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CT-Derived Pulmonary Artery Diameters to Preselect for Echocardiography in COPD Patients Eligible for Bronchoscopic Treatments

Marieke C. van der Molen[a] Jorine E. Hartman[a] Karin Klooster[a]
Huib A.M. Kerstjens[a] Joost van Melle[b] Tineke P. Willems[c] Dirk-Jan Slebos[a]

[a]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [b]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [c] Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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Interventional pulmonology · COPD · Emphysema · Pulmonary hypertension · Computed tomography

Abstract
Background: Currently, patients with COPD who are evaluated for bronchoscopic treatments are routinely screened for pulmonary hypertension (PH) and systolic left ventricle dysfunction by echocardiography. ***Objectives:*** We evaluated the prevalence of PH and systolic left ventricle dysfunction in this patient group and investigated if the previously proposed CT-derived pulmonary artery to aorta (PA:A) ratio >1 and PA diameter measurements can be used as alternative screening tools for PH. ***Methods:*** Two hundred fifty-five patients were included in this retrospective analysis (FEV_1 25%pred, RV 237%pred). All patients received transthoracic echocardiography and chest CT scans on which diameters of the aorta and pulmonary artery were measured at the bifurcation and proximal to the bifurcation. ***Results:*** Following echocardiography, 3 patients (1.2%) had PH and 1 (0.4%) had systolic left ventricle dysfunction. Using a PA:A ratio >1, only 10.3% of the patients with a right ventricular systolic pressure (RVSP) ≥35 mm Hg were detected and none of the patients with an RVSP >50 mm Hg were detected. Patients with an RVSP ≥35 mm Hg had significantly higher PA diameters (29.5 vs. 27.5 mm; $p = 0.02$) but no significantly different PA:A ratios. All patients with an RVSP >50 mm Hg had PA diameters >30 mm. ***Conclusions:*** The prevalence of PH and systolic left ventricle dysfunction is low in this preselected cohort of patients with severe COPD. In this population, a PA:A ratio >1 is not a useful cardiac screening tool for PH. A PA diameter >30 mm could substitute for routinely performed echocardiography in the screening for PH in this patient group.

Introduction

An emerging subgroup of patients with severe COPD may benefit from bronchoscopic treatment modalities [1]. Currently, all patients that are considered eligible for a bronchoscopic treatment are routinely screened for pulmonary hypertension (PH) and systolic left ventricle dysfunction by echocardiography [2, 3] since cardiac comorbidities are frequently present in patients with COPD and severe PH and systolic left ventricle dysfunction are

karger@karger.com
www.karger.com/res

Marieke C. van der Molen
Department of Pulmonary Diseases AA11, University Medical Center Groningen
PO Box 30001
NL–9700RB Groningen (The Netherlands)
m.c.van.der.molen@umcg.nl

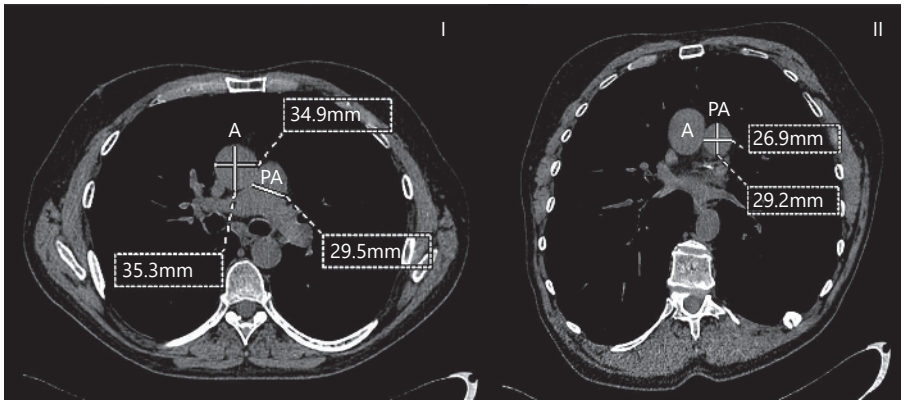

Fig. 1. CT-derived measurements of the PA. I Diameters of the PA and A to calculate the PA:A ratio in the axial view, II Perpendicular diameters of the PA. PA:A, pulmonary artery to aorta; A, aorta; PA, pulmonary artery.

known to increase per procedural risks [4]. Therefore, according to current recommendations, a right ventricle systolic pressure (RVSP) >50 mm Hg and left ventricular ejection fraction (LVEF) <45% disqualify patients for bronchoscopic treatments [2, 3].

