primary model and

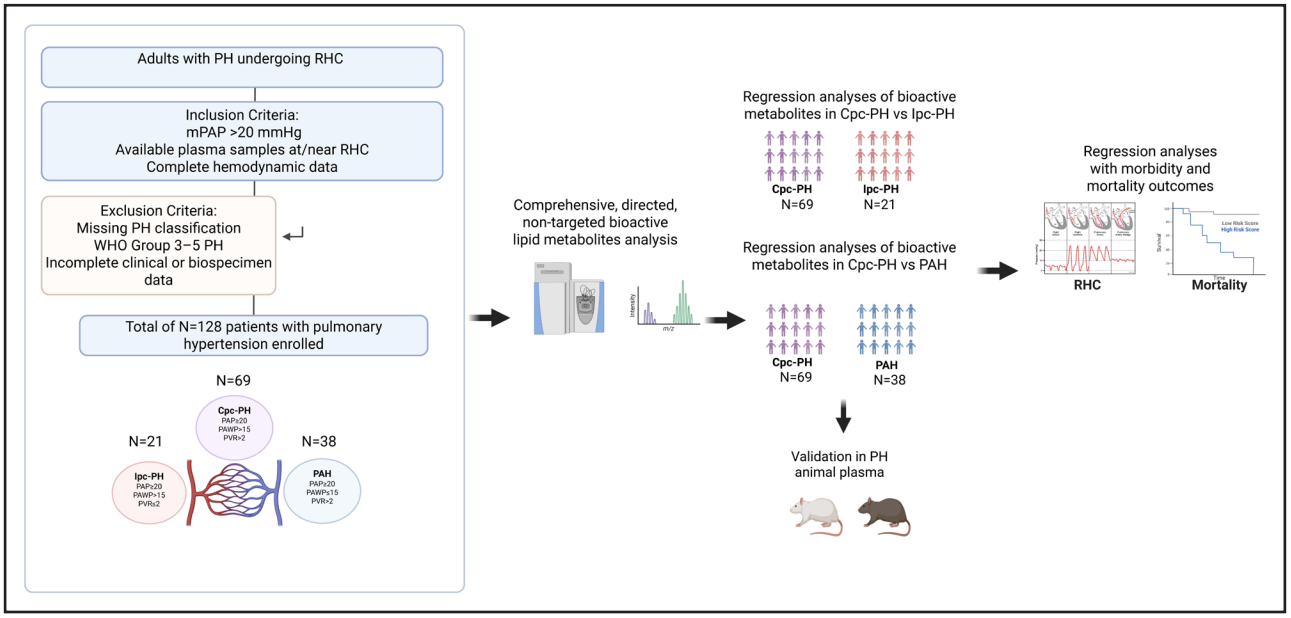


Figure 1. Overview of the study design.
Cpc-PH indicates combined post- and pre-capillary pulmonary hypertension; Ipc-PH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; and WHO, World Health Organization.

Table 1. Cohort Characteristics

	PH clinical group			*P* value, ANOVA	*P* value, Cpc-PH vs PAH	*P* value, Ipc-PH vs Cpc-PH
	Ipc-PH	Cpc-PH	PAH			
n	21	69	38			
Age, y	70.2 (8.2)	66.5 (11.7)	59.77 (13.91)	0.002	0.008	0.18
Female sex, %	16 (76.2)	50 (72.5)	21 (55.3)	0.12	0.22	0.9
Race, %				0.6	0.52	0.03
Asian	0 (0.0)	1 (1.5)	2 (5.1)			
Black	3 (14.3)	6 (9.2)	2 (5.1)			
White	16 (76.2)	48 (73.8)	26 (70.3)			
Other	2 (9.5)	6 (9.2)	6 (16.2)			
Unknown	0 (0.0)	4 (6.2)	1 (2.7)			
Body mass index, kg/m^2	33.5 (11.2)	33.9(8.9)	28.5 (7.7)	0.007	0.002	0.7
WHO functional class, %				0.1	0.16	0.1
I	0 (0.0)	3 (6.5)	0 (0.0)			
II	7 (46.7)	13 (28.3)	10 (25.6)			
III	8 (53.3)	28 (60.9)	10 (25.6)			
IV	0 (0.0)	2 (4.3)	1 (2.6)			
Unknown	11 (28.9)	18 (34.6)	17 (44.7)			
Six-minute walk, m	330 (154.6)	311 (147.8)	327 (100)	0.8	0.5	0.8
BNP, pg/mL	223.3 (409)	428.9(529)	324 (613)	0.4	0.53	0.1
Smoking status, %				<0.001	<0.001	0.5
Current	0 (0.0)	6 (8.7)	6 (15.4)			
Former	10 (47.6)	26 (37.7)	17 (43.6)			
Never	5 (23.8)	19 (27.5)	11 (28.2)			
Unknown	6 (28.6)	18 (26.1)	5 (12.8)			
Alcohol use, %				0.001	0.001	0.8
Current	6 (50)	19 (48.7)	16 (41.0)			
Former	1 (8.3)	6 (15.4)	6 (15.4)			
Never	5 (41.7)	14 (35.9)	7 (17.9)			
Unknown	18 (47.4)	21 (40.4)	10 (25.6)			
Comorbidities						
Sleep apnea, %	9 (42.9)	20 (29.0)	12 (30.8)	0.45	0.87	0.3
COPD, %	2 (9.5)	12 (17.4)	11 (28.2)	0.15	0.45	0.5
Hyperlipidemia, %	4 (19.0)	18 (26.1)	3 (7.7)	0.07	0.044	0.7
Atrial fibrillation, %	6 (28.6)	22 (31.9)	6 (15.4)	0.12	0.07	0.9
Diabetes, %	5 (23.8)	21 (30.4)	6 (15.8)	0.24	0.15	0.74
Hypertension, %	14 (66.7)	36 (52.2)	13 (33.3)	0.04	0.11	0.35

Values are reported as mean and SD unless indicated otherwise. BNP indicates brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; Cpc-PH indicates pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and WHO, World Health Organization.

