

# Influence of Chronic Obstructive Pulmonary Disease on Atrial Mechanics by Speckle Tracking Echocardiography in Patients With Atrial Fibrillation



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**The present study aimed to examine differences in left- and right atrial characteristics between atrial fibrillation (AF) patients with and without chronic obstructive pulmonary disease (COPD). For this, 420 patients (mean age  $68 \pm 10$  years, 73% female) with first diagnosis of AF and baseline echocardiography were included. Of these, 143 COPD patients were compared with 277 patients without COPD matched by age, gender and body surface area. Additionally 38 healthy controls without cardiovascular risk factors, matched for age, were included. For all 3 groups, left atrial (LA) volumes and diameter, LA reservoir strain (LASr), left ventricular ejection fraction (LVEF), right atrial (RA) area and diameter, RA reservoir strain (RASr) and tricuspid annular plane systolic excursion were evaluated on transthoracic echocardiography. Baseline characteristics were similar in patients with and without COPD except for smoking and a history of heart failure (42% vs 11%,  $p < 0.001$  and 48% vs 37%,  $p = 0.036$  for COPD and non-COPD patients, respectively). Also, COPD patients less often used  $\beta$ -blockers (63% vs 75%,  $p = 0.017$ ). There were no significant differences in LVEF, LA volume and RA area between COPD and non-COPD patients. Compared to the controls, AF patients had impaired LVEF, LASr and RASr. Only RASr was significantly worse in COPD patients as compared to non-COPD patients (15.3% [9.0 to 25.1] vs 19.6% [11.8 to 28.5],  $p = 0.013$ ). Additionally, a trend towards worse RASr was observed with increasing COPD severity. In conclusion, AF patients with concomitant COPD have more impaired RA function compared to patients without COPD but with similar atrial size and LA function. © 2020 The Author (s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2021;143:60–66)**

Atrial remodeling is a key feature in the development and management of atrial fibrillation (AF). In particular atrial fibrosis and stiffness are related to treatment success and adverse events such as incident stroke.<sup>1,2</sup> AF is a common comorbidity in patients with chronic obstructive pulmonary disease (COPD).<sup>3</sup> Although previous research has focused mainly on the characterization of the left atrium (LA), AF affects also the right atrium (RA). In patients with COPD, right-sided pressure overload is common due to secondary pulmonary hypertension which could lead to RA remodeling and dysfunction.<sup>4</sup> Additionally, studies have described a higher prevalence of RA foci in AF patients with chronic lung disease.<sup>5,6</sup> The objective of this study was to evaluate differences in left- and right atrial size and function in AF patients with and without COPD by applying conventional and advanced echocardiography. Secondly, comparison with healthy controls will be

performed to assess the degree of RA remodeling and functional impairment in AF.

## Methods

Patients with AF who were referred to our tertiary care center for electrical cardioversion between April 1995 and December 2015 were evaluated. For all patients, the first admission with AF was identified. AF was diagnosed based on the European Society of Cardiology guidelines for the management of AF.<sup>7</sup> COPD was defined preferably by pulmonary function testing in accordance with the most recent guidelines (post-bronchodilator fixed ratio of FEV1/FVC  $< 0.70$ ).<sup>8</sup> Otherwise, thorough chart review including referral letters and inhalation medication use was considered to identify patients with COPD. Subsequently, a control group of AF patients without COPD was selected from patients admitted for AF during the same time period matched by age, gender and body surface area at a 1:2 case-control design. Patients with other pulmonary diseases (i.e., asthma, pulmonary hypertension not secondary to COPD, interstitial disease) were excluded prior to matching. Finally, an age-matched control group of healthy subjects without cardiovascular risk factors and without structural heart disease was selected from a database of patients referred for cardiac evaluation including transthoracic echocardiography

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See page 65 for disclosure information.