Notwithstanding the importance of adequate cardiac screening, echocardiography is a cumbersome process since hyperinflation is known to impede cardiac imaging due to the lack of adequate acoustic windows. RVSP measurements are, therefore, often difficult to perform in patients with severe COPD [5, 6]. Moreover, severe PH and systolic left ventricle dysfunction are present in only a small number of patients with severe COPD [7–9]. This prompted the evaluation of noninvasive alternatives for echocardiography in the screening of patients for PH. Computed tomography (CT)-derived pulmonary artery (PA) diameter measurements and a pulmonary artery to aorta (PA:A) ratio >1 have been proposed as alternative screening tools for PH, but studies in patients with severe COPD are scarce [10, 11].

In this study, we aimed to investigate 2 research questions. First, we addressed the prevalence of PH and systolic left ventricle dysfunction based on echocardiographic findings in this specific patient group. Second, we investigated the feasibility of using CT-derived PA:A ratios and PA diameters and whether these measurements could be a valid alternative for echocardiography in this patient group.

Materials and Methods

Study Population

Baseline data of all patients with severe COPD who were screened for bronchoscopic treatments in the University Medical Center Groningen and underwent echocardiography as part of the screening program were included in the database. Patients were excluded if an underlying cardiac genetic disease was present or if echocardiography was performed >2 years prior to the screening program. Written informed consent was obtained from all participants for the use of their data. According to the local ethics committee, this study did not fall within the scope of the WMO (Dutch Medical Research with Human Subjects Law) and therefore no formal approval was needed.

Echocardiography

Cardiac function was evaluated using transthoracic echocardiography. Patients received standard 2D and Doppler echocardiography in either the UMCG or the referring hospital. The following variables were assessed according to prevailing guidelines of the European Society of Cardiology: systolic left ventricular function using the Simpson method, left ventricle end diastolic diameter, peak velocity of the early E-wave and atrial A-wave and the E/A ratio, early diastolic mitral annular velocity (E′) and the E/E′ ratio, tricuspid annular plane systolic excursion, inferior caval vein diameter on inspiration and expiration, and RVSP.

CT-Derived PA Measurements

All patients underwent CT of the chest as part of the screening program. In all patients, CT of the chest was performed in the University Medical Center Groningen according to standard protocols. First author performed the measurements on all CT scans using TeraRecon AquariusNET iNtuition Software version 4.4.13. P4 (TeraRecon, Foster City, CA, USA). Two methods were earlier described to measure the PA diameter, and both measurements were performed on all CT scans. First, the main PA and A diameters were measured at the level of the PA bifurcation in the axial view. For the A diameters, 2 perpendicular measurements were taken and averaged which conform to the technique that was previously described (Fig. 1-I) [10]. Second, perpendicular PA diameters were measured proximal to the PA bifurcation which conform to the earlier description (Fig. 1-II) [12]. To assess interobserver variation, a second blinded reviewer (TW, radiologist) measured the diameters.

Statistical Analysis

Spearman correlations were calculated to determine the relationship between RVSP, PA:A ratio, and PA diameters. An independent *t* test was performed to measure the difference in RVSP between the PA:A ≤1 and PA:A >1 groups since a PA:A >1 showed

