CHEST

Pulmonary Artery Enlargement Is Associated With Cardiac Injury During Severe Exacerbations of COPD

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BACKGROUND: Relative pulmonary arterial enlargement, defined by a pulmonary artery to aorta (PA/A) ratio > 1 on CT scanning, predicts hospitalization for acute exacerbations of COPD (AECOPD). However, it is unclear how AECOPD affect the PA/A ratio. We hypothesized that the PA/A ratio would increase at the time of AECOPD and that a ratio > 1 would be associated with worse clinical outcomes.

METHODS: Patients discharged with an *International Classification of Diseases, Ninth Revision,* diagnosis of AECOPD from a single center over a 5-year period were identified. Patients were included who had a CT scan performed during the stable period prior to the index AECOPD episode as well as a CT scan at the time of hospitalization. A subset of patients also underwent postexacerbation CT scans. The pulmonary arterial diameter, ascending aortic diameter, and the PA/A ratio were measured on CT scans. Demographic data, comorbidities, troponin level, and hospital outcome data were analyzed.

RESULTS: A total of 134 patients were included in the study. They had a mean age of 65 ± 10 years, 47% were male, and 69% were white; overall, patients had a mean FEV_1 of 47% ± 19%. The PA/A ratio increased from baseline at the time of exacerbation (0.97 ± 0.15 from 0.91 ± 0.17; $P < .001$). Younger age and known pulmonary hypertension were independently associated with an exacerbation PA/A ratio > 1. Patients with PA/A ratio > 1 had higher troponin values. Those with a PA/A ratio > 1 and troponin levels > 0.01 ng/mL had increased acute respiratory failure, ICU admission, or inpatient mortality compared with those without both factors ($P = .0028$). The PA/A ratio returned to baseline values following AECOPD.

CONCLUSIONS: The PA/A ratio increased at the time of severe AECOPD and a ratio > 1 predicted cardiac injury and a more severe hospital course. CHEST 2016; 149(5):1197-1204

KEY WORDS: acute exacerbation of COPD; COPD; CT scan; enzymes (cardiology); pulmonary circulation

ABBREVIATIONS: AECOPD = acute exacerbations of COPD; ANOVA = analysis of variance; BNP = brain natriuretic peptide; CHF = congestive heart failure; PA/A = pulmonary artery to aorta; UAB = University of Alabama at Birmingham

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COPD is a complex disease of airflow limitation accompanied by significant extrapulmonary effects that have major health implications.[1] Acute exacerbations of COPD (AECOPD) are critical events in the natural history of COPD and are a significant cause of morbidity and mortality, accounting for more than $11 billion in direct costs annually.[2-4] AECOPD are defined by an increase in dyspnea, sputum purulence, and sputum volume that warrant a change in therapy.[1] Although these events are typically caused by viral or bacterial infections,[5,6] cardiovascular and pulmonary vascular causes have been implicated in precipitating up to 25% of AECOPD.[7-9]

Pulmonary vascular disease and cardiovascular disease often coexist with COPD and have major effects on its disease course.[10] Pulmonary hypertension in the setting of COPD is associated with accelerated loss of lung function, increased risk for AECOPD, and death.[11-13] Likewise, patients with COPD are at increased risk for hospitalization and mortality related to underlying acute myocardial infarction, congestive heart failure (CHF), or pulmonary thromboembolism.[14,15] Insight into the cardiopulmonary interactions that occur during acute exacerbations is therefore of major importance.[16]

We have previously identified the pulmonary artery to aorta (PA/A) ratio as a noninvasive marker of pulmonary vascular disease[17] that predicts the development of AECOPD, including severe episodes requiring hospitalization.[18] In fact, pulmonary arterial enlargement, defined as a PA/A ratio > 1, outperforms traditional risk factors for development of AECOPD, including prior exacerbations, FEV_1, St George's Respiratory Questionnaire score, and gastroesophageal reflux.[19] Although these studies established the PA/A ratio as a clinically useful tool, little is known about the longitudinal stability of the metric, how it changes during AECOPD, and whether it could lend insight into the pathophysiology of these events. We hypothesized that the PA/A ratio increases from baseline at the time of severe AECOPD (defined by hospitalization) and that patients with pulmonary arterial enlargement would be at risk for greater cardiac injury and worse clinical outcomes.