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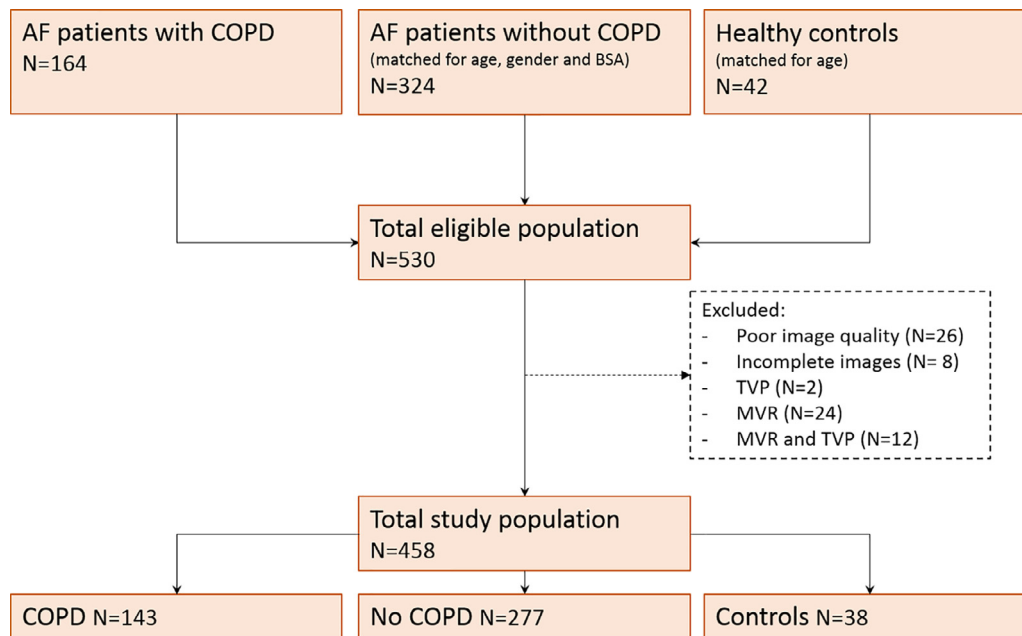


Figure 1. Flowchart of patient selection. AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MVR = mitral valve repair or replacement; TVP = tricuspid valve annuloplasty.

(TTE). Referral reasons for these patients included evaluation of chest pain, dyspnoea, syncope, palpitations or preoperative assessment for non-cardiac surgery. Patients with prior surgical mitral- or tricuspid valve repair or replacement and absence of suitable echocardiographic images for atrial strain analysis were excluded. Figure 1 illustrates the selection of the final study population. For this retrospective analysis of clinically acquired data, the institutional review board waived the need for patient written informed consent.

Demographic and clinical data including cardiovascular risk factors, co-morbidities, laboratory values (haemoglobin and creatinine levels) and medication use were collected from the electronic patient records. Subsequently, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was calculated as previously described.<sup>7</sup> For echocardiographic analysis, the first TTE performed after diagnosis of AF was selected. TTE was performed with the patient in the left lateral decubitus position using a commercially available ultrasound system and transducer (Vivid 7 and E9, 3.5 MHz or M5S probe, GE Healthcare, Horten, Norway). All images retrieved during the time span of the study were digitally stored on hard disks for off-line analysis, including 2D speckle tracking echocardiography (STE) (EchoPAC, version BT13, GE Healthcare, Horten, Norway). Left ventricular ejection fraction (LVEF) was calculated using the Simpson's biplane method in accordance with current recommendations.<sup>6</sup> LV diastolic function was evaluated with E/e' ratio, derived from the pulsed wave tissue Doppler images (TDI) at the septal mitral annulus. LA maximal volume was assessed in the apical 4-chamber view by using Simpson's single plane method. Subsequently, LA volume was indexed to body surface area. Maximal LA diameter was obtained from the parasternal long-axis view. Severity of mitral- and tricuspid regurgitation was categorized (0 = none, 1 = mild, 2 = moderate, 3 = severe) based on

current recommendations.<sup>10</sup> Color-coded tissue TDI was used to assess total atrial conduction time (PA-TDI) by measuring the time between the onset of the P-wave on the surface ECG and the peak of the A wave on the TDI velocity recording, as previously described.<sup>2</sup> For RA assessment, RA transverse diameter and RA area were measured on the right ventricular (RV) focused apical 4-chamber view in end-systole.<sup>9</sup> Tricuspid annular plane systolic excursion was evaluated by applying M-mode in the apical 4-chamber view, as a measure of RV systolic function.<sup>9</sup> Systolic pulmonary artery pressure was estimated as the sum of the peak tricuspid regurgitation and RA pressure derived from the inferior vena cava diameter and inspiratory collapse, as recommended.<sup>9</sup>

