Impact of chronic obstructive pulmonary disease on right ventricular function and remodeling after aortic valve replacement

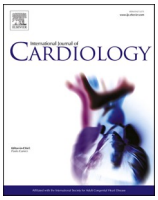
Myagmardorj, R.; Stassen, J.; Nabeta, T.; Hirasawa, K.; Singh, G.K.; Kley, F. van der; ... ; Bax, J.J.

International Journal of Cardiology 395 (2024) 131414

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Impact of chronic obstructive pulmonary disease on right ventricular function and remodeling after aortic valve replacement

Rinchyenkhand Myagmardorj [a,1,*], Jan Stassen [a], Takeru Nabeta [a], Kensuke Hirasawa [a], Gurpreet K. Singh [a], Frank van der Kley [a], Arend de Weger [b], Nina Ajmone Marsan [a], Victoria Delgado [c], Jeroen J. Bax [a]

[a] Department of Cardiology, Heart Lung Center, Leiden University Medical Center, the Netherlands
[b] Department of Cardio-Thoracic Surgery, Heart Lung Center, Leiden University Medical Center, the Netherlands
[c] Department of Cardiovascular Imaging, Hospital University Germans Trias i Pujol, Barcelona, Spain

ARTICLE INFO

Keywords:
Aortic valve replacement
Chronic obstructive pulmonary disease
Right ventricular function
Right ventricular remodeling

ABSTRACT

Background: Both chronic obstructive pulmonary disease (COPD) and right ventricular (RV) dysfunction are common factors that have been associated with poor prognosis after aortic valve replacement (AVR). Since there is still uncertainty about the impact of COPD on RV function and dilatation in patients undergoing AVR, we sought to explore RV function and remodeling in the presence and absence of COPD as well as their prognostic implications.

Methods: Patients who received surgical or transcatheter AVR due to severe AS were screened for COPD. Demographic and clinical data were collected at baseline while echocardiographic measurements were performed at baseline and 1 year after AVR. The study end-point was all-cause mortality.

Results: In total 275 patients were included, with 90 (33%) patients having COPD. At 1-year follow-up, mild worsening of tricuspid annular planar systolic excursion and RV dilatation were observed in patients without COPD, while there were significant improvements in RV longitudinal strain, RV wall thickness but dilatation of RV outflow tract distal dimension in the COPD group compared to the baseline. On multivariable analysis, the presence of COPD provided significant incremental prognostic value over RV dysfunction and remodeling.

Conclusions: At 1-year after AVR, RV function and dimensions mildly deteriorated in non-COPD group whereas COPD group received significant benefit of AVR in terms of RV function and hypertrophy. COPD was independently associated with >2-fold all-cause mortality and had incremental prognostic value over RV dysfunction and remodeling.

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease worldwide, and surgical or transcatheter aortic valve replacement (AVR) is the only treatment that improves survival of patients with severe AS [1]. Prior to AVR preoperative risk prediction scores are routinely used to assess mortality risk, with COPD being an important component in the risk estimation [2–4]. COPD is the most prevalent chronic pulmonary disease, and one-third of deaths in patients with COPD can be attributed to a cardiovascular cause (including severe AS) [5]. Moreover, RV dysfunction also frequently occurs in patients with AS due to pulmonary hypertension (caused by elevated left-sided filling pressures), RV volume overload (caused by fluid retention or concomitant TR), myocardial ischemia (caused by concomitant coronary disease or AS itself), and ventricular interdependence (caused by septal dysfunction) [6].

Various studies have evaluated the prognostic value of RV dysfunction in patients undergoing AVR [7–11], but only few studies focused on patients with COPD with or without RV dysfunction/remodeling who underwent AVR [4,12]. As a consequence, there is still uncertainty concerning the impact of COPD on RV function and dilatation in patients undergoing AVR. Accordingly, we sought to assess RV remodeling and dysfunction in patients with or without COPD after AVR and to determine the prognostic implications of COPD and RV parameters in patients

* Corresponding author at: Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Albinusdreef 2 2300 RC, Leiden, the Netherlands.
E-mail address: r.myagmardorj@lumc.nl (R. Myagmardorj).

[1] These authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2023.131414
Received 24 April 2023; Received in revised form 26 September 2023; Accepted 2 October 2023
Available online 5 October 2023

undergoing AVR.

2. Methods

2.1. Study population and data collection

Patients who underwent surgical or transcatheter AVR (SAVR or TAVR) at Leiden University Medical Center (Leiden, The Netherlands) between January 2001 and July 2017 were screened for the presence/absence of COPD. Severe AS was defined as mean aortic valve gradient ≥40 mmHg and/or peak aortic jet velocity ≥ 4 m/s and/or aortic valve area (AVA) <1.0 cm^2 [or indexed aortic valve area (AVAi) <0.6 cm^2/m^2] [13,14]. Patients who received only medical therapy, aortic valve balloon dilatation or who had incomplete pulmonary functional data (PFT) were excluded. Patients who did not undergo follow-up TTE at 1-year follow-up were also excluded (Supplementary Fig. 1). The therapy (SAVR or TAVR) was decided during heart team discussions. The patients' demographic and clinical data at baseline (symptoms, comorbidities, medical therapy and pulmonary function tests) were retrospectively collected from electronic medical records (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) (HiX; ChipSoft, Amsterdam, The Netherlands). The study was approved by the Institutional Review Board, who waived the need for patient written informed consent due to the retrospective nature of the study.

Prior to AVR, PFT were executed by performing plethysmography with a single-breath technique according to the recommendations of the European Respiratory Society and the American Thoracic Society [15]. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and Tiffeneau index (ratio of FEV_1/FVC) were expressed as absolute values and percentage of a theoretical value calculated by Global Lung Function 2012 Eqs. [16]. Patients were divided into 2 groups: "non-COPD" (FEV_1 > 75% of the predicted value) and "COPD" (FEV_1 ≤ 75% of the predicted value) groups based on the definition by The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database [17].

2.2. Transthoracic echocardiography

TTE was performed within 3 months before and 1 year after AVR using commercially available ultrasound systems (Vivid-7, E9 and E95; GE Healthcare, Horten, Norway). The images were digitally stored and retrospectively analyzed by experienced echocardiographers (EchoPAC version 203; GE-Vingmed, Horten, Norway). The ultrasound systems were equipped with MS5 and 4Vc-D 4D matrix cardiac probes. Two-dimensional, color, spectral continuous- and pulsed-wave Doppler images were obtained from the parasternal, apical and subcostal views.