$P<0.05$ for the secondary analysis). Of these, 28 metabolites were increased in Cpc-PH (odds ratio, 2.05–3.37 per 1-SD log-analyte), and 130 were increased in Ipc-PH (odds ratio, 1.8–2.5 per 1-SD log-analyte). Several of the 28 metabolites that were increased in Cpc-PH have been implicated in fatty acyl esters of hydroxy fatty acids (FAHFAs) and polyunsaturated fatty acid (PUFA) pathways, including nervonic acid, eicosadienoic acid, docosadienoic acid, and dihomo-γ-linolenic acid (Figure 2B and 2C and Table S1). Derivatives of ω-6 PUFAs, such as 12-HETE and 9,10-dihydroxyoctadecenoic acid, were also elevated among patients with Cpc-PH. Interestingly, levels of 24 of the 28 bioactive metabolites, including all the PUFAs, were not significantly different in Cpc-PH compared with PAH suggesting a shared molecular profile between Cpc-PH and PAH (Figure 2D). Furthermore, Ipc-PH patients had higher levels of oxylipins compared with Cpc-PH patients, including antiinflammatory (eg, 5,6-diHETE, 18-HEPE), pro-resolving (eg, MCTR2, resolvins), anticoagulant (eg,

Table 2. Selected Hemodynamic Measures, by PH Clinical Group

	PH clinical group			*P* value, ANOVA	*P* value, Cpc-PH vs PAH	*P* value, Ipc-PH vs Cpc-PH
	Ipc-PH	Cpc-PH	PAH			
RAP, mm Hg	8.9 (4.07)	13.5 (5.9)	9.27 (5.40)	<0.001	<0.001	0.001
mPAP, mm Hg	27.8 (5.9)	44.8 (12.1)	43.45 (12.54)	<0.001	0.52	<0.001
PAWP, mm Hg	17.9 (3.8)	20.26 (4.9)	11.67 (4.38)	<0.001	<0.001	0.04
CO (TD), L/min	6.5 (2.13)	4.7 (1.6)	4.95 (1.73)	0.002	0.58	0.001
PVR, Wood units	1.53 (0.39)	5.78 (4.04)	7.63 (4.70)	<0.001	0.044	<0.001

Values are reported as mean and SD unless reported otherwise. CO indicates, cardiac output; Cpc-PH, pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; and TD, thermodilution.

PGD3), and pulmonary vascular vasodilatory (eg, PGE2) oxylipins.[29]

Metabolites in Cpc-PH Associated With Mortality and Adverse Hemodynamic Profiles

Of the 28 metabolites found to be significantly elevated in Cpc-PH, several metabolites such as FAHFAs, nervonic acid, adrenic acid, and palmitoleic acid, were associated with higher mPAP, PVR, or right atrial pressure (Table S2), although none were associated with higher PAWP. Several metabolites, including adrenic acid, linoleic acid, docosatrienoic acid, palmitoleic acid, and FAHFAs, were also associated with increased mortality after adjusting for age, sex, and BMI (hazard ratio (HR) range, 1.7–2.4; $P<0.05$; Figure 3 and Table S3).

Metabolites in Cpc-PH Associated With Clinical Markers of Disease Severity

Of the enrolled patients, 82 had a documented WHO FC, 81 had a documented brain natriuretic peptide measurement, and only 53 had a documented 6-minute walk distance within 2 weeks of RHC. Five of the metabolites were significantly associated with a WHO FC of III/IV, one was associated with an elevated brain natriuretic peptide level, and 2 of the 28 metabolites were significantly associated with reduced 6-minute walk distance (Table S2).

Evidence of Shared Metabolic Pathways Between Cpc-PH and PAH

To further determine the extent to which Cpc-PH shares a molecular profile with PAH, we measured the oxylipins and bioactive lipids commonly associated with both Cpc-PH and PAH (28 metabolites) in plasma samples from an established rat model of severe PAH induced by exposure to the vascular endothelial growth factor receptor inhibitor SU-5416, with chronic hypoxia followed by normoxia (Su/Hx). Su/Hx rats developed elevated right ventricular systolic pressure and increased Fulton index values, confirming right heart hypertrophy and pulmonary vascular remodeling (Table S4). Although this model does not recapitulate Group 2 PH, it provides a well-characterized system for studying the metabolic landscape of PAH. Of the 28 metabolites examined, 7 were significantly elevated in the plasma of Su/Hx PAH rats compared with controls (Figure 4). Five of these metabolites were also associated with mortality in Cpc-PH ($P<0.05$). These findings suggest shared metabolic pathways and bioactive lipid profiles between Cpc-PH and PAH, notwithstanding differences in their clinical classification.

Table 3. Medication Use, by PH Clinical Group

	PH clinical group			*P* value, ANOVA	*P* value, Cpc-PH vs PAH	*P* value, Ipc-PH vs Cpc-PH
	Ipc-PH	Cpc-PH	PAH			
n	21	69	38			
Phosphodiesterase 5 inhibitors, %	5 (23.8)	12 (17.4)	12 (31.6)	0.2	0.14	0.7
Calcium channel blocker, %	5 (23.8)	14 (20.3)	3 (7.9)	0.18	0.16	0.9
Endothelin receptor antagonist, %	1 (4.8)	2 (2.9)	5 (13.2)	0.16	0.1	0.9
Oral prostacyclin analog, %	0 (0.0)	0 (0.0)	4 (10.5)	0.009	0.02	NA
Intravenous prostacyclin, %	0 (0.0)	0 (0.0)	1 (2.6)	0.31	0.8	NA
Aspirin,%	6 (28.6)	21 (30.4)	7 (18.2)	0.3	0.3	0.9
Statin, %	6 (28.6)	21 (30.4)	5 (13.2)	0.13	0.16	0.9

Values are reported as number and percentage. Cpc-PH indicates pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; NA, not applicable; PAH, pulmonary arterial hypertension; and PH, pulmonary hypertension.