Methods

Study Population and Design

We identified 2,066 patients discharged from the University of Alabama at Birmingham (UAB) Hospital with AECOPD as indicated by using codes from the *International Classification of Diseases, Ninth Revision* (490-492 or 496 as the primary diagnosis code or as secondary with 518.18 [respiratory failure] as primary) between January 1, 2007 and December 31, 2011 (Fig 1). Patients were included in the study if they had a baseline CT scan (defined as a

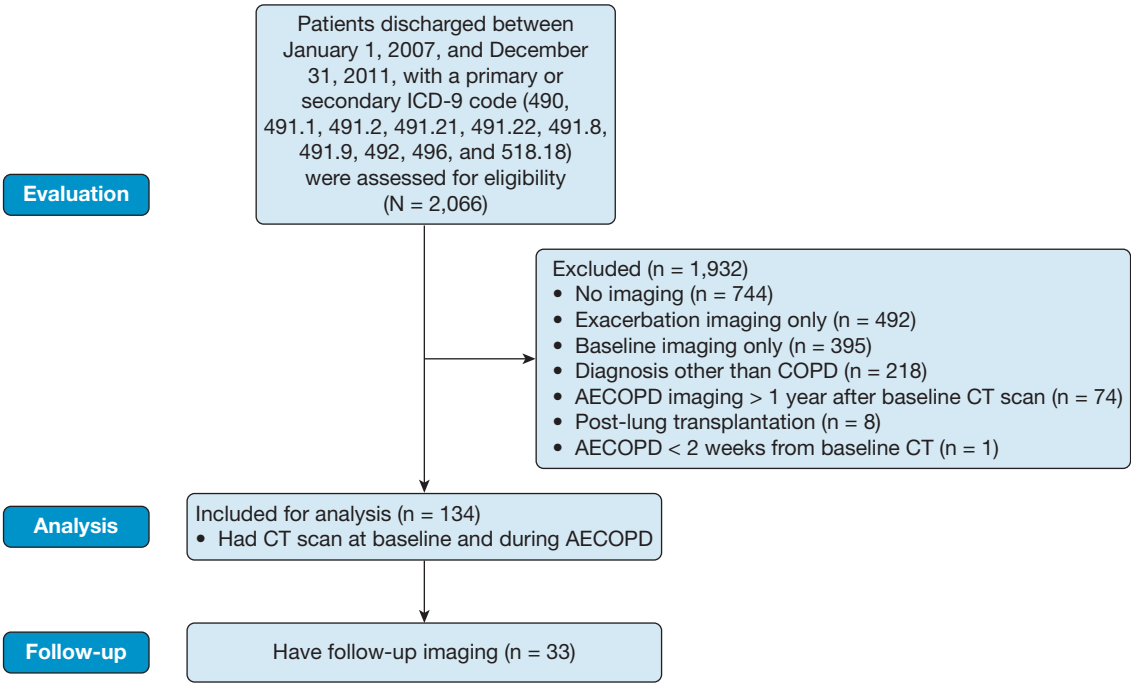

Figure 1 – *Patient flow diagram. AECOPD = acute exacerbations of COPD; ICD-9* = International Classification of Diseases, Ninth Revision.

scan performed during the stable state preceding the index hospitalization) plus an exacerbation scan (defined as a CT scan obtained during the hospitalization for AECOPD) within 12 months of each other. Although not required for inclusion in the study, follow-up CT scans were analyzed and were defined as a CT scan obtained between 1 and 12 months following the index hospitalization in the subgroup that had these data. Patients were excluded from the analysis if they undergone a lung transplantation or if acute pulmonary embolism was present on the AECOPD scan. The latter were excluded to minimize confounder bias based on known associations between acute pulmonary embolism, PA size, and outcomes.[20-22] This study was approved by the UAB Institutional Review Board (number X120730004).