Atrial strain was evaluated with 2D-STE in the apical 4-chamber view using appropriate frame rates. For RASr, the RV focused 4-chamber view was used.<sup>11</sup> Images with foreshortened LA or RA were excluded. The myocardial region of interest was manually traced and the width was adjusted to include the atrial wall and exclude the pericardium, left atrial appendage and pulmonary veins.<sup>11</sup> Subsequently, the software automatically tracks the myocardial cycle and segments with poor tracking quality are rejected, which can be overruled by the observer after visual assessment of tracking quality. LASr and RASr were measured as the peak longitudinal strain during ventricular systole by referencing the ECG to the onset of the QRS complex (Figure 2).

Statistical analysis was performed using the SPSS software (version 24, IBM SPSS statistics for windows, Armonk, New York). Categorical data are presented as frequencies and percentages. Continuous data are presented as mean  $\pm$  standard deviation (SD) or median [25th to 75th percentile] when non-normally distributed. For categorical variables, differences between COPD patients, non-COPD

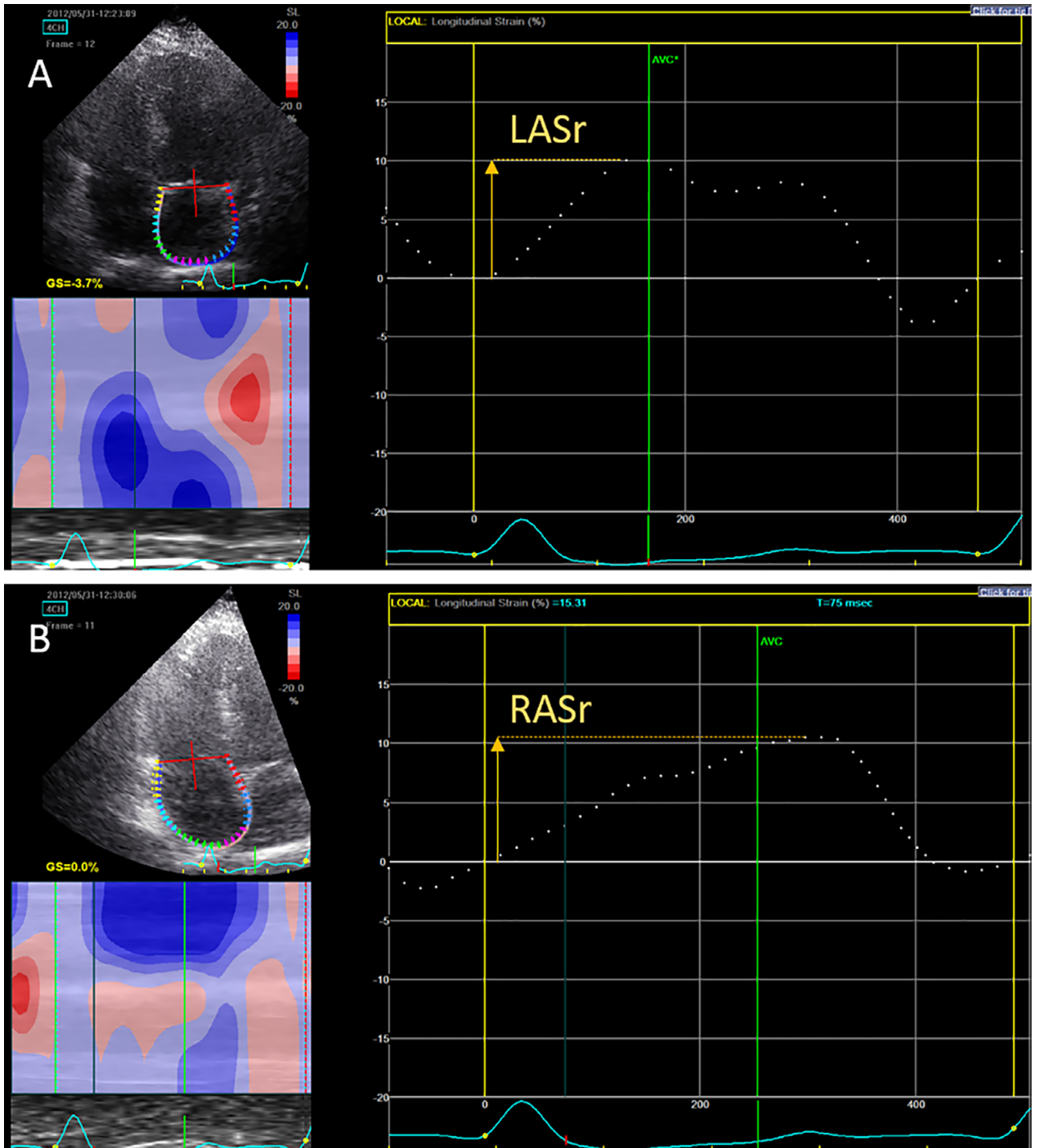


Figure 2. Left- and right atrial strain analysis in atrial fibrillation (AF) patients. Example of left atrial reservoir strain (LASr; panel A) and right atrial reservoir strain (RASr; panel B) analysis in an AF patient with chronic obstructive pulmonary disease. Both RASr (10.5%) as well as LASr (10.0%) are markedly reduced.

patients and healthy controls were compared with the chi-square test. Comparison of continuous data between groups was performed using 1-way analysis of variance or a Kruskal-Wallis test, as appropriate. Post-hoc Bonferroni correction was applied to evaluate differences between COPD and non-COPD patients with adjustment for multiple testing. A 2-tailed p value of <0.05 was considered statistically significant.