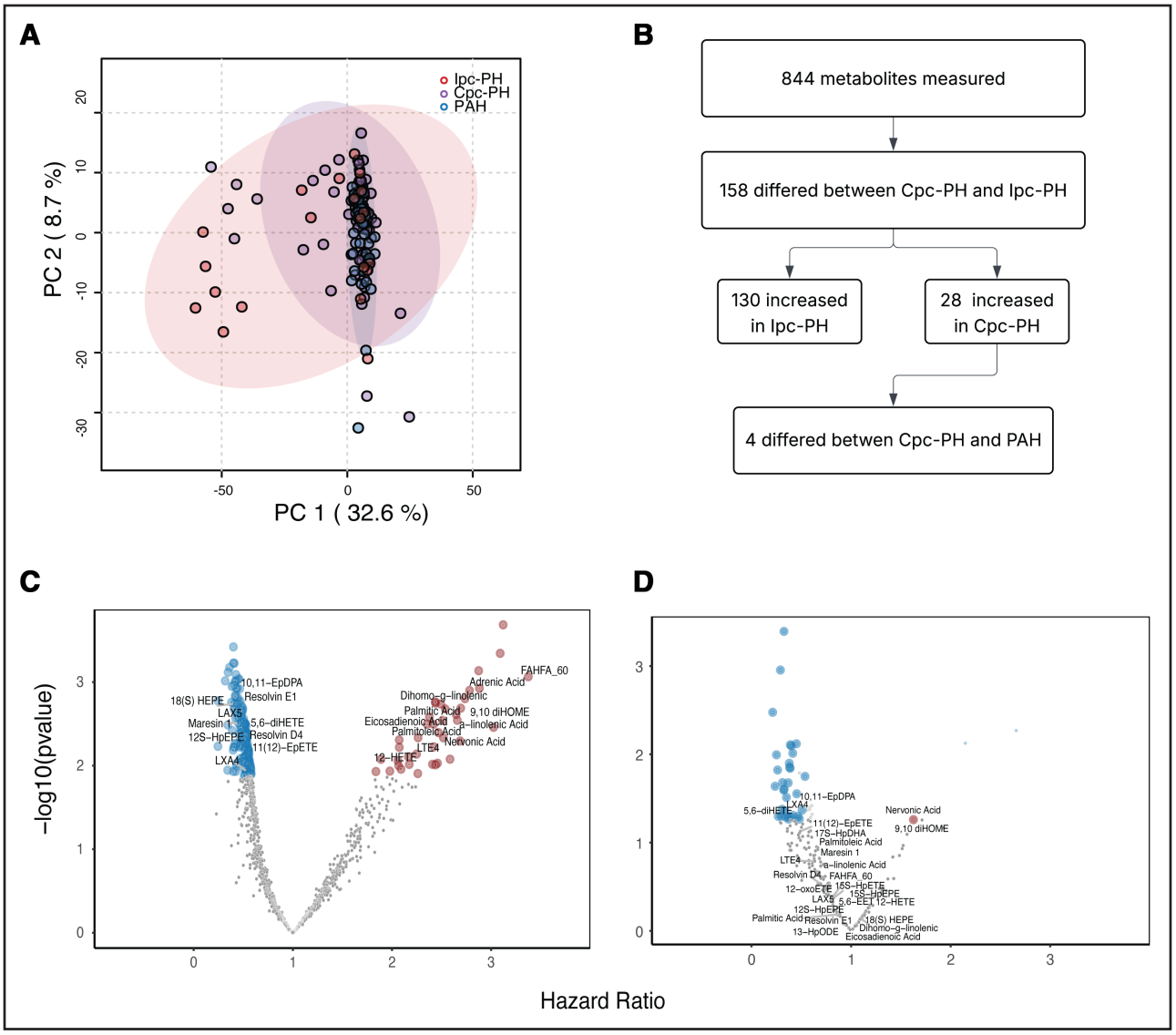


Figure 2. Oxylipins and bioactive lipid associations with the pre- and postcapillary pulmonary hypertension (Cpc-PH) vs isolated postcapillary pulmonary hypertension (Ipc-PH) subtypes of group 2 pulmonary hypertension.
A, Principal component analysis (PCA) demonstrated clustering of oxylipins and bioactive lipid metabolites by pulmonary hypertension (PH) group and subtype. **B**, Venn diagrams highlighting metabolites significant from multivariable regression analyses in Ipc-PH vs Cpc-PH and Cpc-PH vs pulmonary arterial hypertension (PAH). **C**, Volcano plot of multivariable regression analysis in Ipc-PH vs Cpc-PH (primary model: adjusting for age, sex, body mass index (BMI), aspirin and statin use). Metabolites significant after false discovery rate correction (q<0.05) are highlighted. **D**, Volcano plot of multivariable regression analysis in Cpc-PH vs PAH (primary model: adjusting for age, sex, BMI, aspirin and statin use). 10,11-EpDPA indicates 10,11-epoxydocosapentaenoic acid; 11(12)-EpETE, 11(12)-epoxyeicosatetraenoic acid; 12-HETE, 12-HETE; 12-oxoETE, 12-oxo-eicosatetraenoic acid; 12S-HpEPE, 12S-hydroperoxyeicosapentaenoic acid; 13-HpODE, 13-hydroperoxyoctadecadienoic acid; 15S-HpEPE, 15S-hydroperoxyeicosapentaenoic acid; 15S-HpETE, 15S-hydroperoxyeicosatetraenoic acid; 17S-HpDHA, 17S-hydroperoxydocosahexaenoic acid; 18(S) HEPE, 18(S)-hydroxyeicosapentaenoic acid; 5,6-diHETE, 5,6-dihydroxyeicosatetraenoic acid; 5,6-EET, 5,6-epoxyeicosatrienoic acid; 9,10-diHOME, 9,10-dihydroxyoctadecenoic acid; FAHFA, fatty acid esters of hydroxy fatty acids; LAX5, lipoxin A5; LTE4, leukotriene E4; and LXA4, lipoxin A4; PC1, principal component 1; PC2, principal component 2.

DISCUSSION

Our metabolomics analyses revealed a distinct bioactive lipid profile in Cpc-PH that more closely resembles PAH than Ipc-PH. Similar to patients with PAH and animal models of severe PH, individuals with Cpc-PH had higher levels of MUFAs and PUFAs, oxidized derivatives of ω-6 PUFAs and FAHFAs compared with patients with Ipc-PH. These molecular alterations are reflective of dysregulated fatty acid oxidation and metabolism, lipotoxicity, inflammation and oxidative stress, all hallmarks of PAH pathobiology. A few of these metabolites were also associated with markers of disease severity and mortality. On the contrary, Ipc-PH had higher levels of