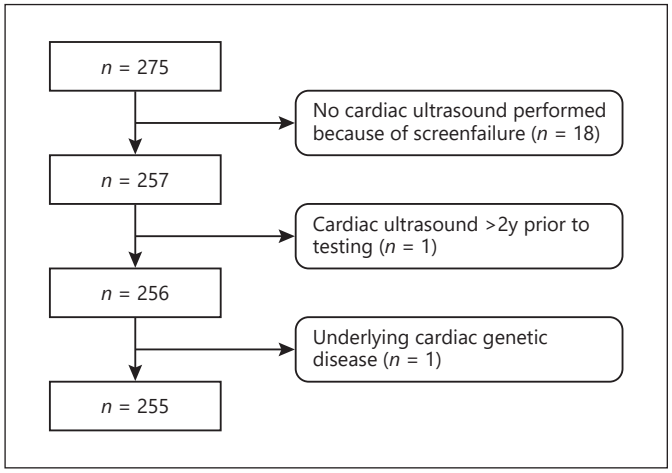

Fig. 2. Flow diagram of patients in whom echocardiography data were used.

the highest sensitivity and specificity in detecting PH in patients with COPD [10]. An independent *t* test was performed to measure the difference in PA:A ratio, A and PA diameters between the RVSP <35 and ≥35 mm Hg groups since PH is considered unlikely in patients with an RVSP ≤35 mm Hg [13]. Receiver operating characteristic analysis was performed to assess discriminatory power of CT-derived PA diameters and the PA:A ratio in predicting the presence of RVSP >35 mm Hg. Intraclass correlation coefficients were calculated to measure interobserver agreement of CT-derived PA measurements. A multiple linear regression model was performed to test for independent predictors of the RVSP. Data analyses were performed using IBM SPSS statistics (IBM SPSS version 23; IBM, New York, NY, USA) and *p* values of <0.05 were considered to be statistically significant.

Table 1. Patient characteristics

	Median (range)	*N*
Demography		
Age, years	61.0 (39–78)	255
Men, *n* (%)	79 (31.0)	255
Pack-years of smoking	39.5 (8–148)	254
BMI, kg/m^2	23.2 (15.8–36.5)	255
Lung function		
FEV_1, %pred	25.4 (11.9–48.8)	255
RV, % pred	237 (109–484)	254
DLCO, %pred	29.4 (12.4–75.9)	179
Cardiac function		
LVIDd, mm	42 (29–57)	216
TAPSE, mm	19.7 (10.3–34.1)	216
MV E/A ratio	0.84 (0.5–1.9)	123
E/e' ratio	7.3 (4.2–16.0)	91
IVC exp, mm	15.0 (6.8–25.3)	110
RVSP, mm Hg	33 (14–67)	86
CT-derived PA measurements		
PA:A ratio	0.82 (0.5–1.1)	254
A diameter, mm	33.7 (23.2–47.4)	254
PA diameter, mm	27.3 (18.9–41.0)	254
PA diameter (pend), mm	27.6 (18.7–40.5)	254

Data are presented as median (range) or *n* (%). FEV_1, forced expiratory volume in 1 second; RV, residual volume; DLCO, diffusing capacity of the lung for carbon monoxide; IC/TLC, inspiratory to total lung capacity; LVIDd, left ventricular internal dimension diastole; TAPSE, tricuspid annular plane systolic excursion; MV E/A, peak late to early mitral inflow velocity; E/e', peak early mitral inflow to peak early diastolic mitral annular velocity; IVC exp, diameter of the inferior caval vein on expiration; RVSP, right ventricular systolic pressure; CT, computed tomography; PA:A ratio, pulmonary artery-to-aorta ratio; A, aorta; PA, pulmonary artery.

Results

Between 2014 and 2018, 275 patients were screened for bronchoscopic treatments. Useable echocardiography data were obtained in 255 patients (Fig. 2). Patient characteristics are shown in Table 1.

Prevalence of Patients with PH and/or CHF

Of the 255 patients who received echocardiography, 3 patients had an RVSP >50 mm Hg (51, 63, and 67 mm Hg, respectively) and 1 patient had an LVEF <45%. An expansion of the numbers of deviating echocardiographic measurements is shown in Table 2.

Feasibility of Echocardiographic Measurements

In 169 of 255 patients (66.3%), RVSP measurements could not be performed due to the absence of tricuspid regurgitation or poor acoustic window. For the same reason, LVEF could not be measured in 14 of 255 patients (5.5%). An expansion of the numbers of obtained echocardiographic measurements is shown in Table 2.