Exacerbation Determination and Parameter Collection

Patients were identified by using *International Classification of Diseases, Ninth Revision,* coding, and detailed chart reviews were then performed via the electronic medical record system used by the UAB Hospital (Cerner IMPACT, Kansas City, Missouri). A pulmonologist (J. B. M.) reviewed all cases and included only patients who met the following criteria according to a standard abstraction tool: enhanced dyspnea with increased cough lasting $>$ 48 h with either increased sputum volume or purulence prompting an ED visit. We recorded age at the time of admission, sex, race, BMI, smoking status, pack-year smoking history, and pulmonary function measurements (prebronchodilator FEV_1, FVC, and FEV_1/FVC ratio), as well as comorbidities (hypertension, coronary artery disease, CHF, obstructive sleep apnea, history of venous thromboembolic disease, gastroesophageal reflux, and known pulmonary hypertension). Any condition listed in the medical history from the admission history and physical examination was included as comorbidity. Outcome variables included length of hospital stay, need for ICU stay, acute respiratory failure defined by the need for noninvasive ventilation or invasive mechanical ventilation, in-hospital mortality, and serum troponin and brain natriuretic peptide (BNP) levels at admission.

Review of Imaging

Chest CT images were viewed by using the iSite digital image viewer (Philips Medical Systems). A single blinded reviewer measured the pulmonary arterial diameters in the tubular portion of the main pulmonary artery at the level of its bifurcation and the mean of two perpendicular measurements of the ascending aorta to represent the aortic diameter, as previously reported (Fig 2).[17,18,23] The median time between baseline and AECOPD scans was 99 days (range, 7-352 days) and 103 days (range, 35-299 days) between AECOPD and follow-up imaging. Reviewers of the CT scans were blinded to all other clinical data.

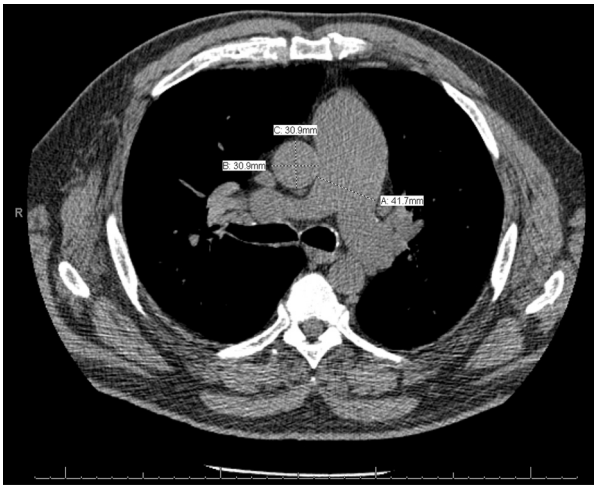

Figure 2 – *Pulmonary artery enlargement measured on CT scans. The pulmonary arterial diameter (A) and perpendicular measurements of the ascending aortic diameter (B and C) are measured on the same axial CT image to calculate the pulmonary artery to aorta ratio.*

Statistical Analysis

Baseline data were expressed as means ± SDs for normally distributed values or median with interquartile ranges for nonnormally distributed values; continuous variables were compared by using two-sided Student *t* tests or Mann-Whitney *U* tests as appropriate. Categorical variables were examined by using the Fisher exact test. Univariate and multivariate backward logistic regression analyses were used to determine associations between demographic characteristics and comorbidity variables and a PA/A ratio $>$ 1 at the time of hospital admission. Student *t* tests and the Fisher exact test were used to measure differences between outcome variables in patients with a PA/A ratio $>$ 1 at admission and those with a PA/A ratio $<$ 1. An analysis of variance (ANOVA) with Tukey's multiple comparison testing and posttests for linear trends were used to evaluate the differences in clinical outcomes between the group of patients with a PA/A ratio $>$ 1 plus a troponin level $>$ 0.01 ng/mL at admission compared with the group with only one positive variable versus those with neither. Paired *t* tests or repeated measures ANOVA were used to evaluate the differences in pulmonary arterial diameter, ascending aortic diameter, and the PA/A ratio over time.

SPSS for Windows version 22 (IBM SPSS Statistics, IBM Corporation) was used for all analyses, and figures were designed in Prism Version 5 (GraphPad Software, Inc). Statistical tests were two-sided, and significance was assigned to tests with *P* values $<$ .05.