The assessment of left ventricular (LV) dimensions and function were performed according to contemporary guidelines and included LV end-diastolic diameter and end-systolic diameter, interventricular septal thickness and posterior wall thickness on parasternal recordings. From the apical 2- and 4-chamber views, the LV end-diastolic volume and end-systolic volume were measured and LV ejection fraction (LVEF) was derived using the biplane Simpson's method [18]. The LV mass was calculated based on the Devereux formula and indexed for body surface area (BSA). Left atrial (LA) volumes were measured according to the biplane method of disks and indexed for body surface area. For evaluating LV diastolic function, peak early (E) and late (A) diastolic velocities were obtained by pulsed-wave Doppler recordings of the transmitral flow [19]. To estimate LV filling pressures, the E/e' ratio was calculated combining the average e' measured at both the lateral and septal mitral annulus by tissue Doppler imaging on the apical four-chamber view. The estimation of pulmonary artery systolic pressure (PASP) was estimated from the tricuspid regurgitation (TR) peak jet velocity, applying the simplified Bernoulli equation and adding 3, 8, or 15 mmHg depending on the diameter and collapsibility of the inferior vena cava [20].

The severity of mitral and tricuspid regurgitation was graded from color and continuous wave Doppler recordings based on previous related recommendations [21]. Mean and peak transvalvular aortic pressure gradients were calculated according to the Bernoulli equation, while peak aortic jet velocity was calculated using continuous-wave Doppler data from the apical three- or five-chamber views [22]. After measuring the LV outflow tract diameter and velocity time integrals of the aortic valve and the LV outflow tract, the AVA was estimated using the continuity equation and indexed for BSA.

LV global longitudinal strain (GLS) was measured based on 2-dimensional speckle tracking analysis from apical 2-, 3-, and 4- chamber views using commercially available software (EchoPac, version 203; General Electric; Vingmed Ultrasound) [18]. The endocardial border was automatically traced including the entire myocardium and manually adjusted when necessary. LV GLS was automatically calculated as the average peak systolic strain of 17 LV segments and presented as absolute value.

2.3. RV function and geometry

All RV measurements were obtained from an RV focused apical view. At end-diastole, basal, mid-cavity and longitudinal dimensions, as well as the tricuspid annulus diameter were measured [20]. RV outflow tract (RVOT) proximal and distal dimensions, as well as RV wall thickness were measured in end-diastole according to the guidelines [20]. RV systolic function was quantified according to tricuspid annular plane systolic excursion (TAPSE) and RV dysfunction was defined as TAPSE <17 mm. The ratio TAPSE/PASP was calculated as measure of RV-pulmonary artery coupling and a cut-off of <0.55 was used to defined uncoupling as previously proposed [23]. RV end-diastolic and end-systolic area were manually assessed by tracing the RV endocardium, while RV fractional area change (FAC) was calculated from these values.

RV free wall strain was evaluated using speckle tracking strain analysis [24]. The region of interest was adjusted manually to contour the RV free wall and interventricular septum. Consequently, the RV consisted of 6 segments (3 segments for the free wall and 3 segments for the interventricular septum). RV free wall strain was calculated as the mean of the RV basal, mid, and apical segments of the free wall, excluding the septal segments. In this study, LV and RV longitudinal strain are presented in absolute values.

2.4. Follow-up and endpoint definition

All patients were followed-up for the occurrence of all-cause mortality (study end-point). Survival data were ascertained from the departmental Cardiology Information System and the Social Security Death Index and were complete for all patients.

2.5. Statistical analysis

Continuous variables are presented as mean ± SD if they had a normal distribution, whereas non-normal distributed variables are presented as median and interquartile range. The adherence of normality was verified using the Kolmogorov-Smirnov test and visual assessment of histograms. Normally distributed continuous data was compared using the Student's *t*-test while the Mann-Whitney test was performed for non-normally distributed data. Categorical variables are expressed as absolute numbers and percentages, and compared using the Chi-square test. Clinical data were completed for all patients; for the echocardiographic parameters, <5% of values were missing for the left heart measures, and <10% were missing for the right heart measures except for RV strain values (available in $n = 236$). We used the paired *t*-test and McNemar test for comparison of the variables between baseline and follow-up. The time of AVR was used as the time of inclusion. Cumulative event-rates were compared across groups with the log-rank test. To evaluate the association between COPD severity and all-cause

mortality in patients treated with AVR, univariate Cox regression analysis were performed. Clinically relevant and statistically significant ($p < 0.05$) associates at the univariable analysis were included in the multivariable Cox regression analysis (with the number limited to the number of events), and the calculated hazard ratios (HR) were presented with 95% confidence interval (CI). To investigate the incremental value of COPD over clinical and conventional echocardiographic parameters to predict outcome, a likelihood ratio test was performed. The change in global Chi-square (χ^2) values was calculated and reported. A 2-sided *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS version 25.0 (SPSS Inc., IBM Corp).

3. Results

3.1. Baseline characteristics

A total of 275 patients with paired baseline and 1-year follow-up echocardiograms were included, of which 185 (67%) patients were assigned to the "non-COPD" group and 90 (33%) patients to the "COPD" group, based on the PFT. Baseline clinical characteristics at the time of AVR are summarized in Table 1. The median age of the study population was 79 years (IQR 72–84 years) and 157 patients (57%) were men. Patients without COPD had more often dyslipidemia and more often used aspirin and statins. Patients with COPD were more likely to have atrial fibrillation, more frequently used diuretics and anticoagulation therapy, more symptomatic (according to the NYHA class), and had more diminished pulmonary function tests, compared to the non-COPD group.

Baseline echocardiographic parameters are shown in Table 2. Patients in the COPD group had higher heart rate, larger LV end-systolic diameter and volume, lower LV ejection fraction and LV GLS values, compared to patients in the group without COPD. Aortic valve severity was not different between both groups.

Patients with COPD presented with more impaired RV longitudinal strain and TAPSE, thicker RV wall, more RV dilatation, higher pulmonary artery systolic pressures and lower TAPSE/PASP ratio as compared to patients in the non-COPD group.