## Results

A total of 458 subjects (mean age  $68 \pm 10$  years, 71% female) were included in the present study. The population consisted of 143 AF patients with COPD, 277 AF patients without COPD and 38 healthy controls without cardiovascular risk factors and structural heart disease (Figure 1). Of the COPD patients, 26 (18%) had mild COPD (GOLD class

Table 1

Baseline characteristics for patients with and without chronic obstructive pulmonary disease and healthy controls

Variable	COPD		Healthy controls (n=38)	p-value (all groups)	p-value* (COPD vs. no COPD)
	Yes (n=143)	No (n=277)			
Age (years)	69 ± 10	68 ± 9	66 ± 9	0.436	ns
Women	105 (73%)	201 (73%)	18 (47%)	0.004	ns
Body surface area (kg/m <sup>2</sup> )	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.005	ns
Smoking	61 (43%)	31 (11%)	0	<0.001	<0.001
Hypertension	108 (76%)	211 (76%)	0	<0.001	ns
Diabetes mellitus	30 (21%)	44 (16%)	0	0.007	ns
Thyroid disease	14 (10%)	27 (10%)	5 (13%)	0.801	ns
Hypercholesterolemia	78 (55%)	157 (57%)	0	<0.001	ns
Obstructive sleep apnea	6 (4%)	9 (3%)	0	0.434	ns
History of coronary artery disease	71 (50%)	109 (39%)	0	<0.001	0.043
History of heart failure	69 (48%)	104 (38%)	0	<0.001	0.035
Previous myocardial infarction	42 (29%)	68 (25%)	0	0.001	ns
CHA <sub>2</sub> DS <sub>2</sub> -VASc ≥2	125 (85%)	231 (83%)	-	-	ns
Hemoglobine (mmol/l)	8.5 ± 1.1	8.6 ± 1.3	8.5 ± 0.7	0.749	ns
Creatinine (μmol/l)	104 ± 57	94 ± 42	78 ± 16	0.017	ns
Anticoagulant	108 (76%)	194 (70%)	0	<0.001	ns
Angiotensin-converting enzyme inhibitor	93 (65%)	173 (63%)	0	<0.001	ns
Diuretic	67 (47%)	116 (42%)	1 (3%)	<0.001	ns
Antiarrhythmic medication:					
β-blocker	91 (64)	208 (75)	0	<0.001	0.014
Amiodarone	17 (12)	17 (6)	0	0.020	0.042
Calcium antagonist <sup>†</sup>	21 (15)	28 (10)	0	0.030	ns
Digoxin	26 (18)	25 (9)	0	0.001	0.006
COPD therapy:					
Short acting β <sub>2</sub> -agonist <sup>‡</sup>	22 (15%)	-	-	-	-
Long acting β <sub>2</sub> -agonist <sup>‡</sup>	82 (57%)	-	-	-	-
Inhaled corticosteroid <sup>‡</sup>	92 (64%)	-	-	-	-

COPD = chronic obstructive pulmonary disease; SD = standard deviation.