Results

Baseline Characteristics

A total of 134 patients were included in the analysis. Patients had a mean age of 65 ± 10 years, 47% were male, 69% were white, and 40% were current smokers; all had airflow obstruction, with a mean FEV_1 of 47% ± 19% predicted (Table 1). Comorbid conditions included hypertension (70%), coronary artery disease (31%), CHF (29%), sleep apnea (19%), thromboembolic disease (19%), gastroesophageal reflux disease (37%), and known pulmonary hypertension (12%). The pulmonary arterial diameter was 2.88 ± 0.52 cm, the ascending aortic diameter was 3.21 ± 0.44 cm, and the PA/A ratio was 0.91 ± 0.17, corresponding to a baseline PA/A ratio $>$ 1 in 35 (26%) patients of the cohort (Table 2).

Changes to the PA/A Ratio at the Time of AECOPD

At the time of hospitalization, the pulmonary arterial diameter increased to 3.07 ± 0.49 cm (P $<$ .001

TABLE 1] Baseline Characteristics at the Time of Index Admission for AECOPD

Characteristic	All (N = 134)	PA/A < 1 (n = 77)	PA/A > 1 (n = 57)	*P* Value
Age, y[a]	65 ± 10	67 ± 10	63 ± 10	.025
White race	93 (69)	57 (74)	36 (63)	.181
Male sex	63 (47)	39 (51)	24 (42)	.383
BMI, kg/m^2	26.8 ± 8.0	25.7 ± 6.4	28.2 ± 9.7	.203
Hypertension	94 (70)	51 (66)	43 (75)	.340
CAD	42 (31)	20 (26)	22 (39)	.135
CHF	39 (29)	17 (22)	22 (39)	.054
OSA	26 (19)	11 (14)	15 (26)	.121
VTE	25 (19)	13 (17)	12 (21)	.655
GERD	50 (37)	28 (36)	22 (39)	.857
Known PH[b]	16 (12)	4 (5)	12 (21)	.007
Current smoker	53 (40)	30 (39)	23 (40)	.999
Pack-year tobacco	52 ± 32	51 ± 32	53 ± 32	.684
Supplemental oxygen use	76 (57)	38 (49)	38 (67)	.054
FEV_1, percent predicted	47 ± 19	45 ± 17	48 ± 20	.363
FEV_1/FVC ratio	52 ± 15	50 ± 13	55 ± 16	.100

Data are represented as mean ± SD or No. (%). AECOPD = acute exacerbation of COPD; CAD = coronary artery disease; CHF = congestive heart failure; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; PH = pulmonary hypertension; VTE = venous thromboembolism.
[a]$P < .05$ by two-sided Student *t* test.
[b]$P < .01$ by the Fisher exact test.

compared with baseline), and the PA/A ratio increased to 0.97 ± 0.15 ($P < .001$ compared with baseline), with no change in the ascending aortic diameter (Table 2). At the time of exacerbation, 57 patients (43%) had a PA/A ratio > 1 (Table 1). Patients with a PA/A ratio > 1 at admission were younger (63 ± 10 years vs 67 ± 10 years; $P = .025$) and had higher rates of known pulmonary hypertension (21% vs 5%; $P = .007$) than those with an exacerbation PA/A ratio < 1. Clinical factors associated with a PA/A ratio > 1 at the time of AECOPD according to univariate logistic regression analysis included the following: age (OR, 0.96; 95% CI, 0.93-0.99; $P = .027$), CHF (OR, 2.18; 95% CI, 1.02-4.66; $P = .044$), home use of supplemental oxygen (OR, 2.05; 95% CI, 1.01-4.17; $P = .047$), and known pulmonary hypertension (OR, 4.87; 95% CI, 1.48-16.0; $P = .009$). Of these factors, age (OR, 0.95; 95% CI, 0.91-0.99; $P = .031$) and known pulmonary hypertension (OR, 5.77; 95% CI, 1.44-21.2; $P = .013$) were independently associated with a PA/A ratio > 1 at exacerbation on multivariate logistic regression analysis; this analysis adjusted for age, race, sex, FEV_1 percent predicted, CHF, supplemental oxygen use, and known pulmonary hypertension.