3.2. Changes in right ventricular function after AVR

At 1-year follow-up, 34 patients (12.4%) died and were excluded from paired comparison analysis. To evaluate the impact of COPD on RV function and dimensions before and after AVR, echocardiographic examinations at baseline and 1-year follow-up in both the COPD and non-COPD groups were compared and reported in Fig. 1 and Supplementary Table 1. In patients without COPD, significant worsening of TAPSE, slight thickening of RV wall and dilatation of RV dimensions at the basal and mid cavity level as well as more frequently RV-pulmonary artery uncoupling were observed at 1-year follow-up after AVR. In contrast, there were significant improvement in RV longitudinal strain, decrease in RV wall thickness but dilatation of RV outflow tract distal dimension in the COPD group. Moderate or severe tricuspid regurgitation was significantly reduced in both groups.

3.3. Long-term outcomes

During a median follow-up of 27 (IQR 16–56) months, 67 (24%) patients died. Kaplan-Meier survival curve showed that COPD patients had significantly lower survival rate compared to non-COPD patients at 6-year follow-up in Supplementary Fig. 2. Univariable and multivariable Cox regression analysis for all-cause mortality is shown in Supplementary Table 2; variables who were significant at the univariate analysis and of clinical relevance (LV GLS was preferred over LV ejection fraction) were included in the multivariable analysis, and COPD was independently associated with all-cause mortality (HR 2.679, 95% CI 1.545–4.645; $p < 0.001$), together with previous myocardial infarction, diabetes mellitus, surgical AVR, and RV dysfunction. Similar results (HR 0.972, 95% CI 0.951–0.993; $p = 0.010$) was obtained when including Tiffeneau index (as continuous variable) instead of COPD. Fig. 2 shows that the addition of COPD to a baseline model (Model 1), consisting of the variables independently associated with all-cause mortality at the multivariate analysis, resulted in a significant increase in χ^2 (from

Table 1
Baseline clinical characteristics in the overall population and when based on presence of COPD.

	Overall ($n = 275$)	Baseline		p-value*
		Without COPD ($n = 185$)	With COPD ($n = 90$)	
Age, years	79.0 (72.0–84.0)	79.0 (71.0–84.0)	78.0 (72.0–83.0)	0.392
Male gender, n(%)	157 (57)	100 (54)	57 (63)	0.145
Body mass index, kg/m^2	25.7 (23.8–28.7)	25.8 (24.1–29.0)	25.5 (23.3–27.9)	0.186
Hypertension, n(%)	193 (70)	130 (70)	63 (70)	0.963
Diabetes Mellitus, n (%)	72 (26)	50 (27)	22 (24)	0.648
Hyperlipidemia, n(%)	164 (60)	120 (65)	45 (49)	**0.011***
Coronary artery disease, n(%)	143 (52)	102 (55)	41 (46)	0.136
Previous myocardial infarction, n(%)	54 (20)	37 (20)	17 (19)	0.828
Smoking history, n (%)	101 (37)	67 (36)	34 (38)	0.801
Active smoker, n(%)	30 (11)	17 (9)	13 (14)	0.190
Atrial fibrillation, n (%)	87 (32)	48 (26)	39 (43)	**0.004***
CIED in pre-AVR, n (%)	36 (13)	22 (12)	14 (16)	0.398
Previous revascularization (PCI or CABG)	119 (43)	84 (45)	35 (39)	0.306
Systolic blood pressure (mmHg)	139.5 ± 52.0	142.7 ± 61.0	132.8 ± 23.9	0.137
Diastolic blood pressure (mmHg)	72.4 ± 14.5	72.8 ± 13.6	71.7 ± 16.3	0.584
Beta-blocker, n(%)	146 (53)	102 (55)	44 (49)	0.330
ACEi/ARB, n(%)	147 (53)	97 (52)	49 (54)	0.754
Calcium antagonist, n (%)	61 (22)	43 (23)	18 (20)	0.544
Diuretics, n(%)	155 (56)	92 (50)	63 (70)	**0.001***
Aspirin, n(%)	131 (48)	97 (52)	34 (38)	**0.022***
OAC/NOAC, n(%)	93 (34)	55 (30)	38 (42)	**0.040***
Statin, n(%)	166 (60)	121 (65)	45 (50)	**0.014***
Estimated glomerular filtration rate (mL/min/1.73m^2)	62.9 (47.8–78.9)	65.0 (49.0–79.3)	56.6 (43.2–75.9)	0.137
NYHA class III or IV, n(%)	141 (52)	88 (48)	53 (61)	**0.049***
Surgical AVR, n(%)	69 (25)	50 (27)	19 (21)	
Transcatheter AVR, n (%)	206 (75)	135 (73)	71 (79)	0.288
Pulmonary function test	92.8 ± 22.3	102.4 ± 18.1	72.5 ± 15.3	**<0.0001***
FVC, %				
FEV_1, %	86.9 ± 25.2	100.1 ± 18.8	59.8 ± 11.1	**<0.0001***
Tiffeneau index (FEV1/FVC)	73.6 (67.2–79.8)	76.0 (71.1–82.0)	66.4 (54.9–73.6)	**<0.0001***

Values are mean ± SD or n(%). **p* Values represent differences between groups with and without COPD and are calculated by Student's *t*-test and Mann-Whitney test for continuous variables (for normal and non-normal distribution, respectively), and by chi-square test for categorical data.
CIED=Cardiac implantable electronic device; AVR = Aortic valve replacement; ACEi = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin-receptor blocker; OAC=Oral anticoagulant; NOAC = Non-vitamin K antagonist oral anticoagulant; EuroSCORE = European system for cardiac operative risk evaluation; NYHA = New York heart association; FVC=Forced vital capacity; FEV=Forced expiratory volume; COPD=Chronic obstructive pulmonary disease;

Table 2
Baseline echocardiographic characteristics in the overall population and when based on presence of COPD.