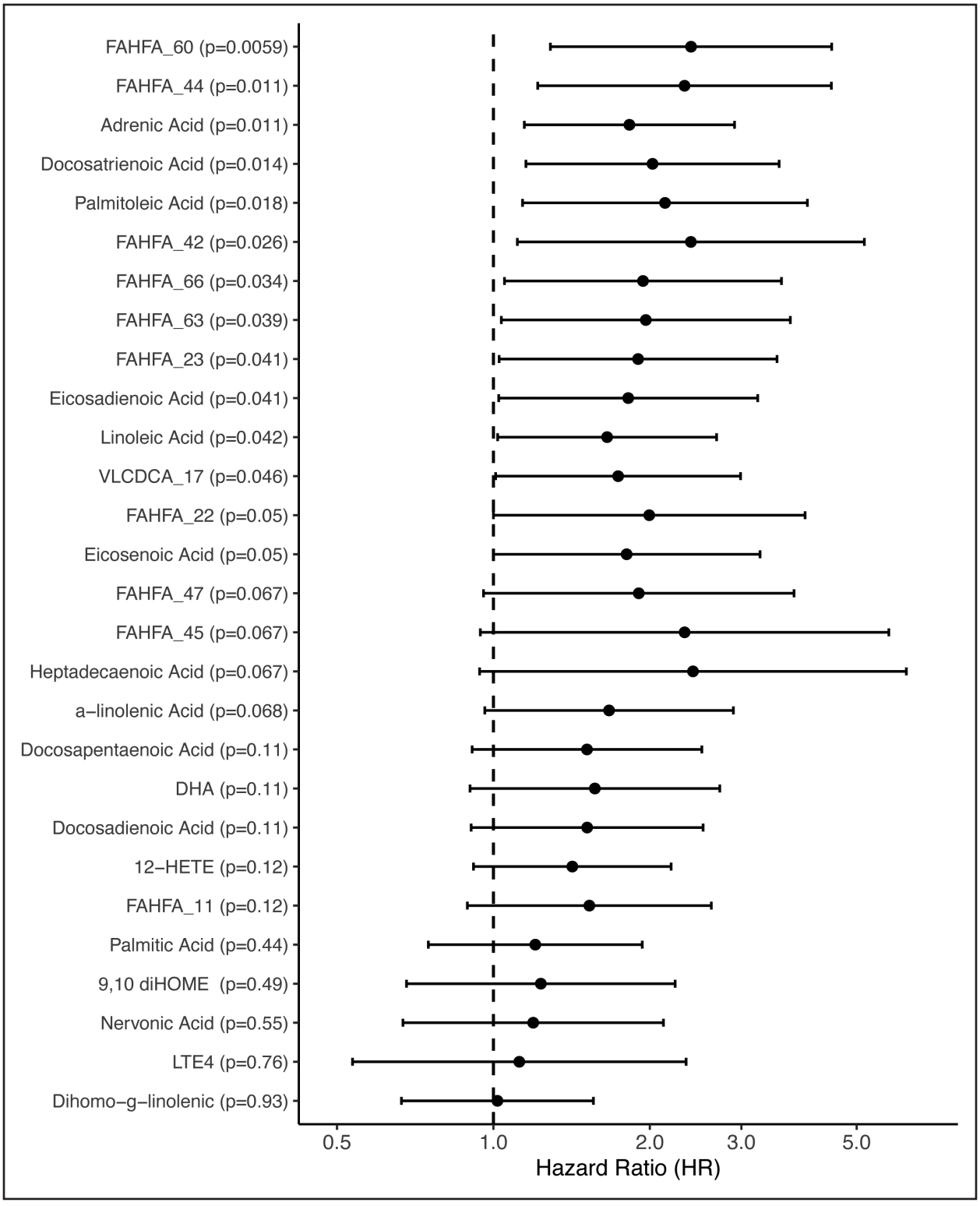


Figure 3. Forest plot of metabolite association with mortality.
For the 28 metabolites significantly elevated in pre- and postcapillary pulmonary hypertension (Cpc-PH) compared with isolated postcapillary pulmonary hypertension (Ipc-PH), forest plots display their associations with mortality. Results are derived from Cox regression analyses. Hazard ratios (HRs) are per 1-SD increase in log-transformed metabolite; models adjusted for age, sex, body mass index. 12-HETE indicates 12-HETE; 9,10-diHOME, 9,10-dihydroxyoctadecenoic acid; DHA, docosahexaenoic acid; FAHFA, fatty acid esters of hydroxy fatty acid; LTE4, leukotriene E4; and VLCDCA, very long chain dicarboxylic acid.