RVSP and CT-Derived PA Measurements

PA:A Ratio

PA:A ratio was not significantly associated with RVSP (rho = 0.21; $p = 0.06$). There was no significant difference in RVSP between the PA:A ≤1 and PA:A >1 groups (33.3 and 32.8 mm Hg, respectively; $p = 0.87$). Alternatively, there was no significant difference in the PA:A ratio between the RVSP <35 mm Hg and RVSP ≥35 mm Hg groups (0.86 and 0.82, respectively; $p = 0.14$). Using a PA:A ratio >1, only 4 of the 39 patients with an RVSP ≥35 mm Hg were detected, and none of the patients with an

Table 2. Number of patients with deviating echocardiographic measurements

	N (%)	Valid measurements, *n* (%)
LVEF <45%	1 (0.4)	241 (94.5)
RVSP ≥35 mm Hg	39 (15.3)	86 (33.7)
RVSP >50 mm Hg	3 (1.2)	86 (33.7)
IVC>21 mm	8 (3.1)	110 (43.1)
IVC collaps <50%	7 (2.7)	103 (40.4)
LVIDd <−2SD	51 (20.0)	216 (84.7)
TAPSE <17 mm	32 (12.5)	216 (84.7)
MV E/A ratio <0.8	40 (15.7)	123 (48.2)
E/e' ratio >6.0	75 (29.4)	91 (35.7)

Data are presented as number of patients with deviating measurements, total number of patients with this measurement, and percentage of the number of patients who received echocardiography. LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure; IVC, inferior caval vein; LVIDd, left ventricular internal dimension diastole; TAPSE, tricuspid annular plane systolic excursion; MV E/A, peak late to early mitral inflow velocity; E/e', peak early mitral inflow to peak early diastolic mitral annular velocity.

RVSP >50 mm Hg (Table 3). Receiver operating characteristic analysis was performed and the area under the curve for PA:A ratio and RVSP ≥35 mm Hg was not statistically significant (0.60; 95% CI, 0.48–0.73; $p = 0.10$). Intraclass correlation coefficients were moderate for interobserver agreement in CT scan measurements of the PA:A ratio (0.56; $p = 0.005$).

PA Diameter Measurements

Both pPA diameter and mPA diameter were significantly associated with RVSP (both $r = 0.29$ and $p = 0.01$). In the RVSP ≥35 mm Hg group, significantly higher pPA diameters (29.5 and 27.5 mm, respectively; $p = 0.02$) and mPA diameters (29.7 and 27.6 mm, respectively; $p = 0.02$) were seen compared to the RVSP <35 mm Hg group. No significant differences in A diameter were found between both groups (34.7 and 33.9 mm, respectively; $p = 0.35$). In the RVSP >50 mm Hg group, only mPA and pPA diameters >30 mm were seen, and the detection rates of patients with an elevated RVSP for various pPA and mPA diameters are shown in Table 3.

In a multiple linear regression model adjusted for age, sex, and height, both mPA and pPA diameters were independent predictors of the RVSP, while A diameter was not (see online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000509719). The area under the curve for pPA diameter and RVSP ≥35 mm Hg was 0.65 (95% CI, 0.53–0.77; $p = 0.02$) and for mPA diameter and RVSP ≥35 mm Hg was 0.66 (95% CI, 0.54–0.77; $p = 0.01$) (online suppl. Fig. S1). Intraclass correlation coefficients were good for interobserver agreement in CT-scan-measured pPA and mPA diameters (0.85 and 0.73, respectively; both $p < 0.001$).

Discussion

The main finding of this study is that following echocardiography, only 3 out of 255 patients (1.2%) had an RVSP >50 mm Hg and 1 (0.4%) systolic left ventricle dysfunction. This finding suggests that routinely performed echocardiography is of limited value in this cohort and highlights the need for alternative screening methods to identify at risk patients who qualify for echocardiography. In this patient group, a PA diameter >30 mm could be used to select patients who qualify for echocardiography and substitute for routinely performed echocardiography in the screening for PH.