	Overall (n = 275)	Baseline		p-value*
		Without COPD (n = 185)	With COPD (n = 90)	
Heart rate at TTE (bpm)	75.3 ± 14.7	74.0 ± 13.8	77.9 ± 16.2	**0.042**
Tricuspid AV, n (%)	246 (90)	163 (88)	83 (93)	0.187
Bicuspid AV, n (%)	28 (10)	22 (12)	6 (7)	
LV function				
LV end-diastolic diameter (indexed), mm/m^2	26.0 ± 4.9	25.7 ± 4.8	26.7 ± 5.1	0.096
LV end-systolic diameter (indexed), mm/m^2	17.7 (14.4–21.9)	17.0 (14.0–20.9)	19.4 (15.6–24.3)	**0.014**
LV mass index, g/m^2	129.1 ± 37.4	126.4 ± 35.6	134.8 ± 40.5	0.084
LV end-diastolic volume (indexed), mm/m^2	52.0 (41.4–71.4)	51.27 (41.56–69.14)	53.49 (40.60–76.12)	0.288
LV end-systolic volume (indexed), mm/m^2	22.8 (15.8–42.4)	21.8 (15.0–37.6)	26.3 (18.3–49.5)	**0.026**
LV ejection fraction, %	55.0 (41.8–63.0)	57.0 (45.0–64.0)	53.0 (35.4–60.0)	**0.005**
LV global longitudinal strain, %	13.6 ± 4.6	14.3 ± 4.3	12.2 ± 4.7	**<0.0001**
Stroke volume index, mL/m^2	35.0 ± 11.6	35.3 ± 11.2	34.4 ± 12.5	0.553
E/e' (>14), n (%)	151 (55)	99 (54)	52 (58)	0.505
Aortic stenosis severity	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.336
Aortic valve area index, cm^2/m^2				
Mean gradient, mm Hg	41.7 ± 16.2	42.1 ± 16.0	41.0 ± 16.8	0.592
Peak velocity, cm/s	4.0 ± 0.7	4.0 ± 0.7	4.0 ± 0.7	0.992
RV systolic function				
RV longitudinal strain‡, %	15.8 ± 5.6	16.4 ± 5.3	14.1 ± 5.9	**0.004**
RV free wall strain, %	19.8 ± 8.5	20.5 ± 8.6	18.2 ± 8.0	0.059
Basal RV free wall longitudinal strain, %	23.6 ± 9.0	24.2 ± 9.0	22.3 ± 9.1	0.149
Mid RV free wall longitudinal strain, %	22.0 ± 8.4	22.7 ± 8.5	20.4 ± 8.1	0.061
Apical RV free wall longitudinal strain, %	13.9 ± 10.9	14.7 ± 11.2	11.9 ± 10.0	0.082
TAPSE, mm	19.8 ± 3.9	20.2 ± 3.8	18.9 ± 4.2	**0.009**
TAPSE <17 mm, n(%)(RV dysfunction)	53 (19)	26 (14)	27 (30)	**0.002**
RV fractional area change, %	41.2 ± 9.1	41.2 ± 8.9	41.2 ± 9.6	0.961
RV geometry				
RV wall thickness, mm	5.6 ± 1.1	5.5 ± 1.1	6.0 ± 0.9	**0.001**
RV outflow tract proximal diameter, mm	33.7 ± 4.4	33.4 ± 4.0	34.8 ± 5.1	**0.031**
RV outflow tract distal diameter, mm	23.5 ± 3.4	23.7 ± 3.4	22.6 ± 3.3	**0.045**
RV basal dimension, mm	40.8 ± 6.6	39.0 ± 5.7	44.4 ± 6.9	**<0.0001**
RV dimension at mid cavity, mm	26.5 ± 4.5	26.9 ± 4.5	25.1 ± 4.1	**0.011**
RV longitudinal diameter, mm	59.5 ± 5.9	59.1 ± 6.0	61.1 ± 5.3	**0.028**
Tricuspid annular dimension, mm	34.2 ± 4.9	33.9 ± 4.7	34.9 ± 5.4	0.176
Moderate and severe TR, n(%)	149 (54)	96 (52)	53 (59)	0.275
PASP, mmHg	33.1 ± 12.5	31.9 ± 12.1	35.7 ± 13.0	**0.031**
TAPSE/PASP mm/mmHg	0.70 ± 0.3	0.73 ± 0.4	0.6 ± 0.3	**0.018**
TAPSE/PASP<0.55, n (%)	73 (32)	40 (25)	33 (45)	**0.003**

Values are mean ± SD or n(%). *p Values represent differences between groups with and without COPD and are calculated by Student's t-test and Mann-Whitney test for continuous variables (for normal and non-normal distribution, respectively), and by chi-square test for categorical data. ‡ availability of variable is $n = 236$.
AV = Aortic valve; LV = Left ventricular; RV = Right ventricular; TAPSE = Tricuspid annular plane systolic excursion; TR = Tricuspid regurgitation; PASP = Pulmonary artery systolic pressure; COPD=Chronic obstructive pulmonary disease.

43.431 to 57.380; $p < 0.001$), suggesting the incremental prognostic value of COPD over RV dysfunction. Similar results were observed when in Model 3 RV dimension were included instead of RV dysfunction in Supplementary Fig. 3.

4. Discussion

The current study explored RV dysfunction and remodeling together with COPD (documented on PFT) in patients undergoing AVR. The main findings are: 1) Patients with COPD undergoing AVR have more pronounced RV dysfunction and remodeling, RV hypertrophy and higher pulmonary systolic pressures compared to non-COPD patients. 2) After AVR, RV longitudinal strain improved, and RV hypertrophy regressed in COPD patients whereas RV function and dilatation as well as RV-pulmonary artery coupling slightly worsened in non-COPD patients. 3) In the COPD group, all-cause mortality was significantly and independently >2-fold increased after adjusting for prognostically relevant variables and parameters of RV dimension and function.