Continuous variables are presented as mean ± SD.

\* p value derived from ANOVA or chi-square test with Bonferroni's multiple comparison in COPD patients vs no COPD patients. Thyroid disease was defined as any recorded history of hypo- or hyperthyroidism or newly diagnosed by first admission with laboratory tests. Hypercholesterolemia was defined as previously diagnosed hypercholesterolemia, treatment with lipid-lowering agents, low-density lipoprotein ≥3.0 mmol/l in low-to- moderate risk groups, ≥2.6 mmol/L in high-risk groups and ≥1.8 mmol/l in very high-risk groups.

<sup>†</sup> Verapamil or diltiazem.<sup>‡</sup> frequency and percentage of COPD patients.

1), 71 (50%) had moderate COPD (GOLD class 2) and 17 (12%) had severe COPD (GOLD class 3 and 4).<sup>8</sup> The GOLD classification could not be applied to 29 COPD patients (20%).

The baseline clinical characteristics of AF patients with and without COPD and control patients are shown in Table 1. AF patients were predominantly female whereas only half of the control patients were female. Compared to patients without COPD, COPD patients were more likely to be smokers and more often had a history of coronary artery disease and heart failure. In terms of antiarrhythmic medication use, COPD patients less frequently used β-blockers and more often used digoxin when compared to patients without COPD. No differences in hemoglobin levels or kidney function were observed between patients with and without COPD although both groups had significantly higher creatinine levels compared to controls.

LASr assessment was feasible in 448 (98%) patients and RASr assessment in 436 (95%) patients. Furthermore, PA-TDI could only be measured in 234 (51%) patients because the remaining patients were in AF during echocardiography. Table 2 displays the echocardiographic characteristics

of the 3 groups. Compared to the control patients, AF patients with and without COPD had larger LV volumes and worse LVEF. AF patients had larger atrial volumes and diameters. PA-TDI, a measure of total atrial conduction time, was significantly shorter in control patients as compared to AF patients with and without COPD. Interestingly, both LASr and RASr were significantly reduced in AF patients (Figure 3). When comparing AF patients with and without COPD, no differences were observed for LVEF, E/e', LA volumes or atrial conduction time. Although LASr was lower in COPD patients, the difference was not statistically significant (Figure 3). Rates of significant (moderate or severe) mitral- or tricuspid regurgitation were similar in both groups. Concerning the right sided measurements, RA diameter and area were similar in COPD and non-COPD patients. However, RA function was significantly worse in COPD patients demonstrated by a lower RASr (Figure 3). Supplementary material Supplementary Table 1 and Supplementary Figure 1 show a tendency towards more reduced atrial strain with increasing COPD severity, which is most pronounced for RASr (p = 0.017 for all groups).



Table 2

Echocardiographic characteristics of patients with and without chronic obstructive pulmonary disease and healthy controls

Variable	COPD		Healthy controls (n=38)	p-value (all groups)	p-value* (COPD vs. no COPD)
	Yes (n=143)	No (n=277)			
Left-sided parameters:					
Left ventricular end-systolic volume (ml)	67 ± 57	63 ± 46	40 ± 13	0.009	1.000
Left ventricular end-diastolic volume (ml)	125 ± 72	119 ± 56	101 ± 23	0.094	1.000
Left ventricular ejection fraction (%)	50 ± 13	50 ± 13	62 ± 6	<0.001	1.000
E/e' ratio	17 ± 12	18 ± 10	11 ± 3	<0.001	0.950
Left atrial volume index (ml/m <sup>2</sup> )	47 ± 20	46 ± 19	23 ± 6	<0.001	1.000
Left atrial diameter (mm)	46 ± 9	45 ± 8	36 ± 6	<0.001	0.531
Left atrial reservoir strain (%)	14.2 [9.7 – 22.3]	16.3 [9.5 – 24.2]	31.1 [26.2 – 38.9]	<0.001	0.836
PA-TDI (ms)	139 ± 30	153 ± 44	130 ± 36	0.003	0.076
Mitral regurgitation grade ≥ 2	19 (13%)	22 (8%)	0	0.025	ns
Right-sided parameters:					
Right atrial area (cm <sup>2</sup> )	21.6 ± 7	20.6 ± 6	16.2 ± 4	<0.001	0.398
Right atrial diameter (mm)	45 ± 8	44 ± 9	38 ± 8	<0.001	0.834
Right atrial reservoir strain (%)	15.3 [9.0 – 25.1]	19.6 [11.8 – 28.5]	42.8 [33.7 – 48.3]	<0.001	0.013
Tricuspid annular plane systolic excursion (mm)	17.4 ± 5.3	18.7 ± 5.5	21.7 ± 4.5	<0.001	0.056
Systolic pulmonary arterial pressure (mmHg)	39 ± 12	37 ± 12	24 ± 6	<0.001	0.076
Tricuspid regurgitation grade ≥ 2	6 (4%)	9 (3%)	0	0.433	ns
Pacemaker lead right ventricle	25 (18%)	48 (17%)	0	0.020	ns