We concluded that the prevalence of PH and CHF is low in this preselected cohort of patients with severe COPD. To our knowledge, this is the only study to evaluate the prevalence of these cardiac comorbidities in patients with COPD who qualify for bronchoscopic treatments. Right heart catheterization (RHC) is the gold standard to diagnose PH (defined as a mean pulmonary arterial pressure [mPAP] >25 mm Hg), and echocardiography is mainly used to select patients for RHC based on the RVSP. According to guidelines, PH is considered unlikely in patients with an RVSP ≤35 mm Hg and likely in patients with an RVSP >50 mm Hg [13]. Some studies have focused on the prevalence of PH following RHC in patients with severe COPD that were referred for lung volume reduction surgery or lung transplantation [7, 8, 14]. In these studies, PH was found in 30–86% of the patients with advanced COPD and severe PH (defined as an mPAP >35 mm Hg) in 4.0–9.7% of the patients, whereas only 1.2% of the screened patients needed to be excluded due to PH in our cohort.

The low prevalence of PH in our cohort could be explained by the selection of patients considered eligible for bronchoscopic treatments. In selecting patients for bronchoscopic treatments, a preselection is made of patients that are expected to encounter primarily ventilator limitations in exercise capacity based on chest CT, pulmonary function tests, and medical history. This preselection is in agreement with earlier findings that other underlying pa-

Table 3. Detection of elevated RVSP according to CT-derived PA measurements

	PA:A >1	mPA ≥27.0 mm	pPA ≥27.0 mm	mPA ≥28.0 mm	pPA ≥28.0 mm	mPA ≥29.0 mm	pPA ≥29.0 mm	mPA ≥30.0 mm	pPA ≥30.0 mm
RVSP <35 mm Hg	5 (10.6%)	26 (55.3%)	26 (55.3%)	21 (44.7%)	21 (44.7%)	16 (34.0%)	18 (38.3%)	12 (25.5%)	10 (21.3%)
RVSP ≥35 mm Hg	4 (10.3%)	29 (74.4%)	31 (79.5%)	26 (66.7%)	27 (69.2%)	25 (64.1%)	22 (56.4%)	21 (53.8%)	14 (35.9%)
RVSP >50 mm Hg	0 (0%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)

Data are presented as *n* (%). PA, pulmonary artery; PA:A, ratio of pulmonary artery-to-aorta diameter; mPA, main pulmonary artery diameter (mm); pPA, perpendicular pulmonary artery diameter (mm); RVSP, right ventricular systolic pressure.

thology is often present and underdiagnosed in patients with PH in COPD [15]. And most importantly, hypoxia is an important risk factor for the development of PH in COPD and a pO2 <6.0 kPa is an exclusion criterion for bronchoscopic treatments [2].

Despite the preclusion of PH as the main aim for echocardiography, RVSP measurements could be obtained in only 33.7% of the cases. Although hyperinflation in COPD is known to impede echocardiography, other studies have reported feasible RVSP measurements in 44 and 66%, respectively, of the patients with severe COPD [5, 6]. RVSP is calculated from tricuspid regurgitation jet measurements and an estimate of the right atrial pressure. Tricuspid regurgitation has been shown to be more frequently present in increasing pulmonary artery systolic pressure (PASP), with detectable tricuspid regurgitation ranging from 10% of the patients with a PASP <35 mm Hg up to 96% of the patients with a PASP >50 mm Hg [16]. Therefore, the lower percentage of successful RVSP measurements could possibly be explained by the preselection of patients with generally lower PASP. Additionally, patients in our cohort had higher mean residual volumes (237 vs. 143% predicted), which is known to impede echocardiographic imaging [6]. Alternatively, in the earlier mentioned studies, performance of echocardiography was part of the study design. Therefore, our results may be a more appropriate reflection of successful RVSP measurements in clinical practice.

Given the limitations of echocardiography, CT-derived measurements of the PA have been investigated to identify patients at risk for PH, including the PA:A ratio. A PA:A ratio >1 has been associated with an increased frequency of severe exacerbations in COPD [17] but has also been proposed as a screening tool for the detection of PH in patients with severe COPD [10].