Associations Between the PA/A Ratio and Markers of Cardiovascular Injury and Exacerbation Severity

As seen in Figure 3, patients with a PA/A ratio > 1 at the time of hospitalization had increased serum troponin levels (0.13 ± 0.04 ng/mL vs 0.06 ± 0.01 ng/mL; $P = .043$) with no difference in BNP (433 ± 123 pg/mL vs 434 ± 140 pg/mL; $P = .407$). We evaluated the contribution of a PA > 1 and a troponin level > 0.01 ng/mL to the risk of ICU admission, acute respiratory failure, or in-hospital mortality. Patients

TABLE 2] Changes in PA Size in the Setting of AECOPD

Variable	Baseline (n = 134)	Exacerbation (n = 134)	Follow-up (n = 33)
PA, cm	2.88 ± 0.52	3.07 ± 0.49[a]	2.85 ± 0.56[b]
A, cm	3.21 ± 0.44	3.12 ± 0.40	3.15 ± 0.42
PA/A	0.91 ± 0.17	0.97 ± 0.15[a]	0.91 ± 0.15[b]

Data are presented as mean ± SD. Paired *t* tests were used to detect differences between baseline and exacerbation-related values. A = aorta; PA = pulmonary artery; PA/A = pulmonary artery to aorta ratio. See Table 1 for expansion of other abbreviation.
[a]$P < .001$ between baseline and exacerbation values.
[b]$P < .001$ between exacerbation and follow-up values according to paired Student *t* tests.

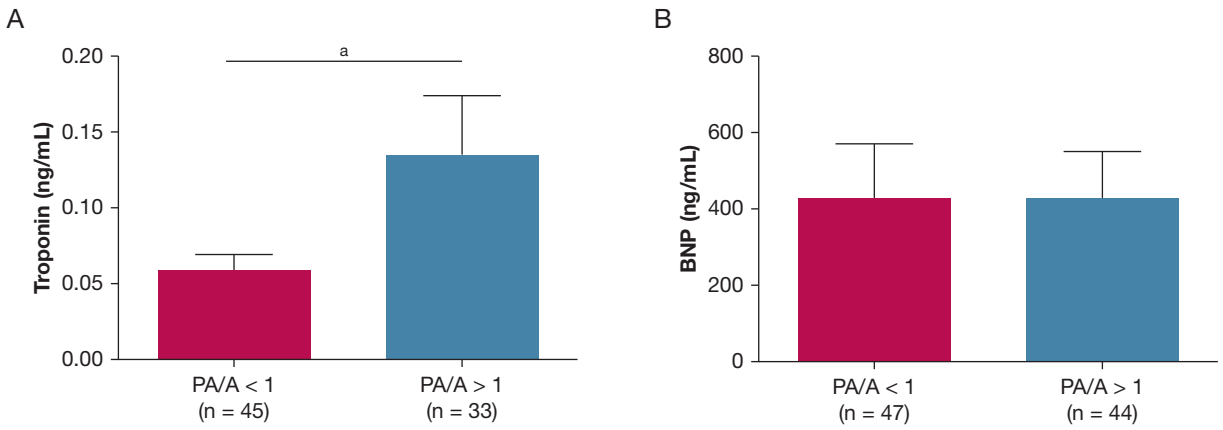

Figure 3 – *Enlargement in pulmonary arterial diameter is associated with increased cardiac injury during AECOPD. A, Serum troponin levels are increased at hospital admission in patients with a PA/A ratio > 1. B, There are no differences between admission serum BNP levels in patients with and without enlargement in pulmonary arterial diameter.* [a]*P < .05 according to Student t test.BNP = brain natriuretic peptide; PA/A = pulmonary artery to aorta ratio. See Figure 1 legend for expansion of other abbreviation.*

who had both a PA/A ratio > 1 and a troponin level > 0.01 ng/mL were more likely to have one of these outcomes vs patients with a PA/A ratio < 1 and troponin levels < 0.01 ng/mL (57% vs 19%; $P = .001$ according to the Fisher exact test). Thirty-nine percent of patients with either a PA/A ratio > 1 or a troponin level > 0.01 ng/mL at admission developed acute respiratory failure, required ICU admission, or died in the hospital ($P = .0029$ by one-way ANOVA, $P = .0008$ for linear trend between groups) (Fig 4). There was no difference in hospital duration (8.6 ± 1.5 days vs 7.0 ± 1.0 days; $P = .36$) for patients with a PA/A ratio > 1 compared with those with a PA/A ratio < 1.