COPD = chronic obstructive pulmonary disease

\*p value derived from ANOVA or Kruskal-Wallis test with Bonferroni's multiple comparison in COPD patients vs no COPD patients. Continuous variables are presented as mean±SD or median (25th to 75th percentile).

## Discussion

It is widely recognized that COPD is a common comorbidity among patients with AF. Large AF registries have demonstrated the detrimental effect of COPD on all-cause and cardiovascular mortality.<sup>3</sup> A substudy of the Euro Heart Survey also demonstrated that COPD was an independent predictor of unsuccessful ECV and AF recurrences within one year after cardioversion.<sup>12</sup> There is a large body of literature describing LA remodeling in AF. LA enlargement is a known risk factor for AF in the general population and our results show a similar degree of LA dilatation in patients with and without COPD. Hence, differences in treatment

success or prognosis between these patient populations might not be explained by LA characteristics only. In addition to size and volume, LA fibrosis is a major determinant of AF development and persistence or recurrence after treatment. 2DSTE strain analysis as well as prolonged PA-TDI, have emerged as surrogates of (atrial) fibrosis and have been correlated with treatment success and stroke risk.<sup>1,2</sup> In concurrence with previous studies, we found an impaired LASr and a prolonged PA-TDI in AF patients with and without COPD, confirming the early presence of structural atrial remodeling. Interestingly, PA-TDI was shorter in AF patients with COPD compared to AF patients

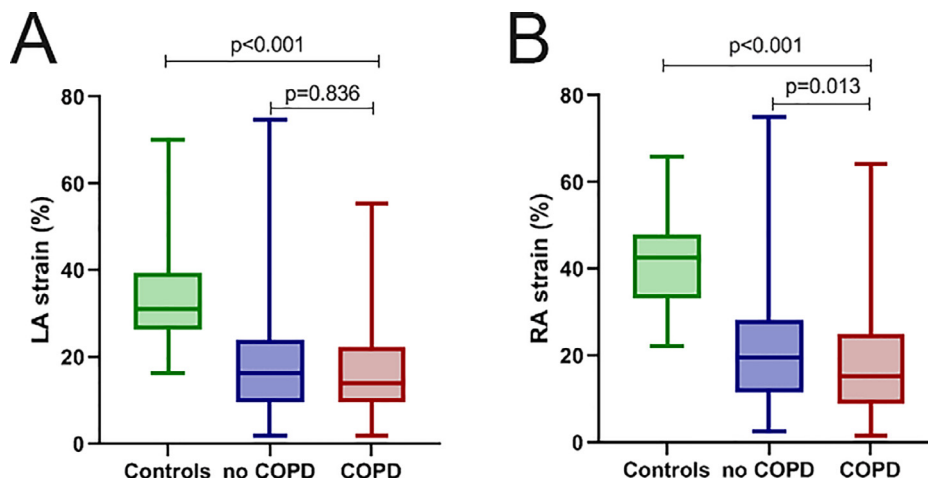


Figure 3. Left- and right atrial strain analysis in control patients and atrial fibrillation (AF) patients with and without chronic obstructive pulmonary disease (COPD). Control patients (green) have a significantly higher left- (LA) and right (RA) atrial reservoir strain compared to AF patients with (red) and without (blue) COPD. AF patients with COPD have significantly reduced RA strain values compared to AF patients without COPD (panel B) and similar LA strain (Panel A). Boxes represent median and interquartile range, whiskers demonstrate the minimal and maximal values. COPD = chronic obstructive pulmonary disease; LA = left atrial; RA = right atrial. (Color version of figure is available online.)

without COPD. This could be explained by the different sensitivity of LASr and PA-TDI in reflecting structural changes of the LA myocardium. In addition, PA-TDI could only be assessed in half of the patients having sinus rhythm during echocardiography.