In our study, the PA:A ratio was not a valid tool to identify patients at risk for PH. Most importantly, all patients with an RVSP >38 mm Hg had PA:A ratios ≤1 in this cohort. In patients with PH, the PA:A ratio was earlier shown to be unrelated to changes in PASP over time [18], which might suggest that an elevated PA:A ratio could be used in the phenotyping of lung diseases rather than in the detection of PH.

Both higher mPA and pPA diameters were associated with higher RVSP in our cohort. Although statistically significant, the correlation coefficients were relatively low. This finding might be the result of both low prevalence of PH in this cohort and use of RVSP as the outcome measure. In general, RVSP is known to correlate only moderately with PASP and mPAP with high standard errors of the mean, [6, 19, 20] but RVSP has been shown to be highly inaccurate in patients with advanced lung disease. Based on echocardiography, 48% of the patients with advanced lung disease were misdiagnosed with PH, [5, 21] and CT-derived PA measurements have been shown to associate better with mPAP measurements than echocardiographic-derived estimates in patients with severe COPD [10].

In patients with severe COPD, an mPA diameter ≥30 mm has been associated with PH [11]. In our study, all 3 patients with an RVSP >50 mm Hg had mPA and pPA diameters ≥30 mm. Since mPA and pPA diameters are strongly correlated and mPA diameter measurements are easier to perform, mPA diameter measurements are preferable to pPA diameter measurements. Therefore, we suggest using an mPA diameter ≥30 mm in the identification of patients at risk for PH in this specific patient cohort.

Our study has some limitations. Given the preselection of patients that were considered eligible for endobronchial treatment, these results are not generalizable to the entire population of patients with severe COPD. Since only 3 patients in our cohort had an RVSP >50 mm Hg, the sample size was too small to calculate sensitivity and

specificity for the different PA diameters. Therefore, we used the threshold of a PA diameter ≥30 mm based on an earlier study [11]. In this study, a PA diameter ≥30 mm was shown to have the highest positive and negative predictive value in the detection of PH in patients with severe COPD. However, patients in this study were screened for lung transplantation and might therefore not be a good reflection of our population. Furthermore, our study is limited by its retrospective design and lack of mPAP measurements. On the other hand, this study is unlikely to be repeated with RHC since the prevalence of PH is low in this cohort, and RHC entails considerable costs and additional risks.

In conclusion, we found that the prevalence of PH and CHF is low in patients selected for bronchoscopic treatments and that routinely performed echocardiography in all patients is not worthwhile. An mPA diameter >30 mm followed by echocardiography could substitute for routinely performed echocardiography in all patients eligible for bronchoscopic treatments in the screening for PH. This measurement is easy to perform and cost effective since it can be performed on the already obtained CT scans and is more patient friendly.

Statement of Ethics

We obtained written informed consent from all participants for the use of their data.

Conflict of Interest Statement

D.J.S. is an investigator, physician advisor, and consultant for PulmonX Inc. Redwood City, CA, USA. All other authors have nothing to disclose.

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Author Contributions

Van der Molen: contributed to the study concept and design, collected and analyzed data, and wrote the manuscript. *Hartman*: contributed to acquisition of data, assisted with statistical analysis, critical revision of the manuscript for intellectual content, and final approval of the submitted manuscript. *Klooster*: contributed to acquisition of data, critical revision of the manuscript for intellectual content, and final approval of the submitted manuscript. *Kerstjens*: contributed to the discussion on the results, critical revision of the manuscript for intellectual content, and final approval of the submitted manuscript. *Van Melle*: contributed expertise as the cardiologist involved in this study, to critical revision of the manuscript for intellectual content, and to final approval of the submitted manuscript. *Willems*: contributed to CT-derived measurements, critical revision of the manuscript for intellectual content, and final approval of the submitted manuscript. *Slebos*: contributed to the study concept and design, critical revision of the manuscript for intellectual content, and final approval of the submitted manuscript.

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