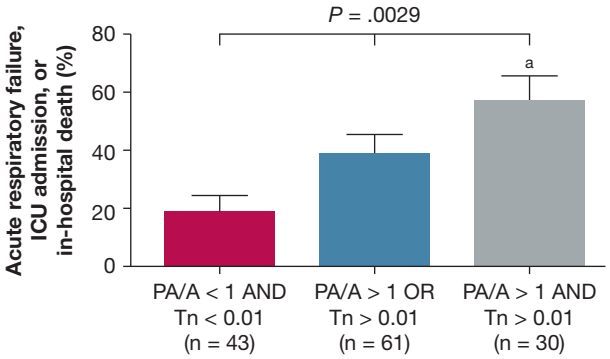

Figure 4 – *Association between enlargement of pulmonary arterial diameter and severity outcomes during AECOPD. Patients with a PA/A ratio > 1 and a Tn level > 0.01 ng/mL at the time of AECOPD had a higher rate of respiratory failure, ICU admission, or in-hospital mortality (59%) vs those with either a PA/A ratio > 1 or Tn level > 0.01 ng/mL (39%) and vs those with a PA/A ratio < 1 and a Tn level > 0.01 ng/mL (19%; P = .0008 for linear trend between groups, P = .0029 by one-way analysis of variance).* [a]*P = .001 between the PA/A ratio < 1 and Tn level < 0.01 ng/mL group and the PA/A ratio > 1 and Tn level > 0.01 ng/mL group by one-way analysis of variance with a Tukey post hoc analysis. Tn = troponin. See Figure 1 and 3 legends for other abbreviations.*

There was no association between the change in PA/A ratio from baseline to exacerbation and either serum troponin levels or clinical outcomes.

Changes in the PA/A Ratio Following Index Hospitalization for AECOPD

Thirty-three patients had follow-up imaging (Table 2). The mean pulmonary arterial diameter and the PA/A ratio significantly decreased to 2.85 ± 0.56 cm and 0.91 ± 0.15, respectively, compared with AECOPD values ($P < .001$ for both). The follow-up pulmonary arterial diameter and PA/A values were not statistically different from baseline values. The ascending aortic diameter was not statistically different during exacerbation or follow-up compared with baseline.

Discussion

This study shows, for the first time, that the PA/A ratio increases during AECOPD, that enlargement of the pulmonary artery at the time of hospitalization is associated with markers of cardiac injury, and that the acute increase in pulmonary arterial size recovers to baseline following the event. The increase in the PA/A ratio was driven by changes in the diameter of the pulmonary artery, as the aortic diameter remained relatively constant at all three time points. These findings build on our prior observations relating pulmonary arterial enlargement to the risk of severe AECOPD by demonstrating that changes to size occur during hospitalization, are associated with cardiac injury, and may portend a worse prognosis.

Although we showed that both the pulmonary arterial diameter and PA/A increase during AECOPD, the

mechanism for this change remains uncertain. As Boerrigter et al[24] reported in patients with pulmonary arterial hypertension, progressive enlargement in the pulmonary arterial diameter measured by using cardiac MRI occurs independent of changes in hemodynamics. A possible explanation for this phenomenon is that underlying pulmonary vascular disease decreases pulmonary arterial wall distensibility during stability,[25,26] but the reduced vascular distensibility is overcome during AECOPD by factors such as dynamic hyperinflation, altered gas exchange, hypoxic vasoconstriction, increased circulating volume (pulmonary edema or diastolic dysfunction), increased cardiac output, and inflammation.[27-29] Following exacerbations, the vessel returns to its normal size due to its impaired distensibility. In addition, these acute changes could be exaggerated by centralization of blood flow, similar to what we have observed in the stable state of COPD.[23,30] We also observed that younger age was associated with pulmonary arterial enlargement at the time of admission. The mechanism for this phenomenon is unknown and requires further study, although it could be due to impaired vascular distensibility in older patients.[27,31,32]