4.1. Impact of COPD on RV geometry and function

Recently, studies have reported on the clinical and prognostic relevance of RV function and size in different (non-)cardiovascular conditions [25]. Previous studies, using 2D echocardiography and right-heart catheterization, showed that RV hypertrophy, dilatation and systolic dysfunction were common in patients with COPD, regardless of pulmonary hypertension [12] [26] [27]. This finding suggests that right-sided cardiac remodeling starts early in the course of COPD and leads to RV function impairment, even at subclinical levels of elevated mean

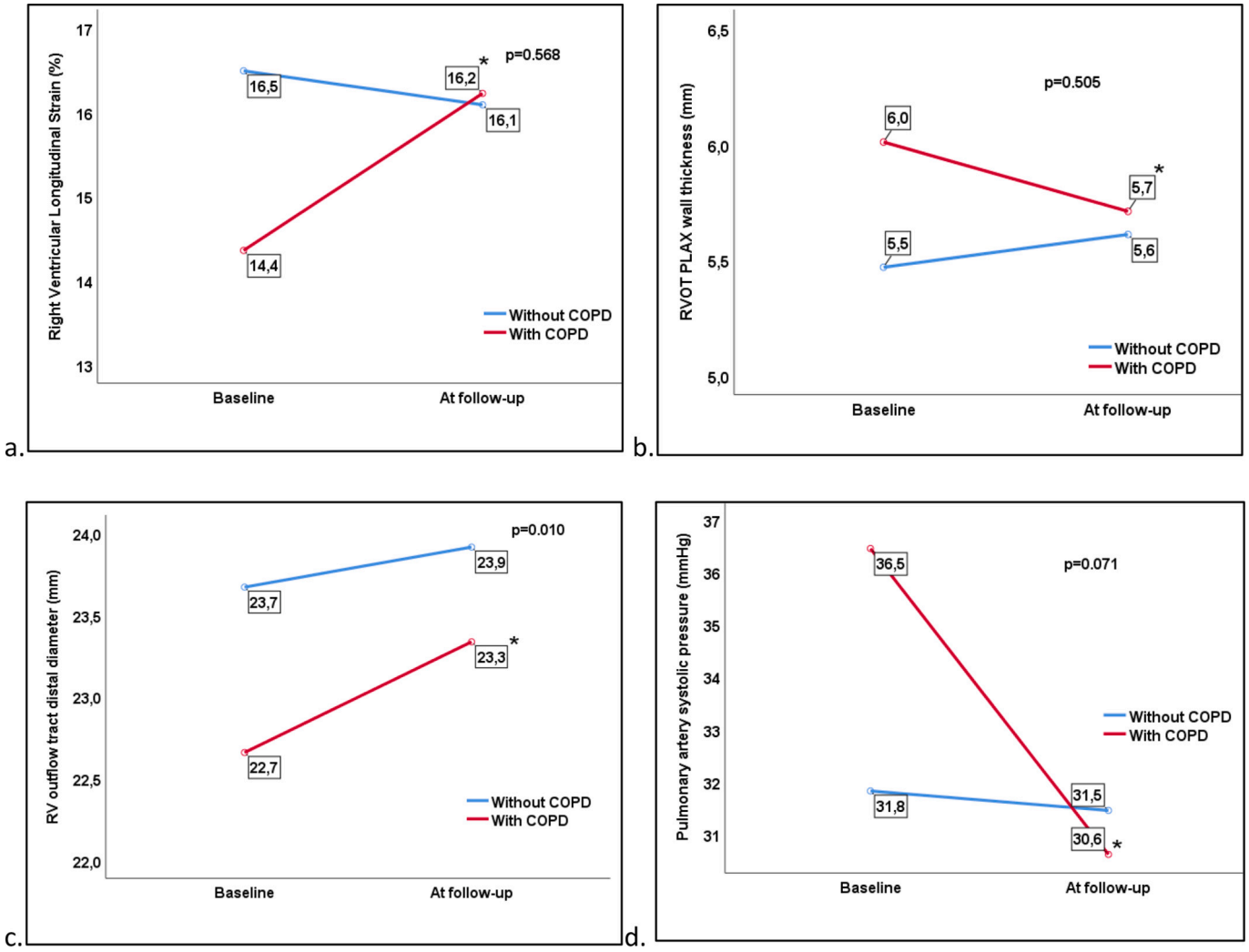


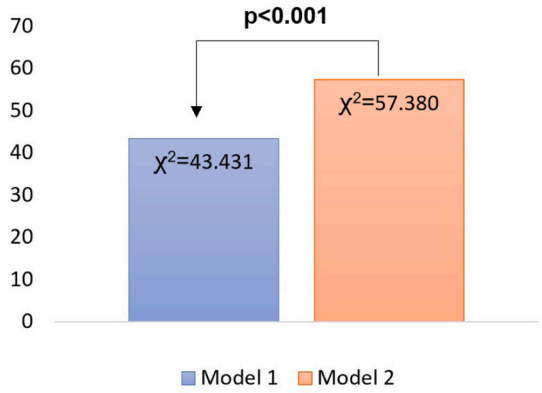
Fig. 1. Significant changes in RV parameters over time.
a. Right ventricular longitudinal strain; b. RV outflow tract wall thickness from PLAX view; c. RV outflow tract distal diameter; d. Pulmonary artery systolic pressure between baseline and 1-year after aortic valve replacement in groups with and without COPD.
*Significantly different from baseline ($p < 0.05$). RVOT = Right ventricular output tract; PLAX = Parasternal long-axis view; RV = Right ventricular; COPD=Chronic obstructive pulmonary disease.

pulmonary artery pressure, pulmonary vascular resistance, and reduced pulmonary artery compliance [12]. The current study also showed more pronounced RV wall thickness, more dilated RV dimensions and more impaired systolic function (assessed with TAPSE as well as RV strain) in the COPD group.

In patients with COPD, RV hypertrophy and dilatation are considered to be a beneficial adaptation, allowing the ventricle to handle an increase in afterload and maintain a normal cardiac output. However, if this remodeling progresses, it ultimately causes RV dysfunction, which is associated with restricted peripheral oxygen delivery and exercise capacity [27]. Furthermore, RV remodeling has been associated with increased pulmonary vascular resistance, caused by various factors. For example, alveolar hypoxia results in pulmonary vasoconstriction and vascular structural changes, subsequently causing RV remodeling and dysfunction [28]. Another important factor is systemic inflammation, which also shares similar pathophysiological pathways with atherosclerosis and AS. Indeed, C-reactive protein, as well as other pro-inflammatory cytokines, such as interleukin (IL)-6 and monocyte chemoattractant protein-1, were correlated with pulmonary artery pressures in two recent studies [29,30]. It therefore seems that neurohormonal activation plays a key role in the preservation of ventriculo-arterial coupling in patients with pulmonary vascular disease.