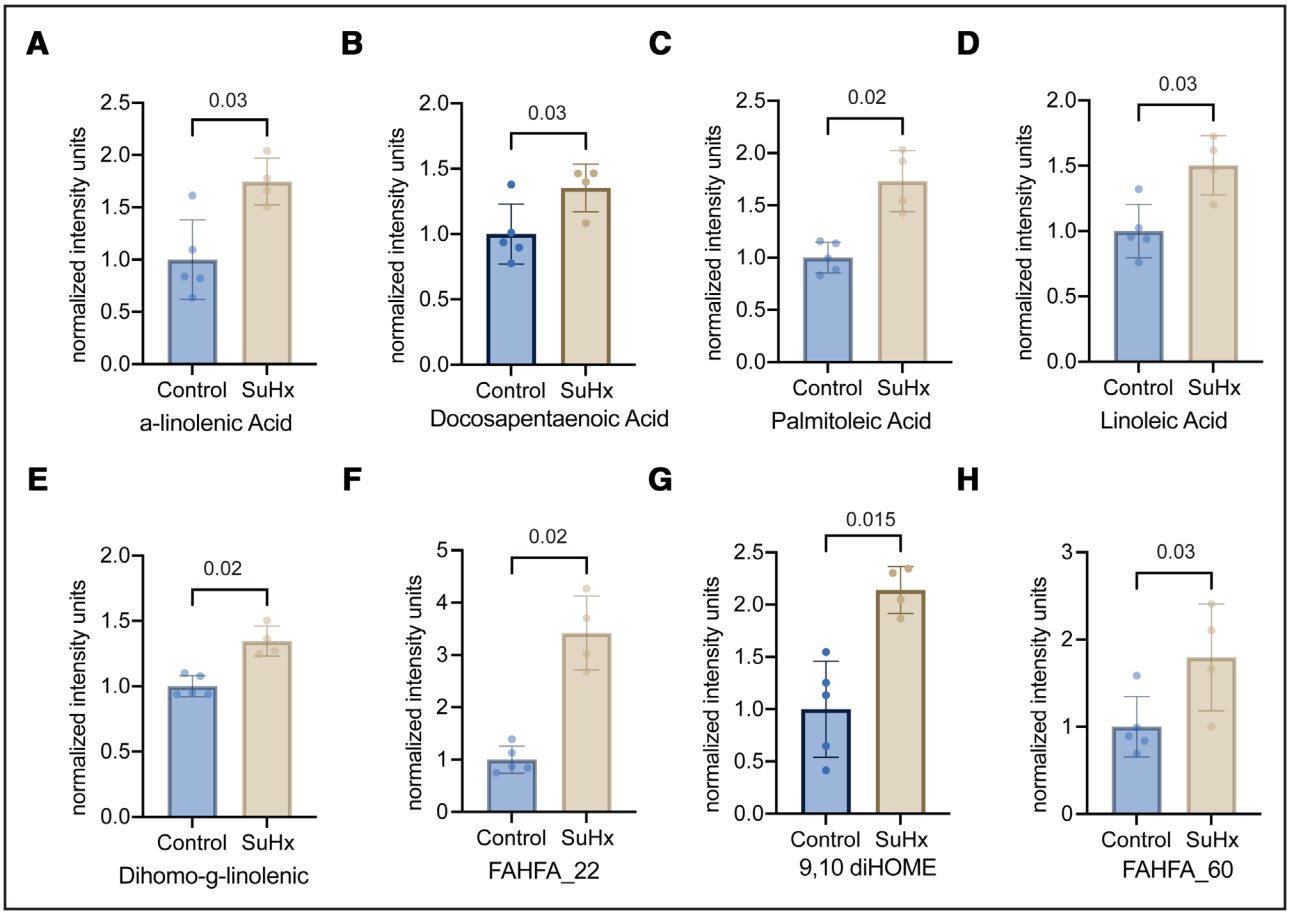


Figure 4. Oxylipins and bioactive lipids in plasma of pulmonary hypertension (PH) animal models.
A through **H**, Levels of selected oxylipins and bioactive lipids are significantly altered in pre- and postcapillary pulmonary hypertension (Cpc-PH) vs isolated postcapillary pulmonary hypertension (Ipc-PH) in the plasma of males Sugen/hypoxia (Su/Hx, N=4) experimental models compared with controls (N=5). Results are derived from unpaired *t* test analyses. **P*<0.05; ***P*<0.01; ****P*<0.001. 9,10-diHOME indicates 9,10-dihydroxy-12-octadecenoic acid; and FAHFA, fatty acid esters of hydroxy fatty acids.

antiinflammatory, pro-resolving and pulmonary vascular relaxant oxylipins. These findings shed light on the pathophysiological underpinnings of Cpc-PH, a morbid yet still poorly understood subtype of PH that coexists with left heart disease. Collectively, these data offer a new view of the molecular pathways underlying Cpc-PH that could be further investigated as potential therapeutic targets for the highest-risk patients with Group 2 PH.

Our metabolomics findings are consistent with previous observations that Cpc-PH may diverge from Ipc-PH while demonstrating notable similarities to PAH.[9,12,30–35] Although Cpc-PH and Ipc-PH have been found to have comparable clinical characteristics and levels of left ventricular dysfunction, Cpc-PH has been associated with a significantly worse hemodynamic profile, severe right ventricular–pulmonary arterial uncoupling, and impaired O_2 delivery and aerobic capacity during exercise.[32,36,37] Genetic analyses also showed that patients with Cpc-PH and PAH shared several common genetic variants, many of which have been previously implicated in pulmonary vascular remodeling.[9] Others have found that targeted therapies used in PAH, such as PDE5 inhibitors, may have some benefit in patients with Cpc-PH but have no role in Ipc-PH.[10,38] These studies suggest that Cpc-PH represents a distinct clinical entity, existing within a continuum that could include PAH.

To our knowledge, this is the first study to examine bioactive lipid mediators in patients with Ipc-PH and Cpc-PH, in comparison with those with PAH, and in conjunction with correlative studies in animal models of severe PH. Similar to PAH and animal models of severe PH, our study found metabolic evidence suggestive of altered lipid metabolism and oxidation, oxidative stress and inflammation that potentially could contribute to endothelial dysfunction and vascular remodeling observed in Cpc-PH. Specifically, MUFAs such as palmitoleic acid have been implicated in various inflammatory, metabolic, and cardiovascular conditions, including increased blood pressure, insulin resistance, and heart failure.[17]

Both ω-3 and ω-6 PUFAs undergo β-oxidation in the peroxisomes and mitochondria, generating diverse eicosanoid and oxylipin mediators that govern vascular tone, endothelial dysfunction, and immune activation.[13] Disruption of these pathways may contribute to the

heightened inflammatory and vasoconstrictive state seen in Cpc-PH.[12,13,17] Among ω-6 PUFAs, adrenic acid and its metabolites modulate prostanoid balance by competing with arachidonic acid for cyclooxygenase enzymes, which can shift the equilibrium toward vasoconstrictive and prothrombotic prostanoids.[39] Adrenic acid accumulation is linked to cytokine activation, oxidative stress, and endothelial injury in cardiometabolic disorders.[40] Furthermore, its incorporation into membrane phospholipids renders it prone to lipid peroxidation and ferroptosis, an iron-dependent form of cell death implicated in pulmonary vascular remodeling and right heart failure. Inhibition of ferroptosis has been shown to attenuate vascular inflammation and remodeling in preclinical models, highlighting its potential therapeutic relevance in PH.[41–43]

Of particular interest were our findings involving linoleic acid and its oxidized derivatives, collectively known as oxidized linoleic acid metabolites, such as 9,10-dihydroxy-12-octadecenoic acid. Linoleic acid metabolism is complex, with derivatives that exert or modulate anti- or proinflammatory activity in a context-dependent manner.[44] These metabolites can activate the nuclear factor kappa-light-chain-enhancer of activated B cells pathway and upregulate vascular cell adhesion molecule-1 in endothelial cells, leading to endothelial dysfunction.[45,46] Bioactive lipids derived from oxidized linoleic acid have been mechanistically linked with a variety of cardiovascular conditions, including PH.[17] Although the field of oxidized linoleic acid metabolite biology remains nascent, dietary modification of precursor fatty acids (eg, α-linolenic acid, γ-linolenic acid) has been shown to influence cardiac maturation, fibrosis, and remodeling in both experimental and human studies.[47] Interestingly, long-term exercise reduces circulating levels of both adrenic acid and oxidized linoleic acid metabolites, representing a potential strategy for mitigating vascular inflammation and remodeling in Group 2 PH.[48]

FAHFAs are an emerging class of bioactive lipids with diverse roles in metabolic and inflammatory regulation. Multiple FAHFA families and regioisomers have been identified, each with distinct biological activities that are highly dependent on isomeric form, tissue distribution and local enzymatic activity.[49–51] FAHFA activity is context dependent: certain species, such as palmitic acid esters of hydroxy stearic acids, demonstrate antiinflammatory and insulin-sensitizing effects,[50] while other FAHFA species are elevated in inflammatory and neoplastic conditions.[52–54] In this study, increased FAHFA levels in Cpc-PH compared with Ipc-PH may reflect either an adaptive response to chronic inflammation or maladaptive lipid accumulation. Further studies are needed to define their isomer-specific and mechanistic roles in PH.