In addition to the LA, recent literature has suggested the importance of RA remodeling in AF. Data regarding RA function in AF is scarce: Govindan et al.<sup>13</sup> have performed 2DSTE in 30 AF patients undergoing ablation therapy, finding greater RA booster strain ( $>11.5\%$ ) to be independently associated with sinus rhythm maintenance up to 1 year. Our study only concerns reservoir strain since this is generally considered to best reflect atrial compliance and fibrosis. In addition, it has the advantage of being measurable when AF is present.<sup>11</sup> A few studies on RA remodeling and dysfunction in COPD patients have been performed: Bai et al.<sup>14</sup> examined LA and RA strain in 87 AF patients with chronic lung disease (63 with COPD) divided according to AF recurrence after ablation therapy. Overall, the patients had reduced peak LA and RA strain of  $19.11 \pm 10.75\%$  and  $19.65 \pm 10.96\%$ , respectively. Patients with AF recurrence had significantly lower LA and RA strain.<sup>14</sup> Importantly, both LA and RA strain separately were associated with AF recurrence after ablation and a combination of RA and LA strain showed the strongest association with the endpoint.<sup>14</sup> Our study focussed on differences between patients with and without COPD, yet considering the impact of combined LA and RA dysfunction might provide useful insights in the future.

Some studies have identified a higher prevalence of non-pulmonary vein foci in COPD patients compared to patients without COPD.<sup>6,15</sup> Moreover, the majority of these non-PV foci originated from the RA. It is hypothesized that pulmonary hypertension in COPD patients leads to hemodynamic overload and stretching of the RA, contributing to the right-sided origin of AF. Gu et al.<sup>6</sup> support this theory by reporting a correlation between pulmonary arterial pressure and RA triggers. An electrophysiological study in 68 AF patients also demonstrated longer RA conduction time in COPD patients.<sup>15</sup> Similarly, RA electromechanical delay measured from the tricuspid annulus with TDI in 41 COPD patients without overt cardiac disease was significantly longer compared to controls.<sup>16</sup>

This observational study is subject to the inherent limitations of the retrospective design. In one fifth of the COPD patients, the severity of the disease could not be identified due to the absence of pulmonary function data. However, the echocardiographic characteristics of this group were very similar to those of the COPD patients with moderate disease severity and may therefore be considered representative of the entire COPD group. The study was not powered to show significant differences among differences between mild, moderate and severe COPD (supplementary material). Furthermore, for all patients the first occurrence of AF was identified but the echocardiogram with the closest proximity was analysed. Few echocardiographic studies were performed within 3 weeks after cardioversion, resulting in a possible effect of atrial stunning on atrial strain analysis. Finally, atrial strain was analysed with 2DSTE software originally designed for left ventricular strain analysis, but has been validated for atrial strain assessment in multiple

studies and is discussed in a recent consensus document for standardization of LA and RA deformation imaging.<sup>11</sup>

To the best of our knowledge, the present study is the first to show a relation between COPD severity and RA dysfunction, warranting early screening when COPD is diagnosed and close monitoring during follow-up. Future studies examining RASr as a surrogate of a right sided AF substrate are essential to confirm the usefulness in clinical practice.

## Authors Contributions

Laurien Goedemans: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing - original draft. Melissa Leung: conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; writing - review & editing. Pieter van der Bijl: conceptualization; data curation; methodology; resources; validation; writing - review & editing. Rachid Abou: conceptualization; data curation; methodology; resources; validation; writing - review & editing. N Mai Vo: conceptualization; data curation; methodology; resources; validation; writing - review & editing. Nina Ajmone Marsan: conceptualization; funding acquisition; methodology; project administration; supervision; validation; writing - review & editing. Victoria Delgado: conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; writing - review & editing. Jeroen J. Bax: conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; writing - review & editing.

## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2020.12.036>.

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