4.2. Changes in RV function and geometry after AVR

In patients with AS, RV dysfunction and remodeling may relate to multiple factors, including pulmonary hypertension caused by elevated left-sided filling pressures, RV volume overload related to fluid retention or associated TR, myocardial ischemia caused by concomitant coronary disease or the AS itself, and ventricular interdependence due to septal dysfunction [6]. Few studies have demonstrated the change in RV function and dimensions after AVR. When comparing surgical versus transcatheter AVR, a previous study showed that RV performance after TAVR remained unchanged, whereas significant deterioration occurred after conventional surgery [31]. This may be related to the detrimental effects of pericardiotomy and, to a lesser degree, the need for cardiopulmonary bypass. These results also suggest that patients with pre-existing RV dysfunction may benefit more from TAVI. Another study showed a significant improvement in RV longitudinal strain at 6 months after TAVR, including patients with elevated baseline PASP, which significantly decreased during follow-up [32], as observed also in the COPD subgroup of the current study. Moreover, a recent study including a large population of patients undergoing AVR (60% TAVR and 40%



	Model 1		Model 2 (incorporated with COPD)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Previous MI, (yes/no)	1.784 (1.039-3.065)	**0.036**	1.862 (1.082-3.204)	**0.025**
Diabetes mellitus, (yes/no)	2.134 (1.300-3.506)	**0.003**	2.486 (1.497-4.126)	**<0.001**
Surgical AVR, (vs Transcatheter AVR)	0.301 (0.148-0.609)	**<0.001**	0.278 (0.136-0.567)	**<0.001**
RV dysfunction, (yes/no)	2.263 (1.340-3.822)	**0.002**	1.843 (1.078-3.151)	**0.025**
COPD, (yes/no)	-	-	2.659 (1.603-4.411)	**<0.001**

Fig. 2. Incremental prognostic value of COPD on top of RV dysfunction.
The bar charts illustrate the incremental prognostic value of COPD in Model 2 adjusted for the baseline characteristics, including RV dysfunction (Model 1), which were significantly associated with all-cause mortality at the multivariate Cox regression analysis. Below the bar charts, there are corresponding Cox regression models including significant variables from univariate Cox regression analysis with hazard ratios with 95% confidence intervals and p-values.

SAVR) and having RV dysfunction (TAPSE <17 mm) at baseline, 35% showed improvement in RV function, 35% remained with RV dysfunction, and 30% died at 1-year follow-up after TAVR [33]. These observations suggest that RV dysfunction may be reversible in up to one third of patients undergoing AVR. Besides these findings, there are no specific data on RV function and remodeling after AVR in patients with COPD. The current data shows that significant improvement was observed in RV longitudinal strain, RV hypertrophy and significant tricuspid regurgitation while the RV distal outflow tract was slightly dilated in the COPD group 1 year after AVR (Fig. 2). In turn, the mild worsening in RV dimension and function observed in the non-COPD patients during follow-up, was still within normal range and the prognostic impact seems non-significant considering the better survival of this group as compared to COPD patients.

4.3. Prognostic implications of RV dysfunction and COPD in patients received AVR

It is well known that RV systolic function plays an important prognostic role in patients with severe AS. In previous studies, which used TAPSE and other criteria (FAC and S′) to define RV dysfunction, the prevalence of RV dysfunction was 24% and 19%, respectively [8,34]. Similarly in the current study, 19.3% of total study population showed RV dysfunction, and RV dysfunction was independently correlated with all-cause mortality.

Moreover, Cremer et al. found that worsening RV function was more common in patients with dilated RV and at least moderate TR, and was associated with higher all-cause and cardiovascular mortality [7]. Patients who had normal RV function at baseline and subsequently developed moderate or severe RV dysfunction at follow-up, had the worst prognosis. Moreover, the prevalence of COPD was higher in the worsening RV function group of TAVR (37.1% vs 30.1%), whereas it was almost equal in the SAVR groups (27.6% vs 29.4%). In addition, RV-pulmonary artery uncoupling, defined as TAPSE/PASP ratio < 0.55 was present in 39% of total population and associated with a 2 fold-increase in the primary endpoint in the study by Cahill et al. [23]. Likewise in the current study, RV-pulmonary artery uncoupling was found in 32% of total patients and significantly associated with all-cause mortality, although only in univariate Cox regression analysis (HR 1.871, 95% CI 1.077–3.250; $p = 0.026$, data of the multivariate analysis not shown).

In the study by Medvedovsky et al., RV FW LS did not change significantly at 1-year follow-up, but RV FW LS was associated with all-cause mortality at 1 year follow-up (HR 1.06; 95% CI, 1.01–1.11) [34]. Similarly in the current study, RV FW LS was not significantly improved in the COPD group after AVR; in turn, RV FW LS was not independently associated with the outcome (although a trend was observed), possibly in relation with a limited statistical power (measure available in a lower number of patients).

In previous studies, using the STS definition with PFT, COPD was an independent predictor of mortality in patients undergoing AVR and suggested the routine use of PFT during patient selection for AVR [35,36]. In particular, Mok et al. suggested that the lower survival seen in patients with COPD was related to a higher rate of noncardiac death caused by respiratory failure (12.8% vs 0.9%, $p < 0.001$) and FEV_1 was independently associated with a higher rate of pulmonary complications [35]. Also, another study showed that moderate or severe COPD was associated with an increased 1-year mortality (adjusted HR = 2.07; 95% CI, 1.30–3.29; $P = 0.002$) and an independent predictor of mortality after SAVR or TAVR [36]. Interestingly, most COPD patients died due to periprocedural pulmonary complications and had higher utilization of ICU, but were also characterized by worse NYHA functional class and lower exercise capacity at baseline, which failed to improve at follow-up (35, 36). Similarly in the current study, we found that COPD patients had worse NYHA class and higher medication use. However, this study highlights for the first time the fact that COPD portends an increased risk

of mortality after AVR, independently from RV dilatation and dysfunction, which were described previously to be very frequent in COPD patients. Therefore, COPD patients can show a significant improvement after in AVR in RV remodeling and function, which will improve their long-term mortality, but they still remain at higher risk as compared to non-COPD patients due to this specific comorbidity.

4.4. Limitations

The present study has some limitations. Since the study design is a single-centered retrospective study, there may be confounders that could not be adjusted for in the statistical analysis. The inclusion criteria of having a PFT and 1-year follow-up echocardiography available could have led to selection bias, especially when follow-up echocardiography is routine practice in our center for patients undergoing transcatheter AVR but not for the ones undergoing surgical AVR. Also, the specific cause of death was not systematically available in this study and a separate analysis for cardiovascular mortality could not be performed. At last, discrepant results of COPD can be caused by STS definition instead of the GOLD classification.