The relatively higher levels of pro-resolving and vasodilatory oxylipins in Ipc-PH compared with Cpc-PH raise the possibility that Cpc-PH may reflect a loss of endogenous resolution and vasodilatory capacity, rather than solely an increase in proinflammatory or vasoconstrictive signaling. However, this interpretation is hypothesis generating, as the cross-sectional nature of our study precludes conclusions about temporal sequence or causality. Longitudinal studies tracking oxylipin profiles during disease progression will be needed to further evaluate this hypothesis.

Study Strengths and Limitations

Several strengths of this study merit consideration. The predominance of women across all 3 groups—76.2% in Ipc-PH, 72.5% in Cpc-PH, and 55.3% in PAH—stands in contrast to most heart failure studies, where women are historically underrepresented, and more accurately reflects the population most commonly affected by these conditions. The use of a comprehensive targeted bioactive lipidomics platform profiling 844 bioactive lipid metabolites represents one of the most granular characterizations of Group 2 PH to date. The inclusion of 3 hemodynamically confirmed PH groups from the same prospective registry, analyzed contemporaneously, minimizes referral and ascertainment biases common to retrospective designs. This study is limited by its cross-sectional design and is therefore only able to detect associations between specific metabolites and selected PH phenotypes. The finding of associations does not imply causality. The absence of external validation cohorts limits the study's generalizability. Additional studies are needed for independent verification of these findings as well as further elucidation of the specific mechanisms by which bioactive metabolites may be involved in the pathogenesis of Cpc-PH. Although analyses adjusted for BMI, detailed measures of fat distribution (eg, visceral or epicardial adiposity), total blood cholesterol, and hemoglobin A1c were not consistently available, limiting our ability to evaluate their potential contribution to the observed metabolic differences. Detailed subclassification of left heart disease (heart failure with preserved ejection fraction [HFpEF], heart failure with mildly reduced ejection fraction [HFmrEF], and heart failure with reduced ejection fraction [HFrEF]) was not systematically available due to limited access to historical echocardiographic data, precluding assessment of differential metabolic patterns across these groups. The use of animal models of severe PAH, however, strengthens our findings. We opted to compare the metabolomic profile of Cpc-PH with the Su/Hx PAH rat model. It is important to note that the Su/Hx model is typically regarded as a model for PAH (Group 1), rather than Group 2 PH. Our rationale for this choice was to investigate the potential for molecular similarities between Cpc-PH, a Group 2 PH, and PAH. In future studies, we plan to investigate Group 2 PH models, such as high-fat/N-nitro-L-arginine methyl ester-treated mice with PH-HFpEF or obese/SU-5416 rats. In addition, the experimental studies were performed exclusively in male

animals, whereas the clinical cohorts were predominantly female; therefore, potential sex-dependent differences in bioactive lipid metabolism and pulmonary vascular remodeling were not evaluated.

Conclusions

In conclusion, Cpc-PH exhibits a distinct molecular signature characterized by elevated PUFAs and FAHFAs and reduced antiinflammatory oxylipins compared with Ipc-PH, closely mirroring that of PAH. These findings highlight shared pathogenic mechanisms and nominate lipid pathways as potential therapeutic targets in Cpc-PH.

ARTICLE INFORMATION

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Disclosures

Dr Chan has served as a consultant for Merck and United Therapeutics. Dr Chan is a director, officer, and shareholder in Synhale Therapeutics. Dr Chan has held grants from United Therapeutics and Bayer. Dr Chan has filed patent applications regarding metabolism and next-generation therapeutics in pulmonary hypertension. Dr Hill has served on the advisory boards of Aerovate, Gossamer, Merck (DMC), and has received research grants from Insmed, Janssen, Liquidia, Respira, and United Therapeutics. The other authors report no conflicts.