No patient in our cohort received a clinical discharge diagnosis of acute myocardial infarction, although a number did have elevated troponin levels. Instead, troponin elevations were more common in those with an increased PA/A ratio at admission. Troponin elevations, often occurring with chest pain and ECG changes, have been reported as frequently as one in 12 patients hospitalized for AECOPD.[33] Previous factors associated with troponin elevations in AECOPD include increased neutrophil count, decreased hemoglobin concentrations, increased creatinine levels, and cardiac injury scores.[34] Increased troponin levels with AECOPD independently predict in-hospital mortality,[35-37] and Brekke et al[38] have also shown that elevated troponin levels in the setting of AECOPD predicted all-cause mortality over a 1.9-year follow-up period. Elevated troponin levels in the setting of severe AECOPD are not exclusively related to acute myocardial infarctions,[33] and our findings may establish a link between acutely decompensated COPD, right ventricular dysfunction, and pulmonary hypertension. In fact, emerging data suggest that elevated troponin levels are independently associated with an increased risk of rehospitalization in patients with chronic right-sided heart failure due to pulmonary hypertension.[39] Although we observed no relationship between BNP and pulmonary arterial size, BNP levels were elevated in our cohort as a whole, suggesting there was increased ventricular stretch during these episodes of severe AECOPD. As others have shown, BNP is commonly elevated during COPD-related hospitalizations, and these elevations are related to early mortality.[40]

Our observations of pulmonary arterial enlargement and worsened clinical outcomes are important in understanding the prognosis of these acute events. Previously identified prognostic factors for patients hospitalized with AECOPD include age, organ failure, comorbidities, BMI, and the need for mechanical ventilation, but these factors do not completely explain the variability in risk of poor outcomes,[41-43] and additional biomarkers are needed. Blood-based biomarkers, including procalcitonin, C-reactive protein, and copeptin, have been investigated at the time of AECOPD hospitalization; only copeptin exhibited associations with prognosis,[44] and procalcitonin may have a role in guiding antibiotic therapy.[45] Although our group and others have used noninvasive imaging modalities as biomarkers for COPD prognosis, none have evaluated imaging at the time of hospital admission.[18,46] The present study evaluating pulmonary arterial enlargement is the first radiologic metric evaluated in this context, and incorporating the PA/A ratio into routinely acquired CT reports in the setting of AECOPD may be useful for identifying those at greatest risk.

Our study has several limitations. First, it was a single-center retrospective analysis and is thus subject to the usual shortcomings of these types of studies; our observations, however, are mechanistically and physiologically sound and compatible with our earlier report as well as others linking the PA/A ratio and COPD-related pathophysiology.[17,18,47] In addition, our sample size was relatively small, limiting our ability to detect statistical differences in some of the observed trends in clinical outcomes. Another limitation is that we did not evaluate the impact of pharmacologic therapies on clinical outcomes. However, $>$ 90% of patients were treated with antibiotics and systemic corticosteroids, limiting any potential for confounding. Finally, $<$ 10% of the discharged patients from our center had CT scans performed at the time of hospitalization for AECOPD, resulting in a selection bias; our findings should thus be prospectively validated.

Conclusions

To the best of our knowledge, this study is the first to longitudinally examine the PA/A ratio and evaluate it in

the setting of severe acute exacerbations. We found that pulmonary arterial enlargement is acutely increased during hospitalizations for AECOPD and is associated with enhanced markers of cardiac injury and trends toward worsened clinical outcomes. These findings highlight the mechanistic plausibility for the PA/A ratio to be used as a biomarker for both acute and stable disease.

Acknowledgments

Author contributions: J. M. W. takes responsibility for the content of the manuscript, including the data and analysis. J. M. W. and M. T. D. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J. M. W., J. B. M., S. P. B., H. N., and M. T. D. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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