5. Conclusion

At 1-year after AVR, RV function and dimension mildly deteriorated in non-COPD patients while patients with COPD had significant benefit from AVR in terms of RV function and hypertrophy. COPD was independently associated with 2-fold all-cause mortality and had the incremental prognostic value over RV dysfunction and remodeling.

Disclosures

The Department of Cardiology of Leiden University Medical Center received research grants from Abbott Vascular, Alnylam, Bayer, Biotronik, Bioventrix, Boston Scientific, Edwards Lifesciences, GE Healthcare, Medtronic, Pie Medical, Medis, Pfizer and Novartis. N.A.M. received speaker fees from Abbott Vascular, Philips Ultrasound, Omron and GE Healthcare. V·D received speaker fees from Abbott Vascular, Medtronic, Edwards Lifesciences, Novartis and GE Healthcare. J.J.Bax received speaker fees from Abbott Vascular, Edwards Lifesciences and Omron. The remaining authors have nothing to disclose.

Funding source

Rinchyenkhand Myagmardorj received funding from the European Association of Cardiovascular Imaging (EACVI Training Grant App000073275). K.H. received an ESC Research Grant (R-2018-18,122).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131414.

References

[1] B. Iung, V. Delgado, R. Rosenhek, S. Price, B. Prendergast, O. Wendler, et al., Contemporary presentation and Management of Valvular Heart Disease: the EURObservational research Programme Valvular heart disease II survey, Circulation 140 (2019) 1156–1169, https://doi.org/10.1161/CIRCULATIONAHA.119.041080.

[2] S.A. Nashef, F. Roques, L.D. Sharples, J. Nilsson, C. Smith, A.R. Goldstone, et al., EuroSCORE II, Eur. J. Cardiothorac. Surg. 41 (2012) 734–744, https://doi.org/10.1093/ejcts/ezs043.

[3] S.M. O'Brien, L. Feng, X. He, Y. Xian, J.P. Jacobs, V. Badhwar, et al., The Society of Thoracic Surgeons 2018 adult cardiac surgery risk models: part 2-statistical methods and results, Ann. Thorac. Surg. 105 (2018) 1419–1428, https://doi.org/10.1016/j.athoracsur.2018.03.003.

[4] J.A. Crestanello, R.S. Higgins, X. He, P. Saha-Chaudhuri, B.R. Englum, J. M. Brennan, et al., The association of chronic lung disease with early mortality and respiratory adverse events after aortic valve replacement, Ann. Thorac. Surg. 98 (2014) 2068–2077, https://doi.org/10.1016/j.athoracsur.2014.06.087.

[5] W. Chen, J. Thomas, M. Sadatsafavi, J.M. FitzGerald, Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis, Lancet Respir. Med. 3 (2015) 631–639, https://doi.org/10.1016/S2213-2600(15)00241-6.

[6] B.R. Lindman, H.S. Maniar, W.A. Jaber, S. Lerakis, M.J. Mack, R.M. Suri, et al., Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the Placement of Aortic Transcatheter Valves II inoperable cohort, Circ. Cardiovasc. Interv. 8 (2015), https://doi.org/10.1161/CIRCINTERVENTIONS.114.002073.

[7] P.C. Cremer, Y. Zhang, M. Alu, L.L. Rodriguez, B.R. Lindman, A. Zajarias, et al., The incidence and prognostic implications of worsening right ventricular function after surgical or transcatheter aortic valve replacement: insights from PARTNER IIA, Eur. Heart J. 39 (2018) 2659–2667, https://doi.org/10.1093/eurheartj/ehy251.

[8] E. Galli, Y. Guirette, D. Feneon, M. Daudin, M. Fournet, A. Leguerrier, et al., Prevalence and prognostic value of right ventricular dysfunction in severe aortic stenosis, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 531–538, https://doi.org/10.1093/ehjci/jeu290.

[9] M. Asami, S. Stortecky, F. Praz, J. Lanz, L. Raber, A. Franzone, et al., Prognostic value of right ventricular dysfunction on clinical outcomes after Transcatheter aortic valve replacement, JACC Cardiovasc. Imaging 12 (2019) 577–587, https://doi.org/10.1016/j.jcmg.2017.12.015.

[10] C. Keyl, J. Schneider, F. Beyersdorf, P. Ruile, M. Siepe, K. Pioch, et al., Right ventricular function after aortic valve replacement: a pilot study comparing surgical and transcatheter procedures using 3D echocardiography, Eur. J. Cardiothorac. Surg. 49 (2016) 966–971, https://doi.org/10.1093/ejcts/ezv227.

[11] D. Medvedofsky, E. Koifman, T. Miyoshi, T. Rogers, Z. Wang, S.A. Goldstein, et al., Usefulness of longitudinal strain to assess remodeling of right and left cardiac Chambers following Transcatheter aortic valve implantation, Am. J. Cardiol. 124 (2019) 253–261, https://doi.org/10.1016/j.amjcard.2019.04.029.

[12] J.M. Hilde, I. Skjorten, O.J. Grotta, V. Hansteen, M.N. Melsom, J. Hisdal, et al., Right ventricular dysfunction and remodeling in chronic obstructive pulmonary disease without pulmonary hypertension, J. Am. Coll. Cardiol. 62 (2013) 1103–1111, https://doi.org/10.1016/j.jacc.2013.04.091.

[13] R.A. Nishimura, C.M. Otto, R.O. Bonow, B.A. Carabello, J.P. Erwin, R.A. Guyton, et al., 2014 AHA/ACC guideline for the Management of Patients with Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, Circulation. 129 (2014) 2440–2492, https://doi.org/10.1161/CIR.0000000000000029.

[14] H. Baumgartner, V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, et al., ESC/EACTS guidelines for the management of valvular heart disease, Eur. Heart J. 38 (2017) (2017) 2739–2791, https://doi.org/10.1093/eurheartj/ehx391.

[15] B.L. Graham, V. Brusasco, F. Burgos, B.G. Cooper, R. Jensen, A. Kendrick, , et al. Executive Summary, ERS/ATS standards for single-breath carbon monoxide uptake in the lung, Eur. Respir. J. 49 (2017) (2017), https://doi.org/10.1183/13993003.E0016-2016.

[16] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, et al., Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (2012) 1324–1343, https://doi.org/10.1183/09031936.00080312.