Supplemental Material

Tables S1–S4

REFERENCES

1. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J*. 2016;37:942–954. doi: 10.1093/eurheartj/ehv512
2. Weitsman T, Weisz G, Farkash R, Klutstein M, Butnaru A, Rosenmann D, Hasin T. Pulmonary hypertension with left heart disease: prevalence, temporal shifts in etiologies and outcome. *Am J Med*. 2017;130:1272–1279. doi: 10.1016/j.amjmed.2017.05.003
3. Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. *Eur Respir J*. 2019;53:1801897. doi: 10.1183/13993003.01897-2018
4. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol*. 2017;69:1718–1734. doi: 10.1016/j.jacc.2017.01.051
5. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–3731. doi: 10.1093/eurheartj/ehac237
6. Inampudi C, Silverman D, Simon MA, Leary PJ, Sharma K, Houston BA, Vachiéry JL, Haddad F, Tedford RJ. Pulmonary hypertension in the context of heart failure with preserved ejection fraction. *Chest*. 2021;160:2232–2246. doi: 10.1016/j.chest.2021.08.039
7. Maron BA, Bortman G, De Marco T, Huston JH, Lang IM, Rosenkranz SH, Vachiéry JL, Tedford RJ. Pulmonary hypertension associated with left heart disease. *Eur Respir J*. 2024;64:2401344. doi: 10.1183/13993003.01344-2024
8. Ibe T, Wada H, Sakakura K, Ugata Y, Maki H, Yamamoto K, Seguchi M, Taniguchi Y, Jinnouchi H, Momomura SI, et al. Combined pre- and post-capillary pulmonary hypertension: the clinical implications for patients with heart failure. *PLoS One*. 2021;16:e0247987. doi: 10.1371/journal.pone.0247987
9. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, et al. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. *J Am Coll Cardiol*. 2016;68:2525–2536. doi: 10.1016/j.jacc.2016.09.942
10. Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, Scelsi L, D'Alto M, Olsson KM, Ulrich S, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: a pathophysiological continuum. *J Am Coll Cardiol*. 2016;68:368–378. doi: 10.1016/j.jacc.2016.05.047
11. Ding M, Rexrode KM. A review of lipidomics of cardiovascular disease highlights the importance of isolating lipoproteins. *Metabolites*. 2020;10:163. doi: 10.3390/metabo10040163
12. Aradhyula V, Vyas R, Dube P, Haller ST, Gupta R, Maddipati KR, Kennedy DJ, Khouri SJ. Novel insights into the pathobiology of pulmonary hypertension in heart failure with preserved ejection fraction. *Am J Physiol Heart Circ Physiol*. 2024;326:H1498–H1514. doi: 10.1152/ajpheart.00068.2024
13. Wang J, Hu S, Xu Y, Wang T. Omega-6 polyunsaturated fatty acids and their metabolites: a potential targeted therapy for pulmonary hypertension. *Respir Res*. 2025;26:102. doi: 10.1186/s12931-025-03172-2
14. Allen BJ, Frye H, Ramanathan R, Caggiano LR, Tabima DM, Chesler NC, Philip JL. Biomechanical and mechanobiological drivers of the transition from postcapillary pulmonary hypertension to combined pre-/postcapillary pulmonary hypertension. *J Am Heart Assoc*. 2023;12:e028121. doi: 10.1161/JAHA.122.028121
15. Al-Husseini A, Wijesinghe DS, Farkas L, Kraskauskas D, Drake JI, Van Tassel B, Abbate A, Chalfant CE, Voelkel NF. Increased eicosanoid levels in the Sugen/chronic hypoxia model of severe pulmonary hypertension. *PLoS One*. 2015;10:e0120157. doi: 10.1371/journal.pone.0120157
16. Al-Naamani N, Sagliani KD, Dolnikowski GG, Warburton RR, Toksoz D, Kayyali U, Hill NS, Fanburg BL, Roberts KE, Preston IR. Plasma 12- and 15-hydroxyeicosanoids are predictors of survival in pulmonary arterial hypertension. *Pulm Circ*. 2016;6:224–233. doi: 10.1086/686311
17. McNeill JN, Roshandelpoor A, Alotaibi M, Choudhary A, Jain M, Cheng S, Zarbafian S, Lau ES, Lewis GD, Ho JE. The association of eicosanoids and eicosanoid-related metabolites with pulmonary hypertension. *Eur Respir J*. 2023;62:2300561. doi: 10.1183/13993003.00561-2023
18. Alotaibi M, Shao J, Pauciulo MW, Nichols WC, Hemnes AR, Malhotra A, Kim NH, Yuan JX, Fernandes T, Kerr KM, et al. Metabolomic profiles differentiate scleroderma-PAH from idiopathic PAH and correspond with worsened functional capacity. *Chest*. 2023;163:204–215. doi: 10.1016/j.chest.2022.08.2230
19. Nayeem MA. Role of oxylipins in cardiovascular diseases. *Acta Pharmacol Sin*. 2018;39:1142–1154. doi: 10.1038/aps.2018.24
20. Lau ES, Roshandelpoor A, Zarbafian S, Wang D, Guseh JS, Allen N, Varadarajan V, Nayor M, Shah RV, Lima JAC, et al. Eicosanoid and eicosanoid-related inflammatory mediators and exercise intolerance in heart failure with preserved ejection fraction. *Nat Commun*. 2023;14:7557. doi: 10.1038/s41467-023-43363-3
21. Ding J, Chu C, Mao Z, Yang J, Wang J, Hu L, Chen P, Cao Y, Li Y, Wan H, et al. Metabolomics-based mechanism exploration of pulmonary arterial hypertension pathogenesis: novel lessons from explanted human lungs. *Hypertens Res*. 2022;45:990–1000. doi: 10.1038/s41440-022-00898-0
22. Pi H, Xia L, Ralph DD, Rayner SG, Shojaie A, Leary PJ, Gharib SA. Metabolomic signatures associated with pulmonary arterial hypertension outcomes. *Circ Res*. 2023;132:254–266. doi: 10.1161/CIRCRESAHA.122.321923
23. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. doi: 10.1183/13993003.01913-2018