[17] The Society of Thoracic Surgeons STS Adult Cardiac Surgery Database, Data Specifications, Version 2.81. https://www.sts.org/sites/default/files/documents/ACSD_DataSpecificationsV2_81.pdf, 2020. Pdf. (accessed April 30 2020).

[18] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 233–270, https://doi.org/10.1093/ehjci/jev014.

[19] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd, H. Dokainish, T. Edvardsen, et al., Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Eur. Heart J. Cardiovasc. Imaging 17 (2016) 1321–1360, https://doi.org/10.1093/ehjci/jew082.

[20] L.G. Rudski, W.W. Lai, J. Afilalo, L. Hua, M.D. Handschumacher, K. Chandrasekaran, et al., Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography, J. Am. Soc. Echocardiogr. 23 (2010) 685–713, https://doi.org/10.1016/j.echo.2010.05.010.

[21] W.A. Zoghbi, D. Adams, R.O. Bonow, M. Enriquez-Sarano, E. Foster, P.A. Grayburn, et al., Recommendations for noninvasive evaluation of native Valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance, J. Am. Soc. Echocardiogr. 30 (2017) 303–371, https://doi.org/10.1016/j.echo.2017.01.007.

[22] H. Baumgartner, J. Hung, J. Bermejo, J.B. Chambers, T. Edvardsen, S. Goldstein, et al., Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography, J. Am. Soc. Echocardiogr. 30 (2017) 372–392, https://doi.org/10.1016/j.echo.2017.02.009.

[23] T.J. Cahill, P. Pibarot, X. Yu, V. Babaliaros, P. Blanke, M.A. Clavel, et al., Impact of right ventricle-pulmonary artery coupling on clinical outcomes in the PARTNER 3 trial, JACC Cardiovasc. Interv. 15 (2022) 1823–1833, https://doi.org/10.1016/j.jcin.2022.07.005.

[24] L.P. Badano, T.J. Kolias, D. Muraru, T.P. Abraham, G. Aurigemma, T. Edvardsen, et al., Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/industry task force to standardize deformation imaging, Eur. Heart J. Cardiovasc. Imaging 19 (2018) 591–600, https://doi.org/10.1093/ehjci/jey042.

[25] D. Muraru, K. Haugaa, E. Donal, I. Stankovic, J.U. Voigt, S.E. Petersen, et al., Right ventricular longitudinal strain in the clinical routine: a state-of-the-art review, Eur. Heart J. Cardiovasc. Imaging 23 (2022) 898–912, https://doi.org/10.1093/ehjci/jeac022.

[26] S. Ito, S.V. Pislaru, W.M. Soo, R. Huang, K.L. Greason, V. Mathew, et al., Impact of right ventricular size and function on survival following transcatheter aortic valve replacement, Int. J. Cardiol. 221 (2016) 269–274, https://doi.org/10.1016/j.ijcard.2016.07.085.

[27] A. Vitarelli, Y. Conde, E. Cimino, S. Stellato, S. D'Orazio, I. D'Angeli, et al., Assessment of right ventricular function by strain rate imaging in chronic obstructive pulmonary disease, Eur. Respir. J. 27 (2006) 268–275, https://doi.org/10.1183/09031936.06.00072005.

[28] B.D. Kent, P.D. Mitchell, W.T. McNicholas, Hypoxemia in patients with COPD: cause, effects, and disease progression, Int. J. Chron. Obstruct. Pulmon. Dis. 6 (2011) 199–208, https://doi.org/10.2147/COPD.S10611.

[29] P. Joppa, D. Petrasova, B. Stancak, R. Tkacova, Systemic inflammation in patients with COPD and pulmonary hypertension, Chest. 130 (2006) 326–333, https://doi.org/10.1378/chest.130.2.326.

[30] S. Eddahibi, A. Chaouat, L. Tu, C. Chouaid, E. Weitzenblum, B. Housset, et al., Interleukin-6 gene polymorphism confers susceptibility to pulmonary hypertension in chronic obstructive pulmonary disease, Proc. Am. Thorac. Soc. 3 (2006) 475–476, https://doi.org/10.1513/pats.200603-038MS.

[31] A. Kempny, G.P. Diller, G. Kaleschke, S. Orwat, A. Funke, R. Schmidt, et al., Impact of transcatheter aortic valve implantation or surgical aortic valve replacement on right ventricular function, Heart. 98 (2012) 1299–1304, https://doi.org/10.1136/heartjnl-2011-301203.

[32] M. Puentes, D. Mesa, M. Ruiz Ortiz, M. Delgado, F. Mazuelos, J. Suárez de Lezo, Changes in right ventricular systolic function after transcatheter aortic valve implantation assessed by two-dimensional speckle tracking echocardiography, Rev. Esp. Cardiol. (Engl. Ed.) 65 (2012) 964–965, https://doi.org/10.1016/j.recesp.2012.02.011.

[33] P. Genereux, P. Pibarot, B. Redfors, J.J. Bax, Y. Zhao, R.R. Makkar, et al., Evolution and prognostic impact of cardiac damage after aortic valve replacement, J. Am. Coll. Cardiol. 80 (2022) 783–800, https://doi.org/10.1016/j.jacc.2022.05.006.

[34] D. Medvedofsky, E. Koifman, H. Jarrett, T. Miyoshi, T. Rogers, I. Ben-Dor, et al., Association of Right Ventricular Longitudinal Strain with mortality in patients undergoing Transcatheter aortic valve replacement, J. Am. Soc. Echocardiogr. 33 (2020) 452–460, https://doi.org/10.1016/j.echo.2019.11.014.

[35] M. Mok, L. Nombela-Franco, E. Dumont, M. Urena, R. DeLarochelliere, D. Doyle, et al., Chronic obstructive pulmonary disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes, prognostic markers, and functional status changes, JACC Cardiovasc. Interv. 6 (2013) 1072–1084, https://doi.org/10.1016/j.jcin.2013.06.008.

[36] M.C. Henn, A. Zajarias, B.R. Lindman, J.W. Greenberg, S.J. Melby, N. Quader, et al., Preoperative pulmonary function tests predict mortality after surgical or transcatheter aortic valve replacement, J. Thorac. Cardiovasc. Surg. 151 (2016) 578–585, https://doi.org/10.1016/j.jtcvs.2015.10.067.