24. Maron BA, Oldham WM, Chan SY, Vargas SO, Arons E, Zhang YY, Loscalzo J, Leopold JA. Upregulation of steroidogenic acute regulatory protein by hypoxia stimulates aldosterone synthesis in pulmonary artery endothelial cells to promote pulmonary vascular fibrosis. *Circulation*. 2014;130:168–179. doi: 10.1161/CIRCULATIONAHA.113.007690
25. Watrous JD, Niiranen TJ, Lagerborg KA, Henglin M, Xu YJ, Rong J, Sharma S, Vasan RS, Larson MG, Armando A, et al. Directed non-targeted mass spectrometry and chemical networking for discovery of eicosanoids and related oxylipins. *Cell Chem Biol*. 2019;26:433–442.e4. doi: 10.1016/j.chembiol.2018.11.015
26. Henglin M, Claggett BL, Antonelli J, Alotaibi M, Magalang GA, Watrous JD, Lagerborg KA, Ovsak G, Musso G, Demler OV, et al. Quantitative comparison of statistical methods for analyzing human metabolomics data. *Metabolites*. 2022;12:519. doi: 10.3390/metabo12060519
27. Rood KM, Patel N, DeVengencie IM, Quinn JP, Gowdy KM, Costantine MM, Kniss DA. Aspirin modulates production of pro-inflammatory and pro-resolving mediators in endothelial cells. *PLoS One*. 2023;18:e0283163. doi: 10.1371/journal.pone.0283163
28. Hoshi RA, Alotaibi M, Liu Y, Watrous JD, Ridker PM, Glynn RJ, Serhan CN, Luttmann-Gibson H, Moorthy MV, Jain M, et al. One-year effects of high-intensity statin on bioactive lipids: findings from the JUPITER trial. *Arterioscler Thromb Vasc Biol*. 2024;44:e196–e206. doi: 10.1161/ATVBAHA.124.321058
29. Matsuda H, Miyatake K, Dahlén SE. Pharmacodynamics of 15(S)-hydroperoxyeicosatetraenoic (15-HPETE) and 15(S)-hydroxyeicosatetraenoic acid (15-HETE) in isolated arteries from guinea pig, rabbit, rat and human. *J Pharmacol Exp Ther*. 1995;273:1182–1189
30. Brittain EL, Hemnes AR. Moment on the lips, a lifetime on the lungs?: improving models of group 2 pulmonary hypertension. *Circ Res*. 2019;125:467–469. doi: 10.1161/CIRCRESAHA.119.315478
31. Meoli DF, Su YR, Brittain EL, Robbins IM, Hemnes AR, Monahan K. The transpulmonary ratio of endothelin 1 is elevated in patients with preserved left ventricular ejection fraction and combined pre- and post-capillary pulmonary hypertension. *Pulm Circ*. 2018;8:2045893217745019. doi: 10.1177/2045893217745019
32. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013;1:290–299. doi: 10.1016/j.jchf.2013.05.001
33. Bassareo PP, D'Alto M. Metabolomics in pulmonary hypertension-a useful tool to provide insights into the dark side of a tricky pathology. *Int J Mol Sci*. 2023;24:13227. doi: 10.3390/ijms241713227
34. Gerges C, Gerges M, Fesler P, Pistritto AM, Konowitz NP, Jakowitsch J, Celermajer DS, Lang IM. In-depth haemodynamic phenotyping of pulmonary hypertension due to left heart disease. *Eur Respir J*. 2018;51:1800067. doi: 10.1183/13993003.00067-2018
35. van de Veerdonk MC, Roosma L, Trip P, Gopalan D, Vonk Noordegraaf A, Dorfmüller P, Nossent EJ. Clinical-imaging-pathological correlation in pulmonary hypertension associated with left heart disease. *Eur Respir Rev*. 2024;33:230144. doi: 10.1183/16000617.0144-2023
36. Assad TR, Brittain EL, Wells QS, Farber-Eger EH, Halliday SJ, Doss LN, Xu M, Wang L, Harrell FE, Yu C, et al. Hemodynamic evidence of vascular remodeling in combined post- and precapillary pulmonary hypertension. *Pulm Circ*. 2016;6:313–321. doi: 10.1086/688516
37. Omote K, Sorimachi H, Obokata M, Reddy YNV, Verbrugge FH, Omar M, DuBrock HM, Redfield MM, Borlaug BA. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications. *Eur Heart J*. 2022;43:3417–3431. doi: 10.1093/eurheartj/ehac184
38. Kramer T, Dumitrescu D, Gerhardt F, Orlova K, Ten Freyhaus H, Hellmich M, Baldus S, Rosenkranz S. Therapeutic potential of phosphodiesterase type 5 inhibitors in heart failure with preserved ejection fraction and combined post- and pre-capillary pulmonary hypertension. *Int J Cardiol*. 2019;283:152–158. doi: 10.1016/j.ijcard.2018.12.078
39. Dong L, Zou H, Yuan C, Hong YH, Kuklev DV, Smith WL. Different fatty acids compete with arachidonic acid for binding to the allosteric or catalytic subunits of cyclooxygenases to regulate prostanoid synthesis. *J Biol Chem*. 2016;291:4069–4078. doi: 10.1074/jbc.M115.698001
40. Horas H Nababan S, Nishiumi S, Kawano Y, Kobayashi T, Yoshida M, Azuma T. Adrenic acid as an inflammation enhancer in non-alcoholic fatty liver disease. *Arch Biochem Biophys*. 2017;623-624:64–75. doi: 10.1016/j.abb.2017.04.009
41. Vogel NT, Annis J, Prisco SZ, Mancripe NL, Blake ML, Brittain EL, Prins KW, Kazmirczak F. Ferroptosis promotes pulmonary hypertension. *bioRxiv*. 2023. doi: 10.1101/2023.01.19.524721
42. Xie SS, Deng Y, Guo SL, Li JQ, Zhou YC, Liao J, Wu DD, Lan WF. Endothelial cell ferroptosis mediates monocrotaline-induced pulmonary hypertension in rats by modulating NLRP3 inflammasome activation. *Sci Rep*. 2022;12:3056. doi: 10.1038/s41598-022-06848-7
43. Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. *Nat Chem Biol*. 2017;13:81–90. doi: 10.1038/nchembio.2238
44. Mustonen AM, Nieminen P. Dihomo-γ-linolenic acid (20:3n-6)-metabolism, derivatives, and potential significance in chronic inflammation. *Int J Mol Sci*. 2023;24:2116. doi: 10.3390/ijms24032116
45. Dichtl W, Ares MP, Jönson AN, Jovinge S, Pachinger O, Giachelli CM, Hamsten A, Eriksson P, Nilsson J. Linoleic acid-stimulated vascular adhesion molecule-1 expression in endothelial cells depends on nuclear factor-kappaB activation. *Metabolism*. 2002;51:327–333. doi: 10.1053/meta.2002.29963
46. Hennig B, Lei W, Arzuaga X, Ghosh DD, Saraswathi V, Toborek M. Linoleic acid induces proinflammatory events in vascular endothelial cells via activation of PI3K/Akt and ERK1/2 signaling. *J Nutr Biochem*. 2006;17:766–772. doi: 10.1016/j.jnutbio.2006.01.005
47. Oppedisano F, Mollace R, Tavernese A, Gliozzi M, Musolino V, Macrì R, Carresi C, Maiuolo J, Serra M, Cardamone A, et al. PUFA supplementation and heart failure: effects on fibrosis and cardiac remodeling. *Nutrients*. 2021;13:2965. doi: 10.3390/nu13092965
48. Jurado-Fasoli L, Di X, Sanchez-Delgado G, Yang W, Osuna-Prieto FJ, Ortiz-Alvarez L, Krekels E, Harms AC, Hankemeier T, Schönke M, et al. Acute and long-term exercise differently modulate plasma levels of oxylipins, endocannabinoids, and their analogues in young sedentary adults: a substudy and secondary analyses from the ACTIBATE randomized controlled-trial. *EBioMedicine*. 2022;85:104313. doi: 10.1016/j.ebiom.2022.104313
49. Tan D, Saghatelian A. The measurement, regulation and biological activity of FAHFAs. *Nat Chem Biol*. 2025;21:796–806. doi: 10.1038/s41589-024-01827-7
50. Riecan M, Paluchova V, Lopes M, Brejchova K, Kuda O. Branched and linear fatty acid esters of hydroxy fatty acids (FAHFA) relevant to human health. *Pharmacol Ther*. 2022;231:107972. doi: 10.1016/j.pharmthera.2021.107972
51. Brejchova K, Balas L, Paluchova V, Brezinova M, Durand T, Kuda O. Understanding FAHFAs: from structure to metabolic regulation. *Prog Lipid Res*. 2020;79:101053. doi: 10.1016/j.plipres.2020.101053
52. Hu C, Du Y, Xu X, Li H, Duan Q, Xie Z, Wen C, Han X. Lipidomics revealed aberrant metabolism of lipids including FAHFAs in renal tissue in the progression of lupus nephritis in a murine model. *Metabolites*. 2021;11:142. doi: 10.3390/metabo11030142
53. Rodríguez JP, Guijas C, Astudillo AM, Rubio JM, Balboa MA, Balsinde J. Sequestration of 9-hydroxystearic acid in FAHFA (Fatty Acid Esters of Hydroxy Fatty Acids) as a protective mechanism for colon carcinoma cells to avoid apoptotic cell death. *Cancers (Basel)*. 2019;11:524. doi: 10.3390/cancers11040524
54. Hirao-Suzuki M, Koga T, Sakai G, Kobayashi T, Ishii Y, Miyazawa H, Takiguchi M, Sugihara N, Toda A, Ohara M, et al. Fatty acid 2-hydroxylase (FA2H) as a stimulatory molecule responsible for breast cancer cell migration. *Biochem Biophys Res Commun*. 2020;531:215–222. doi: 10.1016/j.bbrc.2020.07.043